INTEGRATIVE ONCOLOGY 4.0: A REAL-WORLD-TIME LEARNING SYSTEM FOR VALUE-BASED, PRECISION SARCOMA CARE

OVERVIEW

The Swiss Sarcoma Network (SSN), founded in December 2018, is built on a simple but demanding premise: in rare, heterogeneous cancers, "quality" cannot be reduced to guideline adherence or single endpoints. Quality must be demonstrated as an end-to-end system property—spanning diagnostic accuracy and timeliness, multidisciplinary coordination, oncologic and functional outcomes, toxicity burden, and cost-efficiency. SSN's scientific contribution has therefore evolved beyond reporting outcomes; it increasingly operationalizes *how* outcomes are produced, measured, compared, and improved across institutions through prospective, interoperable real-world-time data capture and analytics.



What distinguishes SSN's publication trajectory is the explicit shift from "documentation as a byproduct" to "data as the intervention": an integrated clinical network (IPU + hub-and-spoke + MDT governance) coupled to a digital backbone (ShapeHub) that enables benchmarking, care pathway mapping/defragmentation, and increasingly, model-assisted decision support and digital-twin logic.

VISION

SSN envisions a future where precision sarcoma care is not aspirational but *operational*: real-world-time data integration allows each patient's trajectory to be continuously updated, comparable, and learnable—supporting risk-adapted decisions, pragmatic optimization of multimodal therapy, and accountability under value-based healthcare (VBHC). The long-term direction is a federated, analytics-ready ecosystem where institutions co-produce evidence through standardized data and transparent methods rather than episodic retrospective studies.

MISSION

SSN's mission is to deliver transdisciplinary, interinstitutional sarcoma care that is (1) clinically excellent, (2) measurable in patient-relevant outcomes, and (3) continuously improvable through prospective real-world-time evidence generation. SSN actively promotes methodological transparency—explicit definitions, interoperable data structures, and reproducible analytics—because rare cancer progress depends on comparability and trust, not volume alone.

OPERATING MODEL

SSN's "means" can be framed as a deliberately coupled clinical–digital architecture:

1. **Integrated Practice Units (IPUs)**
   IPUs concentrate expertise and enable standardized workflows, prospective outcome tracking, and iterative learning loops.
2. **Sarcoma Hub-and-Spoke Model (HASM)**
   HASM is SSN's access-and-equity strategy: complex cases centralized at hubs, standardized diagnostics and follow-up supported at spokes, with real-time exchange and shared governance.
3. **Weekly MDT/Sarcoma Board Conferences**
   MDTs are treated not only as clinical decision forums but as *data-generating governance structures* enabling traceable decisions, auditability, and benchmarking.
4. ShapeHub**: Real-World-Time Data Backbone**
   A federated platform that harmonizes longitudinal clinical, pathology, imaging-linked, toxicity, and cost variables to enable real-time analytics, pathway mapping, and ultimately digital-twin style simulation.
5. **Sarcoma Academy (global knowledge exchange)**
   A structured dissemination and debate platform designed to accelerate methodological convergence and challenge legacy assumptions through expert interaction (not merely passive publishing).
6. **Standardized Quality, Outcome, and Value Metrics**
   SSN's work explicitly connects quality indicators, benchmarking, and cost/outcome logic—positioning VBHC as a measurable operating principle rather than a slogan.

SCIENTIFIC CONTRIBUTIONS: A RESTRUCTURED PILLAR MODEL

Below are six pillars that reflect what the SSN corpus actually does scientifically today – moving from "topics" to "mechanisms of system improvement".

PILLAR 1 – Care Architecture & Defragmentation

Core claim: Fragmentation is not a nuisance; it is a causal driver of diagnostic delay, redundant testing, unplanned resections, and outcome variability. SSN's later work tightens the argument by showing that *care pathway mapping* and interoperable data flow are not just measurement tools, but structural interventions that can change practice patterns ("data-driven defragmentation").

This pillar includes the move from conceptual integrated pathways toward operational pathway mapping, explicitly linking network structure (IPU/HASM/MDT) to learnability, equity, and VBHC feasibility.

PILLAR 2 – Measurement Science: Quality Indicators, Benchmarking, and "What Counts as Quality"

Core claim: In sarcoma, quality cannot be inferred from "doing the right things" alone; it must be demonstrated through transparent indicators and comparative analytics.

SSN's contributions here converge on (a) longitudinal QI assessment and evidence analytics, and (b) benchmarking MDT processes and outputs using harmonized real-world-time datasets. This is a shift from center-by-center narrative reporting to explicit comparators and improvement targets.

A key scientific strength is the repeated insistence on definitional rigor (what is counted, when, and why), because without this, cross-institutional comparisons collapse into noise or politics.

PILLAR 3 – Diagnostic Excellence as a Safety and Value Problem

Core claim: Diagnostic precision and timeliness are *value interventions* (avoid harm, avoid waste, avoid irreversible trajectory errors).

SSN work in this pillar operationalizes diagnostic quality via measurable constructs such as time-to-diagnosis and concordance dynamics, and introduces proxy indicators that capture the "signal-to-noise" of referral/biopsy pipelines (e.g., suspected-to-confirmed ratios) to reduce unplanned resections and inappropriate early excisions.

This pillar is important because it treats the front end (triage → imaging → biopsy → pathology) as the highest-leverage point for preventing downstream morbidity and cost inflation.

PILLAR 4 – Treatment Optimization and Harm Reduction (Against Reflexive Intensification)

Core claim: In rare cancers, escalation is often culturally attractive but scientifically fragile; SSN increasingly argues for *optimization* (de-intensification where safe, acceleration where beneficial) guided by real-world feasibility and patient burden.

This includes SSN's program around ultra-hypofractionated preoperative radiotherapy and the explicit comparison of schedules with attention to wound complications, toxicity burden, and operational efficiency—framed as VBHC, not merely convenience.

It also includes explicit critiques of broad "intensification doctrines" in high-risk STS when toxicity and generalizability are unfavorable, arguing for realistic applicability as a scientific endpoint in itself.

PILLAR 5 – Evidence Methodology for Rare Cancers: From RCT Exclusivity to Real-World-Time Causal Learning

Core claim: For heterogeneous, low-incidence diseases, the evidence engine must be hybrid: RCTs remain crucial but structurally insufficient; prospective RWTD/E plus causal designs (including target trial emulation) are necessary to answer "what works for whom" under real constraints.

SSN's methodological work explicitly positions RWTD/E as a distinct epistemic object (not "retrospective RWD"), and elevates target-trial logic and digital-twin concepts as ways to reduce bias and improve transportability of findings into practice.

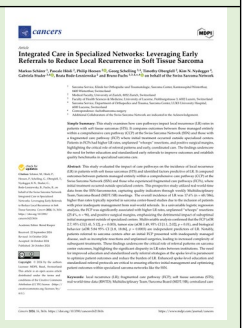
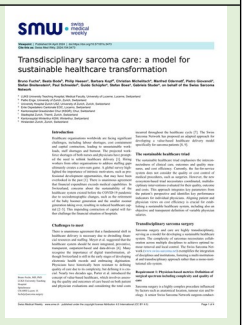
A notable strength is that this pillar is not abstract methods-only; it is consistently tied back to concrete care problems (whoops surgery, pathway failures, treatment feasibility).

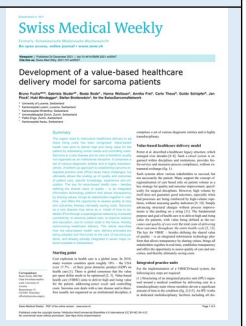
PILLAR 6 – Knowledge Translation as an Intervention: Sarcoma Academy and Constructive Paradigm Challenges

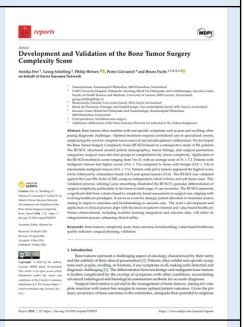
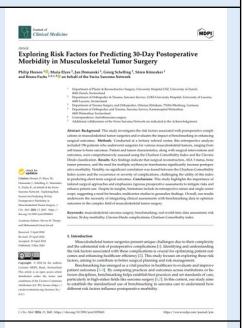
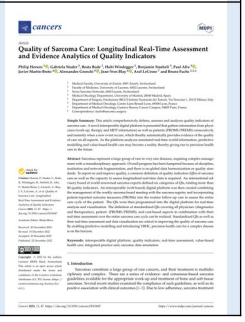
Core claim: In sarcoma care, "education" is not dissemination; it is the mechanism to align definitions, challenge outdated proxies, and accelerate adoption of more valid metrics.

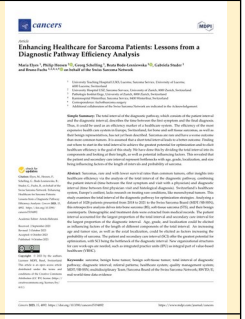
The Sarcoma Academy outputs Sarcoma Academy and its YouTube Channel, (including critical reappraisal pieces, e.g., on therapy-induced necrosis) formalize expert debate into citable, structured contributions that explicitly call for patient-centered endpoints, standardized assessments, and more pragmatic causal designs.

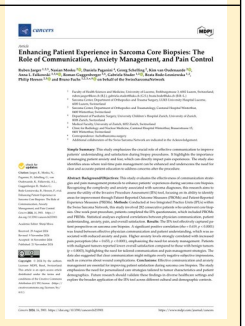
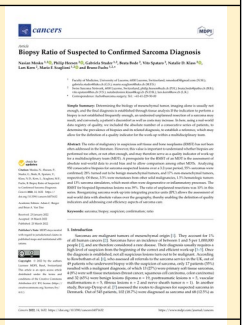
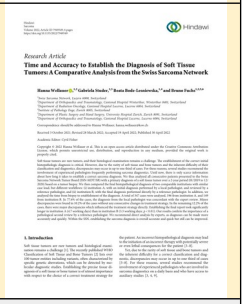
This pillar is SSN's bridge between community building and methodological modernization.

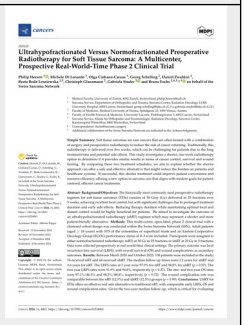
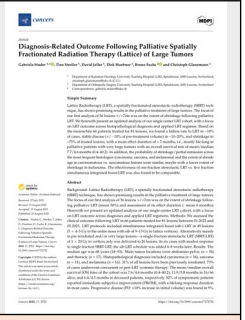
No.	Title	Year / Journal	Summary (as per overview doc)	Preview
P1 — Care Architecture & Defragmentation				
1	**Integrated Care in specialized Networks: Leveraging early Referrals to reduce Local Recurrence in Soft Tissue Sarcoma.**	**2024 Cancers**	This study assesses the impact of care fragmentation on local recurrence (LR) rates in soft tissue sarcoma (STS) patients. It compares outcomes between those managed within a comprehensive care pathway (CCP) at the Swiss Sarcoma Network (SSN) and those who experienced fragmented care pathways (FCPs). The findings indicate that patients in FCPs had higher rates of LR, unplanned "whoops" resections, and positive surgical margins compared to those managed within CCPs. This underscores the critical importance of early referrals and centralized care to improve patient outcomes. The study calls for better educational efforts and standardized referral protocols at the community level to reduce fragmentation and improve the quality of sarcoma care.	
2	**Transdisciplinary Sarcoma Care: A Model for sustainable healthcare transformation**	**2024 Swiss Medical Weekly**	The paper addresses the urgent challenges facing healthcare organizations, such as labor shortages and financial constraints. It introduces the concept of a sustainable healthcare triad, which aims to align clinical care, quality measures, and cost efficiency. Sarcoma care is presented as a model system that requires a transdisciplinary approach for optimal patient outcomes. The paper also discusses the importance of physician-based metrics and patient- reported outcome measures (PROMs) in assessing and improving healthcare quality. An interoperable digital platform is emphasized for real-time data collection and evidence analytics. The paper concludes by outlining the need for the healthcare industry to evolve and adapt, with a focus on digital transformation.	
3	**Data driven defragmentation: Achieving Value-Based Sarcoma and Rare Cancer Care Through Integrated Care Pathway Mapping**	**2025 Journal of Personalized Medicine**	This manuscript introduces a data-driven approach to defragmenting sarcoma and rare cancer care by integrating structured real-world-time data into harmonized care pathway mapping. The authors argue that traditional systems, dominated by passive electronic medical records and fragmented referral structures, fail to provide actionable insights at the point of care. Using the ShapeHub platform, they demonstrate how interoperable data integration enables dynamic care coordination, real-time feedback, and predictive analytics. Beyond critique, the paper advocates for deploying digital twin architectures that support multidisciplinary decision-making, timely risk-adjusted interventions, and the realization of value-based care in rare cancer networks.	
4	**Beyond the Sarcoma Center: Establishing the Sarcoma HASM Network—A Hub and Spoke Model Network for Global Integrated and Precision Care**	**2024 ESMO Open**	This review introduces the Sarcoma Hub and Spoke Model (HASM) Network, a novel approach to enhance global sarcoma care by centralizing complex case management at specialized hubs while peripheral spokes handle routine diagnostics and treatments. The HASM Network leverages digital interoperable platforms for real-world-time data exchange, facilitating multidisciplinary team meetings and advanced predictive analytics, including Sarcoma Digital Twins and causal machine learning. The integration of the Sarcoma Care Data Warehouse supports comprehensive quality assessment and continuous improvement through aggregated patient data. This model aims to optimize resource use, expand access to specialized care, and set a new standard for integrated and personalized sarcoma treatment worldwide.	
P2 — Measurement Science				

5	**Swiss Sarcoma Network (SSN) – Enhancing Care Quality though Collaboration**	**2019 SwissKnife**	The paper focuses on the quality of care for patients with soft tissue sarcomas, emphasizing the importance of interdisciplinary and inter-institutional collaboration. It introduces the Swiss Sarcoma Network's (SSN) telemedicine-based sarcoma board, which aims to enhance expert exposure to sarcoma cases and improve patient management. The paper also discusses the critical role of accurate histopathological diagnosis and critiques existing data registries for their limitations, advocating for better data management throughthe SSN's Swiss Sarcoma Registry. Overall, the paper aims to improve sarcoma treatment through quality assurance, expert collaboration, and effective data management.	
6	**Quality assurance in the treatment of sarcoma: an interdisciplinary and interinstitutional challenge**	**2019 Schweizer Krebsbulletin**	The editorial discusses the challenges of ensuring quality in the treatment of sarcomas, a rare disease requiring interdisciplinary and interinstitutional collaboration. It debates the merits of centralizing treatment in a single, high-volume center versus establishing a network of smaller centers. The editorial advocates for a Quality Management System (QMS) and highlights the Swiss Sarcoma Network (SSN) as an example that aims to centralize expertise and ensure quality and transparency. It also emphasizes the need for real-time data collection and international collaboration to improve treatment quality.	
7	**SSN – Activities and first results**	**2022 Luzerner Arzt**	The article discusses the importance of a multidisciplinary approach in the diagnosis and treatment of sarcomatous diseases. It cites data from international sarcoma networks to show that such an approach significantly improves patient outcomes. The Swiss Sarcoma Network (SSN) is highlighted as a key player in Switzerland for providing comprehensive care for sarcoma patients. The article also updates the key figures and first outcome data based on SSN's documentation over the last four years. Quality indicators for effective sarcoma management are also discussed. The article serves as a comprehensive guide for professionals and offers contact information for further consultations.	
8	**Development of a value-based healthcare delivery model for sarcoma patients**	**2021 Swiss Medical Weekly**	This article addresses the urgent need to restructure healthcare delivery to control rising costs. It proposes the implementation of a Value-Based Healthcare Delivery (VBHCD) model, particularly focusing on sarcoma, a rare and complex disease. The authors argue for the establishment of Integrated Practice Units (IPUs) that are organized around the medical condition and involve a transdisciplinary team. A key component for the success of VBHC is an integrated information technology platform that allows for real-time data sharing, quality assessment, and ultimately cost-saving. The article also discusses the challenges in implementing this model, such as the current siloed healthcare systems and issues with reimbursement. However, it highlights the opportunities presented by digital platforms to overcome these challenges. In the Swiss context, efforts are already underway to implement this model through the Swiss Sarcoma Network, aiming to make VBHC a reality.	
9	**Definition of the surgical case complexity in the treatment of soft tissue tumors of the extremities and trunk.**	**2022 Cancers**	The study introduces a Soft Tissue Tumor Surgery Complexity Score (STS-SCS) aimed at categorizing the complexity of soft tissue tumor surgeries. Applied to a sample of 711 patients, the STS-SCS was effective in stratifying surgeries into four complexity categories. The score aligns with Porter's model of value-based healthcare, potentially enabling better patient allocation to appropriate treatment centers. The study also opens the door for using STS-SCS as a quality indicator in sarcoma surgery.	

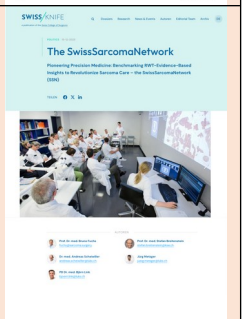
10	**Rethinking the Prognostic Role of Necrosis in Soft Tissue Sarcoma: Multidisciplinary Insights from the Sarcoma Academy**	**2025 Cancers**	This Sarcoma Academy consensus paper critically re-evaluates the role of therapy-induced necrosis as a prognostic marker in soft tissue sarcoma (STS), arguing that it is inconsistently defined, poorly standardized, and often reflects treatment intensity rather than intrinsic tumor biology. While necrosis has been historically used as a surrogate endpoint, especially in osteosarcoma-informed paradigms, the authors caution against its routine use in STS without subtype-specific validation. Instead, they recommend developing and validating more meaningful response criteria, such as radiologic-pathologic correlation frameworks, imaging biomarkers (e.g., functional MRI or radiomics), immune or cellularity-based histologic metrics, and interdisciplinary scoring systems that integrate radiology, pathology, and surgical context.	
11	**Development and Validation of the Bone Tumor Surgery Complexity Score**	**2024 Reports**	The paper introduces the Bone Tumor Surgery Complexity Score (BT-SCS) and applies it to a cohort of 501 patients undergoing bone tumor surgeries. The BT-SCS aims to quantify surgical complexity based on various factors, enabling efficient healthcare resource allocation and potentially improving treatment quality.	
12	**Impact of Institutional Practices and Surgical Complexity on Sarcoma Surgery Costs: Driving Efficiency in Value-Based Healthcare**	**2024 Cancers**	This paper explores the economic impact of sarcoma surgeries across three Swiss tertiary healthcare institutions. By analyzing data from 356 surgeries, the study assesses surgical and hospital costs in relation to institutional characteristics and surgical complexity. It finds significant cost variations driven more by institutional resource management and pricing strategies than by surgical techniques. Higher complexity and malignancy significantly increase costs, with surgical costs accounting for only one-third of the total hospitalization costs. The study underscores the need for standardized cost assessment practices and highlights the potential of predictive models in enhancing resource allocation and surgical planning. The findings advocate for value- based healthcare models and standardized treatment guidelines to optimize healthcare delivery for sarcoma patients.	
13	**Exploring Risk Factors for 30-day postoperative Morbidity in Musculoskeletal Tumor Surgery**	**2024 J Clinical Medicine**	The paper aims to establish benchmarks for complication rates in sarcoma surgery and identify significant risk factors for postoperative complications. It found that ASA 3 status, bone tumors, presence of metastasis, and the number of erythrocyte concentrates administered were significant predictors of complications. However, the Charlson Comorbidity Index (CCI) was not associated with complications. The study also provides actionable clinical recommendations and acknowledges its limitations, calling for further research.	
14	**Quality of sarcoma care: longitudinal real- time assessment and evidence analytics of quality indicators**	**2022 Cancers**	The paper discusses the development of an interoperable digital platform aimed at enhancing the quality of sarcoma care. It emphasizes the importance of international collaboration and introduces real- time assessment of quality indicators throughout the entire care cycle. The platform is designed to strengthen the collaboration of Integrated Practice Units (IPUs) and aims to pave the way for precision medicine and Value-Based Health Care (VBHC) in treating complex diseases like sarcoma. Overall, the paper advocates for a data-driven, collaborative approach to improve patient outcomes.	

15	**Unlocking the Power of Benchmarking: Real-World-Time Data Analysis for Enhanced Sarcoma Patients Outcome**	**2023 Cancers**	The paper focuses on the utilization of benchmarking and Real-World-Time harmonized data to improve outcomes for sarcoma patients, emphasizing the transition to a value-based care model. It introduces Sarconnector® as a tool for this transition. The paper also discusses the role of chemotherapy and biopsy in sarcoma treatment, highlighting the potential for enhanced, personalized care through real-world-time (meta-) data analysis.	
16	**The sarcoma-specific instrument to longitudinally assess health-related outcomes of the routine care cycle**	**2023 Diagnostics**	This paper emphasizes the urgent need for a sarcoma- specific HRQoL instrument due to the disease's complexity. It proposes a novel approach that utilizes a sum of established generic PROMs, tailored to the patient's longitudinal care cycle. This allows for broader comparison and benchmarking. The paper introduces an interoperable digital platform to manage the large volume of data generated, aiming for real-world-time analytics and predictive modeling. The platform is designed to be an integral part of an institutional electronic health record (EHR) system, paving the way for value-based healthcare. The paper acknowledges the challenges in implementation and emphasizes the need for a new ecosystem of data management, facilitated by digital transformation.	
	P3 — Diagnostic Excellence			
17	**Enhancing Healthcare for Sarcoma Patients: Lessons from a Diagnostic Pathway Efficiency Analysis**	**2023 Cancers**	The study fills a significant gap in the literature by examining the total interval for diagnosing mesenchymal tumors, including benign types. It identifies patient interval and secondary care interval as the most significant contributors to the total diagnostic pathway. The study also highlights the role of age, tumor grade, and localization in affecting these intervals. Despite Switzerland's efficient healthcare system, the study suggests that there is room for improvement, particularly in the structure of the healthcare system and the multidisciplinary approach required for diagnosing sarcomas.	
18	**Pain Accelerates, Swelling And Sensory Disturbances Delay Diagnosis in Mesenchymal Tumors**	**2025 Cancers**	This retrospective real-world data study investigates how initial symptom presentation influences diagnostic delays in patients with mesenchymal tumors. The authors find that pain is significantly associated with shorter diagnostic intervals, while swelling and sensory disturbances are linked to prolonged delays—particularly when these symptoms are misinterpreted or attributed to benign conditions. Rather than merely describing patterns, the paper underscores the need to integrate symptom logic into triage algorithms and referral decision tools. It advocates for a more nuanced, symptom-driven diagnostic pathway design, aiming to accelerate early detection and reduce the risk of unplanned surgery or metastatic progression in sarcoma care.	
19	**Benchmarking Time-to-Treatment Initiation in Sarcoma Care Using Real-World-Time Data**	**2023 Cancers**	The paper presents a detailed study on the time-to- treatment initiation (TTI) for sarcoma patients. Utilizing data from 266 cases from the Swiss Sarcoma Network, the study reveals a median TTI of 30 days across the cohort. It finds that the length of TTI varies significantly depending on sarcoma type and care institution. The study emphasizes the use of real- world-time data (RWTD) for a more comprehensive capture of patient journeys. It highlights the need for standardized processes across treatment centers and advocates for selective referral to specialized centers. The study identifies significant delays in TTI, particularly in unplanned 'whoops'-resections, underscoring the importance of early specialist referral. The findings are critical for developing healthcare systems that focus on delivering value- based care.	

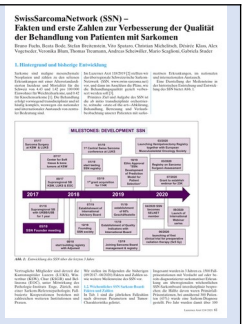
20	**Planned and Unplanned Sarcoma Resections: Comparative Analysis of Local Recurrence, Metastasis, and Mortality**	**2024 Cancers**	This study compares the outcomes of planned resections (PEs) versus unplanned resections (UEs) of sarcomas. Planned resections achieve better immediate resection margins but are associated with more advanced tumors, higher metastasis rates, and increased cancer-specific mortality. Unplanned resections are linked to higher local recurrence rates but do not significantly affect metastasis-free or overall survival. The findings highlight the need for early detection and timely referrals to specialized sarcoma centers to improve patient outcomes.	
21	**Enhancing Patient Experience in Sarcoma Core Biopsies: The Role of Communication, Anxiety Management, and Pain Control**	**2024 Cancers**	This study examines the integration of patient- reported outcome measures (PROMs) and patient- reported experience measures (PREMs) into the sarcoma biopsy process. It evaluates factors such as anxiety, pain perception, and satisfaction in 258 patients undergoing core biopsies. Key findings highlight that effective communication before and during the procedure significantly reduces patient anxiety and improves satisfaction. Pain control measures, though secondary to communication, are also essential to enhancing the overall patient experience. The study concludes that incorporating PROMs and PREMs into biopsy workflows not only enhances patient-centered care but also aligns with the principles of value-based healthcare by optimizing care processes and outcomes. Future work is encouraged to standardize these measures and implement them across multidisciplinary teams.	
22	**Biopsy ratio of suspected to confirmed sarcoma diagnosis**	**2022 Cancers**	The paper presents a comprehensive analysis of 950 consecutive biopsies performed for suspected sarcoma over a 3.2-year period. It introduces the concept of the Ratio of Malignancy in Suspicious Tumors (RMST) as a potential quality indicator for sarcoma care. The study emphasizes the need for standardized definitions and categories for better comparison among multidisciplinary teams and suggests that RMST could help in reducing the rate of unplanned resections.	
23	**Time and accuracy to establish the diagnosis of soft tissue tumors: a comparative analysis from the SSN**	**2022 Sarcoma**	The study conducted by the Swiss Sarcoma Network analyzed the time and accuracy of diagnosing soft tissue tumors in two different institutions with varying workflows. The study found that 77.6% of diagnoses were concordant between local and reference pathologists. Institution B, where diagnoses were directly performed by a reference pathologist, had a significantly shorter time to diagnosis (3.3 working days) compared to Institution A (4.7 working days). The study emphasizes the importance of expert review in sarcoma diagnosis and recommends direct analysis by experts for quicker and more accurate results.	
P4 — Treatment Optimization				
24	**Wie entwickelt sich die Sarkomchirurgie?**	**2021 Orthopädie & Rheumatologie**	The paper discusses the complexities and challenges in sarcoma surgery. It emphasizes the critical role of achieving an R0 resection, where the tumor is microscopically completely removed, as no other therapy can compensate for an inadequate resection. It highlights unplanned resections (“whoops lesions”) and argues for transdisciplinary sarcoma competence teams and comprehensive registries including PROMs for quality control and outcome measurement.	

25	**How is the spectrum of sarcoma surgery assessed?**	**2023 Cancers**	The paper presents a comprehensive study on sarcoma care over a 10-year period, involving 3130 patients and 5930 sarcoma board decisions from one sarcoma surgeon. It introduces an interoperable digital platform for structured surgical data collection and emphasizes the need for a multidisciplinary approach in sarcoma care. The study also critiques the limitations of volume-based metrics for assessing surgical quality and advocates for data harmonization and a nuanced, data-driven approach to meet the challenges of precision medicine.	
26	**From Intensification to Optimization: Balancing Efficacy, Safety, and Costs in High-Risk Localized Soft Tissue Sarcomas**	**2025 Cancers**	This paper challenges the prevailing paradigm of treatment intensification in high-risk localized soft tissue sarcoma (STS), arguing that escalation strategies—such as multi-agent chemotherapy and extensive radiotherapy—often fail to translate into survival benefit and carry substantial toxicity burdens. Drawing on real-world-time data from the SHAPEHub platform, the authors advocate for a shift toward treatment optimization, emphasizing individualized, risk-adapted approaches that prioritize biological responsiveness, clinical feasibility, and quality of life. The study supports ultra-hypofractionated preoperative radiotherapy as a streamlined alternative, and calls for outcome-aligned treatment de-escalation strategies guided by histotype, stage, and patient-centered metrics, embedded within value-based care frameworks.	
27	**Preoperative Ultra-hypofractionated Radiation Therapy for soft- tissue sarcomas: low rate of wound complications**	**2024 Advances in Radiation Oncology**	This study evaluates the efficacy and safety of preoperative ultra-hypofractionated radiotherapy (uhRT) using a regimen of 25 Gy in 5 fractions over one week in soft-tissue sarcoma patients. The prospective registry analysis demonstrates that uhRT yields low rates of wound complications (12%) and maintains high local control (94% at 1.5 years), comparable to traditional normofractionated radiotherapy (nRT) outcomes. The findings suggest that uhRT is a viable alternative to nRT, offering reduced treatment duration and potentially greater economic efficiency without compromising clinical results. This approach underscores the importance of advanced, transdisciplinary collaboration in refining sarcoma care protocols.	
28	**Ultrahypofractionated versus Normofractionated Preoperative Radiotherapy for Soft Tissue Sarcoma: A Multicenter, Prospective Real-World-Time Phase 2 Clinical Trial**	**2024 Cancers**	This multicenter, prospective real-world-time phase 2 trial compared ultrahypofractionated radiotherapy (uhRT; 25 Gy in 5 fractions over 1 week) to normofractionated radiotherapy (nRT; 50 Gy in 25 fractions over 5 weeks) for soft tissue sarcoma patients. The study enrolled 138 patients, with a median follow-up of 2.2 years for uhRT and 3.6 years for nRT. Local recurrence-free survival (LRFS) at 1 and 2 years was comparable between uhRT (94.8%) and nRT (91.9%). Overall survival (OS) rates were also similar, and wound complication rates were low in both groups (uhRT: 12.5%; nRT: 12.0%). The results suggest that uhRT offers a shorter, patient-friendly alternative to nRT with comparable efficacy, potentially improving healthcare resource utilization and aligning with value-based healthcare principles. Future studies are required to validate long-term outcomes and broader adoption.	
29	**Diagnosis-Related Outcome Following Palliative Spatially Fractionated Radiation Therapy (Lattice) of Large Tumors**	**2025 Cancers**	Real-world evaluation of palliative spatially fractionated radiotherapy (Lattice) for very large tumors. The paper reports diagnosis-related outcomes after Lattice RT and discusses where this technique may offer symptom control and tumor shrinkage for patients with limited options.	

P5 — Evidence Methodology

30	**Improving Sarcoma Outcomes: Target Trial Emulation to Compare the Impact of Unplanned and Planned Resections on the Outcome.**	**2024 Cancers**	This study employs the novel Target Trial Emulation (TTE) framework to compare the effects of unplanned resections (UE) and planned resections (PE) on sarcoma patient outcomes, utilizing data from 429 patients in the Swiss Sarcoma Network. The use of TTE allows for the rigorous exploration of treatment outcomes by emulating the design principles of randomized controlled trials (RCTs) while utilizing real-world-time data, thus overcoming the ethical and practical limitations of traditional RCTs in surgical research. The study reveals that UEs are significantly linked to higher risks of local recurrence, though there were no significant differences in metastasis-free survival, cancer-specific survival, or overall survival between the groups in the short term. Tumor grade is affirmed as a crucial prognostic factor, highlighting the necessity of optimal initial surgical management. The study advocates for improved referral systems to specialized sarcoma centers to reduce UEs and suggests integrating TTE in sarcoma research to enhance clinical guidelines and decision-making, ultimately aiming to improve patient outcomes.	
31	**From Data Integration to Precision Medicine: A Value-Based Healthcare Approach for Sarcoma Care**	**2024 Journal of Clinical Medicine**	This review outlines the transformation of sarcoma care from a fee-for-service model to a value-based healthcare (VBHC) framework, emphasizing structured and harmonized data integration as a critical precursor to precision medicine. The paper highlights the use of standardized data formats, ontologies, and coding systems to integrate clinical, economic, and patient-reported outcomes across institutions, paving the way for predictive analytics and personalized treatment strategies. Key challenges addressed include system standardization, privacy concerns, and the high costs of implementation. The work establishes the necessary steps for building a data-driven approach to support precision medicine, ultimately enhancing patient outcomes and optimizing healthcare resources.	
32	**Real-time interactive analysis of the treatment quality of sarcoma patients**	**2022 info@ONCO-SUISSE**	The text emphasizes the complexities of treating sarcomas, a rare but molecularly diverse form of cancer. It highlights the need for a transdisciplinary approach and the challenges posed by the lack of real- time, patient-defined data. The article suggests that digital transformation, particularly in data collection and predictive analytics, could significantly advance sarcoma treatment. It also touches on the potential for these technologies to facilitate a shift towards value-based healthcare. This interoperable platform was awarded the German Medical Award in 2021.	
33	**Pioneering Precision Medicine: Benchmarking RWT-Evidence-Based Insights to Revolutionize Sarcoma Care – The SwissSarcomaNetwork (SSN)**	**2023 SwissKnife**	The manuscript provides a comprehensive roadmap for revolutionizing sarcoma care through the integration of precision medicine. It emphasizes a multidisciplinary, data-driven approach and discusses the roles of interoperable digital platforms, automated analysis, benchmarking, and value-based healthcare. The paper also introduces innovative concepts like predictive AI/ML modeling and digital twins to further enhance patient outcomes. Overall, it offers a promising vision for the future of sarcoma care, grounded in data-driven methodologies and continuous improvement loops.	
34	**Clinical Prognostic Models for Sarcomas: A Systematic Review and Critical Appraisal of Development and Validation Studies**	**2025 Diagnostic & Prognostic Research**	This systematic review critically appraises existing clinical prognostic models (CPMs) for soft tissue sarcoma (STS) using TRIPOD and PROBAST criteria, revealing widespread methodological shortcomings, including high risk of bias, lack of external validation, and limited applicability to contemporary clinical practice. The authors argue that most models are constrained by small, single-center datasets and rigid assumptions, making them poorly suited for dynamic, real-world environments. In response, the paper calls for a paradigm shift toward robust, externally validated, and interoperable models built on harmonized real-world data, emphasizing the need for modular, subtype-specific, and continuously learning systems that support precision oncology and	

			decision-making at scale.	
35	**The Next Frontier in Sarcoma Care: Digital Health, AI, and the Quest for Precision Medicine.**	**2023 Journal of Personalized Medicine**	This paper discusses the transformative potential of digital health and AI in advancing sarcoma care towards a value-based healthcare model. It introduces the concept of a "Sarcoma Digital Twin," a comprehensive digital avatar of a patient's medical profile, which can be used for predictive modeling and treatment optimization. While acknowledging the challenges in terms of ethics, regulation, and practical implementation, the paper calls for a multidisciplinary approach to seize this transformative opportunity.	
36	**Real-World-Time Data and RCT Synergy: Advancing Personalized Medicine and Sarcoma Care through Digital Innovation.**	**2024 Cancers**	This paper explores the integration of real-world-time data (RWTD/E) with traditional randomized controlled trials (RCTs) to advance personalized medicine in sarcoma care. By leveraging the comprehensive, real-time insights provided by RWTD/E alongside the structured environment of RCTs, the study demonstrates how this synergy can enrich healthcare research and operational insights. The combination of RWTD/E's broad, real-world applicability with the precision of RCTs allows for more nuanced and effective treatment strategies. Methodological innovations such as digital twinning and target trial emulation are highlighted, emphasizing their role in improving the precision and applicability of RWTD/E. The paper advocates for the strategic incorporation of RWTD/E into healthcare frameworks to create an evidence-driven ecosystem that significantly enhances patient outcomes and healthcare efficiency, with sarcoma care serving as a key example of these advancements.	
37	**Reporting Matters: Severe Adverse Events in Soft Tissue Sarcoma Therapy—A 30-Year Systematic Review of Placebo- and Non-Systemic-Controlled Randomized Trials**	**2025 Cancers**	Systematic review of 30 years of randomized trials in soft tissue sarcoma focusing on the reporting and burden of severe adverse events. The manuscript argues that safety reporting is frequently insufficient for high-certainty risk–benefit appraisal and proposes stronger standards for SAE/AE capture and transparency in sarcoma trials.	
38	**From Lindbergh's cockpit to predictive, AI-driven health care: a roadmap for high-reliability medicine**	**2025 ESMO Real World Data and Digital Oncology**	Perspective article proposing an aviation-inspired roadmap toward high-reliability medicine, progressing from standardized interoperable data to AI-assisted decision support and continuous oversight. Uses learning-system concepts to illustrate how predictive analytics can reduce preventable error and fragmentation.	
39	**Triangulating Timing, Tropism and Burden of Sarcoma Metastases: Toward Precision Surveillance and Therapy in a Real-World-Time Cohort**	**2025 Cancers**	Real-world-time cohort analysis that triangulates timing, organ tropism, and burden of sarcoma metastases to support histotype- and risk-adapted surveillance and treatment planning. Frames metastatic dynamics as an actionable precision-surveillance layer rather than a one-size-fits-all follow-up routine.	
P6 — Knowledge Translation				

40	**SSN – Facts and first figures to improve quality in the treatment of patients with sarcoma**	**2021 Luzerner Arzt**	The article discusses the Swiss Sarcoma Network (SSN), a transdisciplinary initiative aimed at improving the quality of care for patients with sarcomas. It provides an overview of the SSN's activities, milestones, and quality indicators. The SSN has established a weekly Sarcoma Board where cases are discussed, and it has also set up a real-world-time data registry. The article emphasizes the importance of accurate diagnosis and timely treatment, highlighting the challenges and pitfalls, such as "Whoops Operations," where a sarcoma is unexpectedly found after unplanned surgery without prior imaging. The SSN aims to standardize care through quality indicators and to foster education and research in the field.	
41	**Prätherapeutische Abklärung und Strategie-Festlegung bei Patienten mit Knochen- und Weichteiltumoren**	**2017 Luzerner Arzt**	This referrer- and practice-oriented article emphasizes early interdisciplinary coordination for suspected bone and soft tissue tumors. It outlines standardized imaging (e.g., contrast MRI and chest CT), biopsy planning to avoid contamination, and early tumor-board discussion to prevent avoidable ‘whoops’ resections and downstream harm.	
42	**Frühzeitig richtig handeln: Der Einfluss direkter Überweisungen auf Sarkom-Behandlungsergebnisse**	**2026 LUKS medical insight**	Referrer-oriented article summarizing why early, direct referral into specialized sarcoma pathways matters. It illustrates how structured SSN/IPU processes shorten time-to-decision and reduce downstream harm associated with fragmented, unplanned diagnostic and surgical steps.	

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MDPI

Article

Integrated Care in Specialized Networks: Leveraging Early Referrals to Reduce Local Recurrence in Soft Tissue Sarcoma

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Simple Summary: This study examines how care pathways impact local recurrence (LR) rates in patients with soft tissue sarcomas (STS). It compares outcomes between those managed entirely within a comprehensive care pathway (CCP) at the Swiss Sarcoma Network (SSN) and those with a fragmented care pathway (FCP) where initial treatment occurred outside specialized centers. Patients in FCPs had higher LR rates, unplanned "whoops" resections, and positive surgical margins, highlighting the critical role of referral patterns and early, coordinated care. The findings underscore the need for better education and standardized early referrals to improve outcomes and establish quality benchmarks in specialized sarcoma care.

Abstract: This study evaluated the impact of care pathways on the incidence of local recurrence (LR) in patients with soft tissue sarcomas (STS) and identified factors predictive of LR. It compared outcomes between patients managed entirely within a comprehensive care pathway (CCP) at the Swiss Sarcoma Network (SSN) and those who experienced fragmented care pathways (FCPs), where initial treatment occurred outside specialized centers. This prospective study utilized real-world-time data from the SSN-Sarconnector, capturing quality indicators through weekly Multidisciplinary Team/Sarcoma-Board (MDT/SB) meetings. The overall incidence of LR was 17.6% (n = 68/386), higher than rates typically reported in sarcoma center-based studies due to the inclusion of patients with prior inadequate management from real-world referrals. In a univariable logistic regression analysis, the FCP was significantly associated with higher LR rates, unplanned "whoops" resections (25.4%, n = 96), and positive surgical margins, emphasizing the detrimental impact of suboptimal initial management outside of specialized centers. Multivariable analysis confirmed that the FCP (aOR 2.7, 95% CI [1.41, 5.12], $p = 0.003$), tumor size (aOR 1.49, 95% CI [1.1, 2.02], $p = 0.01$), and biological behavior (aOR 5.84 95% CI [1.8, 18.86], $p = 0.0003$) are independent predictors of LR. Notably, patients referred to sarcoma centers after an initial FCP presented with inadequately managed disease, such as incomplete resections and unplanned surgeries, leading to increased complexity of subsequent treatments. These findings underscore the critical role of referral patterns on sarcoma center outcomes, highlighting the significant disparity in LR rates between institutions. The need for improved education and standardized early referral strategies at the spoke level is paramount to optimize patient outcomes and reduce the burden of LR. Enhanced spoke-level education and standardized referral protocols are critical to ensuring effective initial management and optimizing patient outcomes within specialized sarcoma networks like the SSN.

Keywords: local recurrence (LR); fragmented care pathway (FCP); soft tissue sarcomas (STS); real-world-time data (RWTD); Multidisciplinary Team/Sarcoma Board (MDT/SB); centralized care

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1. Introduction

The heterogeneous nature of soft tissue sarcomas (STS) presents significant challenges in patient care, often leading to misrecognition and misdiagnosis [1,2]. Due to their rarity and symptom overlap with benign conditions, initial treatments frequently occur outside specialized centers, resulting in inappropriate management, such as unplanned "whoops" resections—excisions performed without prior imaging or biopsy [3,4]. The absence of standardized diagnostic and treatment protocols in non-specialized settings exacerbates outcome variability, underscoring the critical need for management within specialized sarcoma centers [5–7]. Treatment guidelines strongly advocate for centralizing care high-volume reference centers where multidisciplinary teams can provide coordinated, guideline-conforming management. This approach significantly reduces the likelihood of unplanned surgeries and has been shown to improve survival rates [2,8–10]. This underscores the importance of a coordinated hub-and-spoke model, where specialized sarcoma centers (hubs) guide initial management through timely and accurate referrals from community providers (spokes) [11].

LR, alongside metastasis, serves as a pivotal indicator of disease control and surgical quality [8,12]. LR rates, typically ranging between 7.5 and 15% reflect the presence of residual tumor cells, often due to inadequate resection margins [13–15]. Surgery remains the primary treatment modality for STS, aiming for complete control while minimizing functional impairment [16]. The quality of initial surgery was shown to be a major prognostic factor for recurrence-free survival [17]. Therefore, highly trained surgeons in specialized centers are crucial as their expertise in sarcoma surgery and understanding of adjunct treatment options such as radiotherapy can significantly improve resection quality and reduce the need for extensive resections [18–21]. Preventing LR is critical, as inadequate initial treatments complicate the management of recurrent disease, leading to increased morbidity, higher treatment costs, and poorer patient outcomes [13]. Adhering to treatment guidelines and centralizing care in specialized centers have been shown to reduce LR rates [22,23]. This highlights the necessity of integrated care strategies within specialized centers to balance local control and quality of life effectively. The complex available and constantly renewed treatment strategies need to be based on multidisciplinary care for having the best possible outcome for the patient. This can only be achieved in specialized treatment centers allowing for units of different treatment teams and having the possibility of different treatments.

This study aims to assess the impact of care fragmentation on LR rates in patients treated within the Swiss Sarcoma Network (SSN), specifically evaluating how unplanned "whoops" resections and positive surgical margins contribute to recurrence. Additionally, this study explores how variations in referral patterns across different institutions influence LR outcomes, highlighting the critical role of early and accurate referrals from non-specialized settings. By analyzing the differences between comprehensive and fragmented care pathways, this research seeks to identify potential areas for improvement in patient management to mitigate LR rates. Treatment pathways were analyzed and the differences in comprehensive and fragmented care were assessed. This research aims to serve as a quality assurance benchmark for the SSN, highlighting potential areas for improving patient pathways to mitigate LR rates.

2. Materials and Methods

2.1. Study Design and SSN

This study uses prospective real-world-time data (RWTD) from patients registered within the SSN-Sarconnector®, established in 2018 [24]. The registry acts as a national data warehouse that captures quality indicators related to care pathways, surgical practices, and patient outcomes, all discussed during weekly Multidisciplinary Team/Sarcoma-Board (MDT/SB) meetings. This approach fosters transdisciplinary collaboration and transparent practices in sarcoma therapy, providing a comprehensive data set to assess the impact of care fragmentation on surgical quality. The process of data entry is a collaborative endeavor

that engages physicians from diverse disciplines who are integrated into the MDT/SB meetings. It is important to note that in the SSN, patients with sarcoma or suspected sarcoma can enter the process of MDT/SB either through the SSN-Network or directly by the physician, leading in both cases to a final MDT/SB review after central pathology confirmation. The MDT/SB meetings serve as a forum for reviewing patient information, treatment adjustments, and outcomes, thereby ensuring the integrity of the data.

2.2. Subjects and Data Extraction

This study included consecutive patients presented to the SSN MDT/SB between 2018 and 2023, either with a suspected diagnosis of ST or as secondary referrals following initial treatment at external institutions. Patients were analyzed based on the date of the first histologically confirmed sarcoma diagnosis and the occurrence of their first LR. Due to the real-world timeline and the inclusion of patients initially managed outside a sarcoma center, the date of diagnosis could precede the study's inclusion period. Patients treated at a sarcoma center during the 2018–2023 window were followed for the development of LR within this timeframe. Comprehensive data were extracted using the Adjumed platform (Adjumed Services AG, Zurich, Switzerland; accessed on June 2024) including details on patient referrals, treatment modalities, and surgical outcomes.

2.3. Definitions, Outcomes, Measurements, and Clinical Characteristics

Utilizing our RWTD (Adjumed, Zürich, Switzerland), comprehensive demographic and treatment-specific data were systematically extracted and documented for each patient. The variables recorded included age, sex, and treatment institution (1 and 2). In addition, we specifically recorded variables related to the surgical quality and treatment pathway, such as the occurrence of unplanned "whoops" resections, which are closely associated with inadequate surgical margins and increased LR. The patient pathway was categorized into two distinct types: a comprehensive care pathway (CCP) within the SSN; and a fragmented care pathway (FCP), which indicates patients who received initial treatment outside the SSN,—irrespective of the treatment modality—but with subsequent completion in the SSN. The patient pathway is depicted in Figure 1. Furthermore, the tumor's pathological characteristics were documented, including the biological behavior (intermediate or malignant), and critical dates such as the histological diagnosis, date of the unplanned "whoops" resection, and dates of initial and subsequent treatments (chemotherapy, radiotherapy, or surgery).

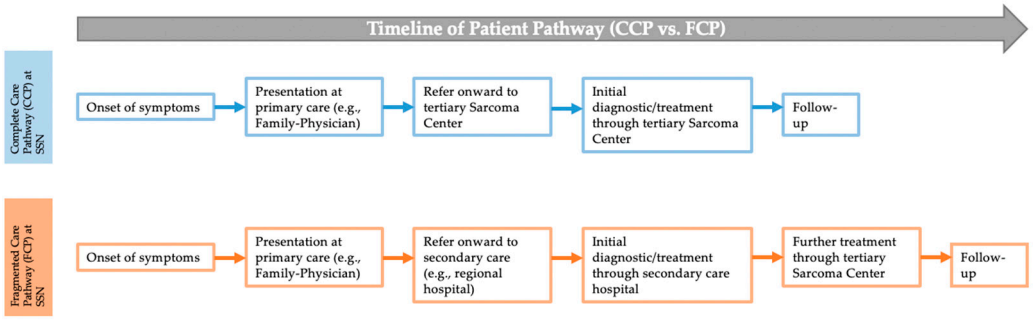


Figure 1. Definition of comprehensive (CTP) and fragmented (FTP) treatment pathway of patient management. The figure illustrates the definition of the different patient pathways: comprehensive care pathway at SSN (CCP) versus fragmented care pathway at SSN (FCP).

Sarcomas of the extremities (affecting both the upper and lower extremities), of the abdomen, including retroperitoneal sarcomas, axial sarcomas (e.g., trunk), head and neck sarcomas as well as sarcomas of the urogenital, perineal, and anal regions were incorporated into this study. Sarcomas were categorized by anatomical compartments (superficial soft-tissue sarcomas (SST-S) and deep soft-tissue sarcomas (DST-S)), and size was assessed in categories (0–50 mm, 51–100 mm, 101–150 mm, and >150 mm) [25]. The surgical exci-

sion type was meticulously recorded, differentiating planned resections from unplanned "whoops-resections". Both neo- and adjuvant therapies were noted. Surgical margins were classified according to Enneking et al. (1980) [26] and Gundle et al. (2018 [27] (R0, R1, R2) and tumor grading (according to Angervall and Kindblom (1993)) [28] (G1, G2, G3) were noted.

2.4. Statistical Analysis

Continuous variables are presented as median (interquartile range), while categorical variables are presented as number (percentage). Differences between categorical variables were tested using a Chi-square test or Fisher's exact test (if the cell frequency was below 5).

A logistic regression analysis was conducted to identify factors associated with LR, focusing on the interplay between care pathways and surgical outcomes. The dependent variable was the presence of LR (yes/no), while independent variables included tumor size, tumor grade, resection margin status, anatomical region, treatment aspects (planned/unplanned ("whoops") surgery, radiotherapy, or chemotherapy), and the initial treatment pathway (CCP vs. FCP). Univariable logistic regression was first conducted for each independent variable. Variables with a p-value < 0.05 in the univariable analysis and possible outcome-affecting variables as well as possible confounding variables were included in the multivariable logistic regression model. The final model for estimating influencing factors for LR included gender, tumor size, tumor grade, biological behavior, anatomic region, compartment, institution, resection margin status, radio-/chemotherapy, and FCP. A p-value < 0.05 was considered statistically significant. All analyses were conducted using SAS V.9.4 (SAS Institute, Minato, Japan).

3. Results

3.1. Study Patient Population

Over a 6-year period (2018–2023), a total of 1542 patients with suspected sarcoma were presented to the MDT/SB of the SSN. Of these, 386 patients with an STS were included in the study, focusing on those whose care pathways and surgical outcomes could be clearly linked to comprehensive or fragmented care, as outlined in Figure 2. This distinction is crucial to understanding the impact of care fragmentation on surgical quality and LR rates. Data were analyzed across two tertiary sarcoma centers: Institution 1 managed 40.9% (n = 158) of the patients, while Institution 2 managed 59.1% (n = 228).

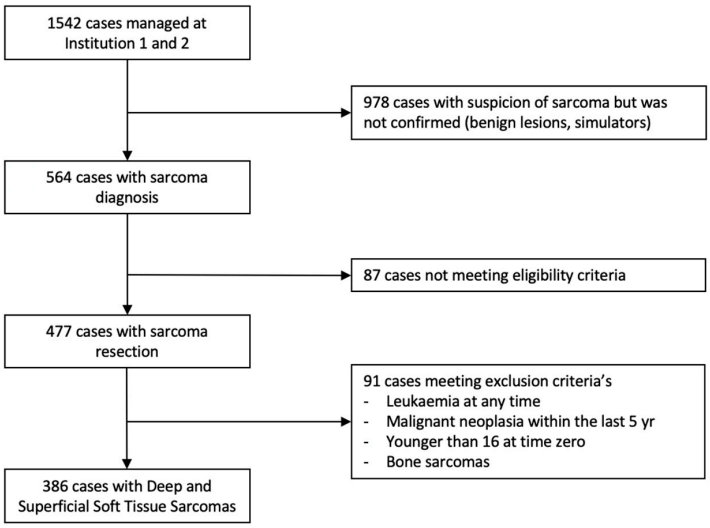


Figure 2. Decision tree on patient inclusion criteria. N, number of patients; SSN, Swiss Sarcoma Network.

Among the patients analyzed, LR occurred in 17.6% (n = 68). The regional distribution of recurrences, detailed in Figure 3, indicates that the highest recurrence rates were observed

in the intra- and retroperitoneal regions at 7.0% (n = 27). Notably, a substantial proportion of these cases involved patients managed via fragmented care pathways (FCPs), underscoring the potential link between FCPs and increased LR.

Anatomic region of soft tissue sarcoma (n=386)	Number of LR (% according to region / % according to total STS)
Upper extremity (n = 33)	11 (33.3% / 2.9%)
Lower extremity (n = 161)	16 (9.9% / 4.2%)
Axial (n = 61)	10 (16.4%/ 2.6%)
Intra- and retroperitoneal (n = 87)	27 (31% / 7.0%)
Regio urogenitalis, perinealis & analis (n = 31)	2 (6% / 0.5%)
Face, head and neck (n = 13)	2 (15.4 / 0.5%)
Total soft tissue sarcomas (n = 386)	Total LR (n = 68, 17.6%)

Figure 3. Local recurrence according to anatomical region. Distribution of local recurrence by anatomical region, with data presented as absolute patient numbers and percentages by region, along with percentages relative to the total number of patients with soft tissue sarcoma (STS) in brackets; LR, local recurrence; n, number.

3.2. Characteristics and Factors Associated with Local Recurrence

Factors associated with LR were analyzed differentiating between patient management, tumor characteristics, and treatment-related aspects. The analysis of patient management pathways, FCP versus CCP, revealed that patients with LR were significantly more likely to have been managed through the FCP, with 42.7% (n = 29) compared to 18.9% (n = 60) of patients with non-LR ($p = 0.0001$) (further analysis in the Results Section, Section 3.3).

The comparison of tumor-specific factors between patients with and without LR is summarized in Table 1. LR was significantly more common in patients with DST-S (19.2%, n = 61) compared to SST-S (10.1%, n = 7) ($p = 0.03$, Fisher's exact test). Furthermore, LR was significantly more frequent in malignant tumors (89.7%, n = 61) compared to those with intermediate biological behavior (70.8%, n = 225; $p = 0.001$), reflecting the increased risk associated with higher-grade tumors often managed through FCPs. Tumors with higher resection grading also showed higher LR rates, with grade 3 resections (G3) being more common in patients with LR (61.2%, n = 41) compared to those without LR (42.2%, n = 133; $p = 0.006$). The abdominal and retroperitoneal regions were most frequently associated with LR (39.7%, n = 27), whereas in non-LR cases tumors were most commonly located in the lower extremity (45.8%, n = 145).

All patients underwent primary surgery, with 74.2% (n = 290) receiving planned surgeries and 25.8% (n = 96) undergoing unplanned "whoops" resections. Notably, whoops resections were associated with positive resection margins in 88.3% (n = 83) of cases, significantly higher than the 22.7% (n = 65) observed in planned resections ($p < 0.001$). This highlights the critical impact of unplanned surgeries, predominantly seen in FCPs, on the quality of surgical margins and subsequent LR risk. There was no significant difference in the occurrence of whoops resections between patients with and without LR; however, positive resection margins were significantly more frequent in patients with LR (53.9%, n = 35) compared to those without LR (35.9%, n = 113; $p = 0.007$) (Table 1).

Table 1. Assessment of patient-specific tumor characteristics and treatment aspects between patients with and without local recurrence.

Characteristics	Overall (%)	No Local Recurrence (%)	Local Recurrence (%)	*p*-Value
n, (%)	386	318 (82.4)	68 (17.6)	
Female, n (%)	186 (48.2)	154 (82.8/48.4)	32 (17.2/47.1)	0.84
Compartment				
DST-S	317 (82.1)	256 (80.8/80.5)	61 (19.2/89.7)	0.03
SST-S	69 (17.9)	62 (89.9/19.5)	7 (10.1/10.3)	
Institution				0.16/0.04 [a]
1	158 (40.9)	125 (79.1/39.3)	33 (20.9/48.5)	
2	228 (59.1)	193 (84.6/60.6)	35 (15.4/51.5)	
Patient pathway				0.0001
CCP	297 (76.9)	258 (86.9/81.1)	39 (13.1/57.4)	
FCP	89 (23.1)	60 (67.4/18.9)	29 (32.6/42.7)	
Biological behavior				0.001
Malignant	286 (74.1)	225 (78.7/70.8)	61 (21.3/89.7)	
Intermediate	100 (25.9)	93 (93.0/29.3)	7 (7.0/10.3)	
Region, (%)				0.0001
Face, Head, Neck	13 (3.4)	11 (84.6/3.5)	2 (15.4/2.9)	0.29
Upper extremity	33 (8.6)	22 (66.6/6.9)	11 (33.3/16.2)	0.01
Lower extremity	161 (41.7)	145 (90.1/45.8)	16 (9.9/23.5)	0.0008
Axial	61 (15.8)	51 (83.6/16.0)	10 (16.4/14.7)	0.79
Intra- and retroperitoneal	87 (22.5)	60 (69.0/18.9)	27 (31.0/39.7)	0.0002
Urogenital, perineal, and anal regions	31 (8.0)	29 (93.5/9.1)	2 (6.5/2.9)	0.09
Initial Size, mm				0.12
0–50 mm	108 (28.0)	94 (84.3/29.6)	14 (15.7/20.6)	0.14
51–100 mm	133 (34.5)	111 (83.5/34.9)	22 (16.5/32.4)	0.69
101–150 mm	74 (19.2)	61 (82.4/19.2)	13 (17.6/19.1)	0.99
>150 mm	71 (18.4)	52 (73.2/16.4)	19 (26.8/27.9)	0.03
Tumor grading	[d]	[c]	[b]	0.01
G1	138 (36.1)	123 (89.1/39.1)	15 (10.9/22.4)	0.009
G2	70 (18.3)	59 (84.3/18.7)	11 (15.7/16.4)	0.64
G3	174 (45.6)	133 (76.4/42.2)	41 (23.6/61.2)	0.006
Resection margin	[e]	[c]	[c]	0.02
R0 wide margin/R0	232 (61.1)	202 (87.1/64.1)	30 (12.9/46.2)	0.003
R1 marginal margin/R1	122 (32.1)	92 (75.4/29.2)	30 (24.6/46.2)	0.01
R2 intralisional margin/R2	26 (6.8)	21 (80.8/6.7)	5 (19.2/7.7)	0.2
Radiotherapy part of first treatment	159 (41.2)	133 (83.7/41.8)	26 (16.3/38.2)	0.58
Chemotherapy as part of first treatment	42 (10.9)	34 (81.0/10.7)	8 (19.0/11.8)	0.8
Whoops resection	96 (25.8)	79 (82.3/24.8)	17 (17.37/25.0)	0.94

Data presented in numbers (n) of patients, with percent values in brackets (according to the total overall of the specific variable/according to non-local recurrence or local recurrence patients). Patients are categorized by the presence or absence of local recurrence. *p*-values indicate statistical significance of differences between groups, with a threshold of <0.05 considered significant. If two *p*-values are provided, the first *p*-value is calculated by Chi-square test and the second indicated by Fisher's exact test. Biological behavior was defined according to the WHO criteria into malignant and intermediate, and tumor grading according to Angervall and Kindblom (1993) [28]. Resection margins were defined according to Enneking et al. (1980) [26] (R0, R1, R2). DST-S, deep soft-tissue sarcoma; IQR, interquartile range; n, number; SST-S, superficial soft-tissue sarcoma. [a] *p*-value calculated by Fisher's exact test [b] one patient not classified; [c] three patients not classified; [d] four patients not classified, [e] six patients missing.

Radiotherapy was part of the initial treatment in 41.2% (n = 159) of all patients. Among those with LR, 38.2% (n = 26) received radiotherapy during their first treatment cycle, compared to 41.8% (n = 133) in the non-LR group, a difference that was not statistically significant ($p = 0.58$). Chemotherapy was administered in the first treatment cycle to 10.9% (n = 42) of patients, with no significant difference between the LR group (11.8%, n = 8) and the non-LR group (10.7%, n = 34; $p = 0.8$) (Table 1).

In a univariable logistic regression analysis, FCP, tumor size, tumor grade, biological behavior, and positive resection margins were associated with a higher odds of LR (Table A1). In a multivariable logistic regression model, tumor size (adjusted OR 1.49, 95% CI [1.1, 2.02], $p = 0.01$), biological behavior (adjusted OR 5.84 95% CI [1.8, 18.86], $p = 0.0003$), and FCP (adjusted OR 2.7, 95% CI [1.41, 5.12], $p = 0.003$) stayed independently associated with a higher LR (Table A2).

3.3. Comparative Analysis of Patient Treatment Pathways: Evaluating Factors Contributing to Increased Risk of LR in FCP vs. CCP

Given the strong association between treatment pathways, particularly the increased risk of LR linked to the FCP, a detailed analysis was conducted to identify contributing factors. Key findings revealed that FCP patients were significantly more likely to undergo unplanned "whoops" resections (50.7%, n = 45) compared to those managed through CCP (17.2%, n = 51; $p < 0.0001$), directly correlating to higher rates of positive resection margins and subsequent LR.

Among the 386 patients, 76.9% (n = 297) were treated using the CCP, while 23.1% (n = 89) underwent FCPs (Table 2). The FCP was significantly more common in patients with SST-S compared to DST-S (30.4%, n = 21 vs. 21.5%, n = 68, $p = 0.04$). Figure 4 illustrates the distribution of patients who developed LR, managed through either the FCP or CCP and divided into DST-S and STS-S.

Table 2. Comparison of patient characteristics based on the different treatment pathways: comprehensive care pathway providing full treatment by a sarcoma center (CCP) vs. fragmented care pathway with initial care outside a dedicated sarcoma center (FCP).

Characteristics	Overall (%)	CCP (%)	FCP (%)	*p*-Value
n, (%)	386	297 (76.9)	89 (23.1)	na
Female, n (%)	186 (48.2)	139 (74.7/46.8)	47 (25.3/52.8)	0.32
Institution				
1	158 (40.9)	105 (66.5/35.4)	53 (33.5/59.6)	0.001
2	228 (59.1)	192 (84.2/64.7)	36 (15.8/40.5)	
Biological behavior				0.05
Malignant	286 (74.1)	213 (74.5/71.7)	73 (25.5/82.0)	
Intermediate	100 (25.9)	84 (84.0/28.3)	16 (16.0/18.0)	
Compartment				0.04
DST-S	317 (82.1)	249 (78.5/83.8)	68 (21.5/76.4)	
SST-S	69 (17.9)	48 (69.6/16.2)	21 (30.4/23.6)	
Region, n %				0.02
Face, Head, Neck	13 (3.4)	10 (76.9/3.4)	3 (23.1/3.4)	0.99
Upper extremity	33 (8.6)	19 (57.6/6.4)	14 (42.4/15.7)	0.006
Lower extremity	161 (41.7)	134 (83.2/45.1)	27 (16.8/30.3)	0.01
Axial	61 (15.8)	45 (73.8/15.2)	16 (26.2/18.0)	0.52
Intra- and retroperitoneal	87 (22.5)	62 (71.3/20.9)	25 (28.7/28.1)	0.15
Urogenital, perineal, and anal regions	31 (8.0)	27 (87.1/9.1)	4 (12.9/4.5)	0.16
Initial Size, mm				0.6
0–50 mm	108 (28.0)	81 (75.0/27.3)	27 (25.0/30.3)	0.57
51–100 mm	133 (34.5)	99 (74.4/33.3)	34 (25.6/38.2)	0.4
101–150 mm	74 (19.2)	59 (79.7/19.9)	15 (20.3/16.9)	0.53
>150 mm	71 (18.4)	58 (81.7/19.5)	13 (18.3/14.6)	0.29
Tumor grading	[c]	[b]	[a]	0.78
G1	138 (36.1)	106 (76.8/36.1)	32 (23.2/36.4)	0.96
G2	70 (18.3)	56 (80.0/19.1)	14 (20.0/15.9)	0.5
G3	174 (45.6)	132 (75.9/44.9)	42 (24.1/47.7)	0.65

Table 2. *Cont.*

Characteristics	Overall (%)	CCP (%)	FCP (%)	*p*-Value
Resection margin	e	d	a	0.001
R0 wide margin/R0	232 (61.1)	199 (85.8/68.2)	33 (14.2/37.5)	0.0001
Positive resection margins (R1 + R2)	148 (38.9)	93 (62.8/31.3)	55 (37.2/61.8)	0.0001
Chemotherapy part of first treatment	42 (10.9)	33 (78.6/11.1)	9 (21.4/10.1)	0.08
Radiotherapy part of first treatment	159 (41.2)	128 (80.5/43.1)	31 (19.5/34.8)	0.9
Whoops resections	96 (24.8)	51 (53.1/17.2)	45 (46.9/50.6)	<0.0001
Local recurrence n, %	68 (17.6)	39 (57.4/13.1)	29 (43.6/32.6)	<0.0001

Data presented in numbers (n) of patients, with percent values in brackets (according to the total overall of the specific variable/according to comprehensive or fragmented care pathway). Patients are categorized by comprehensive or fragmented care pathway. *p*-values indicate statistical significance of differences between groups, with a threshold of <0.05 considered significant. Biological behavior was defined according to the WHO criteria into malignant and intermediate and tumor grading according to Angervall and Kindblom (1993) [28]. Resection margins were defined according to Enneking et al. (1980) [26] (R0, R1, R2). DST-S, deep soft-tissue sarcoma; IQR, interquartile range; n, number; SST-S, superficial soft-tissue sarcoma. [a] one patient not classified; [b] three patients not classified; [c] four patients not classified, [d] five patients missing; [e] six patients missing.

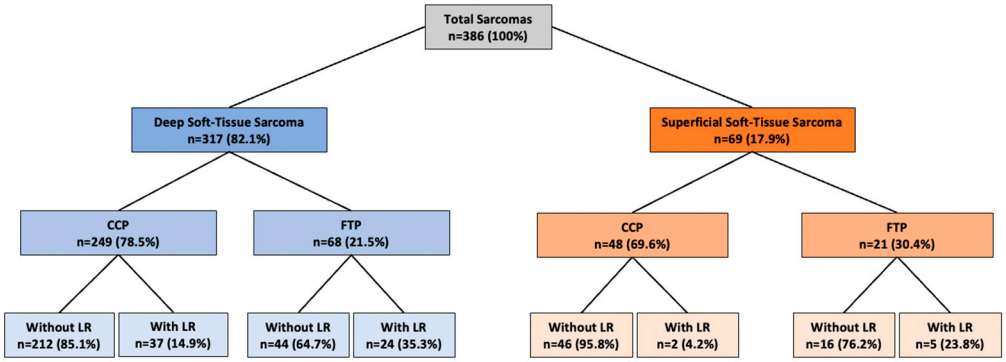


Figure 4. Analysis of treatment pathways (comprehensive vs. fragmented care pathway) for patients presented to the sarcoma board, distinguishing between deep soft-tissue sarcoma and superficial soft-tissue sarcoma, with a focus on local recurrence outcomes. Data presented in numbers (n) and percentage (%); CCP, comprehensive care pathway; FCP, fragmented care pathway; LR, local recurrence; n, number of patients.

Notably, most SST-S patients treated with the FCP had undergone a whoops resection (85.7%, n = 18) and were subsequently referred to the SSN. Tumor sizes in this group were often between 0 and 50 mm. Comparing further tumor-specific factors between the FCP and CCP, a higher proportion of patients with the FCP had malignant disease (82%, n = 73) compared to those with the CCP (71.7%, n = 213). Initial tumor size and tumor grading as well as treatment-specific aspects such as radio-/chemotherapy in the primary treatment plan did not differ significantly between the two patient groups (Table 2).

Notably, patients with the FCP had significantly more frequent whoops resections compared to those with the CCP (50.7%, n = 45 vs. 17.2%, n = 51; $p < 0.0001$). In addition, significantly more often positive resection margins were observed in patients treated by FCPs compared to CCPs (61.8%, n = 55 vs. 31.3%, n = 93; $p = 0.0001$). Patients with the FCP were managed significantly more often at Institution 1 compared to those with the CCP (59.6%, n = 53 vs. 35.4%, n = 105; $p = 0.001$) (Table 2).

Figure 5 outlines the reasons why patients were initially treated by FCPs and the decisions at the subsequent sarcoma board. The primary reasons for referral were whoops resection (52.8%, n = 47) and LR (33.7%, n = 30). Following referral, the SSN predominantly recommended further interventions, including re-operation (21.4%, n = 19), radiotherapy (29.2%, n = 26), or chemotherapy (14.6%, n = 13).

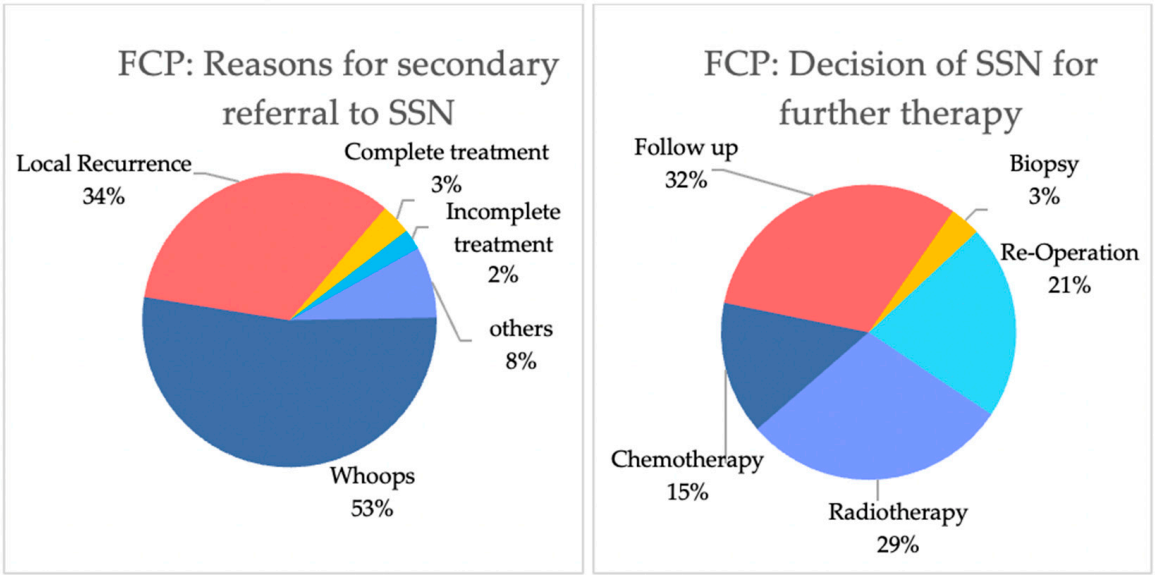


Figure 5. Patients with a fragmented care pathway: reasons for secondary referral towards a sarcoma hub (**left**) and decision of the sarcoma board (**right**). On the left, other reasons include metastasis or requests for a second opinion. "Complete treatment outside SSN" refers to patients treated outside a sarcoma hub but referred for follow-up at a sarcoma hub. "Incomplete treatment outside" includes patients whose treatment was not completed outside the sarcoma hub. (**Right**) Decisions and treatments determined by the sarcoma board.

The impact of the FCP was evaluated using univariable logistic regression analysis, which indicated associations between the FCP and sarcoma center institution, positive resection margins, LR, and whoops resections (Table A3). Multivariable logistic regression analysis revealed independent associations between the FCP and whoops resections (adjusted OR = 6.62, 95% CI [2.99, 14.7], $p < 0.0001$), specific sarcoma center institution (adjusted OR = 0.32, 95% CI [0.18, 0.56], $p < 0.0001$), and LR (adjusted OR = 2.96, 95% CI [1.5, 5.79], $p = 0.001$). Details are presented in Table A4.

3.4. Differences Between Dedicated Sarcoma Centers

Significant differences were observed between the dedicated sarcoma referral networks, with Institution 1 managing a higher percentage of patients with LR (20.9%) compared to Institution 2 (15.3%, $p < 0.0001$). This disparity reflects variations in referral patterns and the prevalence of FCP, where Institution 1 had a notably higher proportion of patients managed through FCP (33.5% vs. 15.8%, $p < 0.0001$). Our data suggest that the initial quality of care at the spoke level, represented by these referral patterns, plays a decisive role in patient outcomes. Despite subsequent management at the specialized sarcoma hubs, initial fragmented care contributed significantly to unplanned surgeries, inadequate resection margins, and increased LR rates, underscoring the importance of optimizing referral quality and pathways at the spoke level.

Tumor-specific factors were similar across the two institutions, with no statistical significance. Additionally, there were no differences regarding the use of radiotherapy (Institution 1: 39.2%, Institution 2: 52.5%, $p = 0.55$) and chemotherapy (Institution 1: 12.0%, Institution 2: 10.1%, $p = 0.55$) as part of the first treatment cycle. The rates of planned versus whoops resections were also similar (Institution 1: 26.0%, Institution 2: 24.1%, $p = 0.68$). tumor grading, initial size, and positive resection margins were comparable and statistically not significant between the institutions. Further details are presented in Table 3.

Table 3. Analysis of patient, tumor, treatment aspects, and local recurrence addressing regional referral differences through a comparison of the sarcoma centers.

Characteristics	Overall (%)	Sarcoma Center Institution 1 (%)	Sarcoma Center Institution 2 (%)	*p*-Value
n, (%)	386	158 (40.9)	228 (59.1)	
Female, n (%)	186 (48.2)	71 (38. 2/44.9)	115 (61.8/50.4)	0.29
Treatment pathway				0.0001
CCP	297 (76.9)	105 (35.4/66.5)	192 (64.6/84.2)	
FCP	89 (23.1)	53 (59.6/33.5)	36 (40.4/15.8)	
Biological behavior				0.63
Malignant	286 (74.1)	115 (40.2/72.8)	171 (59.8/75.0)	
Intermediate	100 (25.9)	43 (43.0/27.2)	57 (57.0/25.0)	
Compartment				0.74
DST-S	317 (82.1)	131 (41.3/82.9)	186 (58.6/81.6)	
SST-S	69 (17.9)	27 (39.1/17.1)	42 (60.9/18.4)	
Initial Size, mm (IQR)	80 (50–130)	81 (50–130)	80 (50–133)	0.8
Tumor grading	[d]	[a]	[a]	
G1	138 (36.1)	62 (44.9/39.2)	76 (55.1/33.3)	0.23
G2	70 (18.3)	30 (42.9/19.0)	40 (57.1/17.5)	0.72
G3	174 (45.6)	64 (36.8/40.5)	110 (63.2/48.3)	0.13
Whoops resections	96 (24.8)	41 (42.7/26.0)	55 (57.3/24.1)	0.68
Positive resection margins	148 (39.0) [c]	68 (45.9/43.7) [b]	80 (54.1/35.6) [b]	0.1
Local recurrence n, %	68 (17.6)	33 (48.5/20.9)	35 (51.5/15.3)	0.0001

Data presented in numbers (n) of patients, with percent values in brackets (according to the total overall of the specific variable/according to the sarcoma center institution 1 or 2). Patients are categorized into groups of treatment by sarcoma center 1 or 2. *p*-values indicate statistical significance of differences between groups, with a threshold of <0.05 considered significant. [a] two patients not classified; [b] three patients not classified; [c] six patients missing; [d] four patients not classified.

4. Discussion

This study highlights the critical importance of centralized care in reducing LR rates, minimizing the incidence of unplanned "whoops" resections, and ensuring access to comprehensive adjunctive treatments. Importantly, the findings underscore a key aspect of healthcare delivery: the significant impact of referral patterns on sarcoma center outcomes. The disparity in LR rates between institutions reflects not only the challenges faced by centers in compensating for prior inadequate care but also underscores the need for better education and early referral strategies at the spoke level. This represents a pivotal area for health service improvement as optimizing referral practices could significantly reduce LR rates and improve overall patient outcomes.

Our findings reveal that FCPs are significantly associated with increased LR rates, primarily driven by the higher incidence of unplanned "whoops" resections and the resulting positive resection margins. These findings underscore the detrimental effects of initial management outside of specialized centers and highlight the crucial role of coordinated, guideline-conforming care in specialized settings.

Our findings underscore the critical role of referral quality in the hub-and-spoke model of sarcoma care. The significant disparity in LR rates between the two institutions directly correlates with the prevalence of FCP, indicating that initial management at the spoke level is a primary determinant of long-term outcomes [8,10,29]. Even when patients are subsequently managed within specialized hubs, the damage from initial inadequate care often remains irreversible, as evidenced by the higher rates of unplanned surgeries and positive resection margins in FCP patients. This highlights a pivotal area for health service improvement: enhancing the education and protocols at the spoke level to ensure timely and accurate referrals to specialized hubs, thereby reducing LR risks and improving surgical outcomes. These findings advocate for a strategic approach that integrates care

pathways across the entire sarcoma network, reinforcing the importance of comprehensive care from the outset.

Our study reported an overall LR rate of 17.6%, which is slightly higher than the 7–15% LR rates typically reported in studies conducted within sarcoma centers [13–15]. This discrepancy underscores the adverse impact of care fragmentation, as a substantial proportion of our cohort included patients initially treated outside these centers, reflecting the critical influence of the initial care setting on long-term outcomes (and inclusion of all real-world referrals of a specialized sarcoma network). We identified a strong correlation between LR and factors such as care pathways (CTP vs. FCP), tumor size, biological behavior, and resection margins, consistent with previous research [14,30]. Notably, the FCP emerged as a significant independent predictor of LR, further validating the critical impact of treatment fragmentation on patient outcomes. According to both the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), multidisciplinary management is mandatory for all sarcoma patients [2,16]. This approach has been validated by large-scale studies, such as those by Voss et al. and Bonvalot et al., which demonstrated survival advantages for patients treated in specialized centers [10,29]. LR poses substantial clinical challenges, frequently necessitating complex reoperations and, in severe cases, resulting in significant tissue loss or limb amputation [13,15]. These severe consequences underscore the need for stringent adherence to centralized, high-standard care from the outset to minimize the risk of LR and its associated complications. Despite the well-established benefits, our study found that 23.1% (n = 89) of patients were still treated via FCPs, which multivariable logistic regression analysis confirmed as an independent risk factor for LR.

Our evaluation of FCP patients revealed several distinguishing characteristics, including a higher prevalence of unplanned "whoops" resections, positive resection margins, LR, and aggressive biological tumor behavior. These findings highlight the compounded risks associated with FCPs and underscore the necessity for early referral to specialized centers to mitigate these risks. By contrast, patients managed through the CTP experienced significantly fewer whoops resections and fewer positive resection margins. Both resection margins and whoops resections play a critical role in LR, as data of the SSN showed that whoops resections are associated with reduced local-recurrence-free survival [31]. These two parameters, resection margins and whoops resections, are also important benchmarks of surgical quality in sarcoma treatment [2,18,32,33].

Secondary referrals to sarcoma centers most frequently stemmed from whoops resections (53%) or LR (34%). Many of these patients required reoperations (21%) or additional radiotherapy (29%) or chemotherapy (15%). Surgical quality in sarcoma care is closely tied to the surgeon's expertise and specialization [2]. While wide excisions with negative margins are the standard treatment, complex tumor anatomy may necessitate individualized excision strategies and additional treatments, underscoring the need for a multidisciplinary approach [2,9]. Centralized sarcoma care delivers superior surgical and overall outcomes, driven largely by the collaborative expertise of multidisciplinary teams, including radiologists, pathologists, oncologists, and specialized surgeons, working in concert to optimize patient care [2,9]. Our study highlights the essential role of these teams, particularly in the management of rare and complex diseases like sarcoma.

Importantly, our study identified a significant correlation between FCPs and the specific sarcoma centers, suggesting regional disparities in referral patterns and access to specialized care. This variation may contribute to inconsistent patient outcomes, highlighting the need for standardized referral practices and improved access to centralized care across all regions. One center managed a higher proportion of FCP patients and had more frequent cases of recurrent disease. Notably, tumor-specific factors such as size, resection margins, and grading did not significantly differ across centers, indicating that regional differences in healthcare infrastructure and referral practices may contribute to varying LR rates. Centers that manage patients from the point of diagnosis benefit from a more consistent and comprehensive treatment approach, while those receiving patients after

initial treatment elsewhere may face difficulties due to inadequate early management. These findings underscore the importance of early and consistent referral to specialized sarcoma centers. Once the damage from initial treatment outside these centers occurs, it may not be fully correctable. Standardizing referral practices and improving access to centralized sarcoma care are essential to mitigating regional disparities and optimizing treatment outcomes across different regions.

While our study primarily focused on the impact of care pathways on local recurrence (LR) rates in soft tissue sarcoma (STS) patients, it is crucial to consider whether these differences translate into variations in overall survival (OS) and disease-specific survival (DSS). The relationship between care pathways and survival outcomes is complex and influenced by multiple confounding factors, including tumor size, grade, anatomical location, and biological behavior. Previous research, including our Target Trial Emulation (TTE) study [31], has shown that unplanned resections—more prevalent in fragmented care pathways (FCPs)—increase the risk of LR but do not significantly affect metastasis-free survival (MFS) or OS when compared to planned resections. This may be attributed to the fact that unplanned resections often involve smaller, superficial tumors with less aggressive histology, particularly in the upper extremities. These tumors, despite higher LR rates due to inadequate initial management, inherently have a better prognosis concerning distant metastasis and survival outcomes. Conversely, patients undergoing planned resections within comprehensive care pathways (CCPs) are more likely to present with larger, higher-grade tumors at a more advanced stage [34]. These factors inherently increase the risk of distant metastasis and negatively impact OS and DSS. Therefore, while CCPs are associated with better local control, the overall prognosis is predominantly determined by tumor biology and stage at presentation rather than the care pathway alone. Analyzing survival outcomes between CCP and FCP was beyond the scope of this study due to the complexity of adjusting for these confounding variables in a real-world data setting. Meaningful comparisons would require sophisticated methodologies, such as predictive modeling and TTE approaches, to account for the myriad of factors influencing survival. Our ongoing research is dedicated to exploring these aspects in greater detail, aiming to provide a more comprehensive understanding of how care pathways influence long-term patient outcomes. These insights underscore the paramount importance of early and accurate diagnosis—"predictive diagnostics"—and timely referral to specialized centers. By facilitating appropriate management strategies at an earlier stage, especially for aggressive tumors, we can not only improve local control but potentially enhance overall survival outcomes. This aligns with our findings emphasizing the critical role of integrated care strategies within specialized networks like the Swiss Sarcoma Network (SSN).

This study has several limitations that warrant consideration in interpreting findings. One of the primary limitations is the potential for selection bias due to the referral process. Patients referred secondarily to the SSN are more likely to represent complex cases, often involving complications or suboptimal management, while those with good outcomes outside the SSN may not be presented at all. This may lead to an overrepresentation of complex cases, potentially skewing the findings towards higher rates of LR and complications. These limitations underline the need for studies to further validate the impact of care pathways on LR in soft tissue sarcoma patients.

The generalizability of the findings may also be limited as the cohort is drawn exclusively from Switzerland, where healthcare systems and referral patterns may differ from those in other countries. Moreover, focusing on two main institutions may not fully represent the care provided across all centers within the SSN, introducing potential institutional bias. Lastly, incomplete patient records and varying follow-up durations could influence the observed LR rates, potentially weakening the conclusions regarding the impact of comprehensive versus fragmented care pathways.

5. Conclusions

In conclusion, our study demonstrates that the FCP is significantly associated with higher LR rates in STS patients. While FCPs increase the risk of LR primarily due to unplanned "whoops" resections and positive resection margins, the OS and DSS outcomes appear to be more closely linked to tumor biology and stage of presentation rather than the care pathway alone. The variability in referral practices across institutions significantly impacts patient outcomes, underscoring the need for a cohesive and integrated approach within the hub-and-spoke model of sarcoma care. Enhancing education, standardizing referral protocols, and ensuring early referral at the spoke level are strategic imperatives to mitigate LR risks and optimize patient outcomes across specialized networks like the Swiss Sarcoma Network (SSN). These findings highlight the necessity of a comprehensive, coordinated care strategy that transcends individual institutions and addresses the full continuum of sarcoma management, from early diagnosis to long-term follow-up.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Kantonale Ethikkomission Zurich, Switzerland (BASEC-Nr. 2019-01107/NCT04300257); 24 August 2021.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Table A1. Univariable logistic regression analysis for predictors of local recurrence in soft tissue sarcoma.

Variable	Local Recurrence		
	OR	**95% CI**	***p*-Value**
Gender	0.95	(0.56, 1.6)	0.84
Institution	0.69	(0.41, 1.16)	0.16
FCP	3.2	(1.83, 5.58)	<0.0001

Table A1. *Cont.*

Variable	Local Recurrence		
	OR	95% CI	*p*-Value
Compartment	0.48	(0.21, 1.09)	0.08
Tumor size	1.32	(1.04, 1.69)	0.03
Tumor grading	1.6	(1.16, 2.19)	0.004
Biological behavior	3.6	(1.59, 8.17)	0.002
Anatomic region	1.09	(0.88, 1.35)	0.41
Positive resection margins	2.09	(1.22–3.58)	0.008
Radiotherapy part of first treatment	0.86	(0.5, 1.47)	0.59
Chemotherapy part of first treatment	1.11	(0.49, 2.53)	0.8
Whoops resection	1.01	(0.6, 1.85)	0.9

Univariable logistic regression analysis: data are odds ratios (ORs) with 95% confidence interval (CI) in brackets from univariable logistic regression analysis; OR, odds ratio; 95% CI, 95% Confidence interval. *p*-value < 0.05 was defined as statistically significant.

Table A2. Multivariable logistic regression analysis results for predictors of local recurrence in soft tissue sarcoma.

Variable	Local Recurrence		
	aOR	95% CI	*p*-Value
Gender	1.004	(0.56, 1.8)	0.99
Institution	0.9	(0.49, 1.6)	0.72
Compartment	0.47	(0.18, 1.24)	0.13
FCP	2.7	(1.41, 5.12)	0.003
Biological behavior	5.84	(1.8, 18.86)	0.003
Size	1.49	(1.1, 2.02)	0.01
Anatomic region	0.89	(0.69, 1.16)	0.4
Tumor grading	1.28	(0.85, 1.9)	0.23
Positive resection margins	1.8	(0.99, 3.35)	0.05
Radiotherapy part of first treatment	0.55	(0.29, 1.05)	0.07
Chemotherapy part of first treatment	0.77	(0.29, 1.88)	0.57

Multivariable logistic regression analysis: data showing adjusted odds ratio with 95% Confidence interval in brackets and *p*-values for the different variables in the model. aOR, adjusted odds ratio; FCP, fragmented care pathway; 95% CI, 95% confidence interval. *p*-value < 0.05 was defined as statistically significant.

Table A3. Univariable logistic regression analysis for fragmented care pathway.

Variable	Fragmented Care Pathway		
	OR	95% CI	*p*-Value
Gender	1.27	(0.79, 2.04)	0.32
Institution	0.37	(0.23, 0.6)	<0.0001
Compartment	1.6	(0.9, 2.86)	0.11
Tumor size	0.87	(0.69, 1.09)	0.22
Tumor grading	1.03	(0.79, 1.35)	0.82
Biological behavior	1.8	(0.99, 3.27)	0.05
Anatomic region	0.96	(0.79, 1.17)	0.69
Resection margins	3.57	(2.17, 5.86)	<0.0001
Radiotherapy as part of first treatment	0.96	(0.6, 1.54)	0.86
Chemotherapy as part of first treatment	0.75	(0.95, 2.68)	0.08
Local recurrence	3.2	(1.83, 5.56)	<0.0001
Whoops resection	4.93	(2.95, 8.24)	<0.0001

Univariable logistic regression analysis: data are odds ratios (ORs) with 95% confidence interval (CI) in brackets from univariable logistic regression analysis; OR, odds ratio; 95% CI, 95% confidence interval. *p*-value < 0.05 was defined as statistically significant.

Table A4. Multivariable logistic regression analysis for the associations between tumor, patients, treatment characteristics, and the fragmented care pathway.

Variable	Fragmented Care Pathway		
	aOR	95% CI	*p*-Value
Gender	1.57	(0.9, 2.74)	0.1
Institution	0.32	(0.18, 0.56)	<0.0001
Tumor size	1.21	(0.89, 1.63)	0.22
Biological behavior	2.61	(1.1, 6.4)	0.04
Tumor grading	0.9	(0.61, 1.32)	0.58
Positive resection margins	1.4	(0.71, 2.79)	0.34
Local recurrence	2.96	(1.5, 5.79)	0.001
Whoops resection	6.62	(2.99, 14.7)	<0.0001

Multivariable logistic regression analysis: data showing adjusted odds ratio with 95% confidence interval in brackets and *p*-values for the different variables in the model. aOR, adjusted odds ratio; 95% CI, 95% confidence interval. *p*-value < 0.05 was defined as statistically significant.

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Transdisciplinary sarcoma care: a model for sustainable healthcare transformation

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Introduction

Healthcare organisations worldwide are facing significant challenges, including labour shortages, cost containment and capital contraction, leading to unsustainable workloads, staff shortages and burnout. The projected workforce shortages of both nurses and physicians have prompted the need to rethink healthcare delivery [1]. Hiring workers from other organisations to address staffing gaps ultimately creates a zero-sum game. A global survey highlighted the importance of intrinsic motivators, such as professional development opportunities, that may have been overlooked in the past [1]. There is unanimous agreement that financial expenditure exceeds medical capabilities. In Switzerland, concerns about the sustainability of the healthcare system existed before the COVID-19 pandemic due to sociodemographic changes, such as the retirement of the baby boomer generation and the smaller zoomer generation taking over, resulting in reduced healthcare capital [2–5]. This impending contraction of capital will further challenge the financial situation of hospitals.

Challenges to meet

There is unanimous agreement that a fundamental shift in healthcare delivery is necessary due to dwindling financial resources and staffing. Meyer et al. suggested that the healthcare system should be more integrated, preventive, transparent, outpatient-based and data-driven [6]. Many recognise the importance of digital transformation, although Switzerland is still in the early stages of developing electronic health records and embracing digitisation. Physicians have historically been resistant to defining quality of care due to its complexity, but defining it is crucial. Nearly two decades ago, Porter et al. introduced the concept of value-based healthcare, which involves assessing the quality and outcomes of care based on both patient and physician evaluations and considering the total costs incurred throughout the healthcare cycle [7]. The Swiss Sarcoma Network has proposed an adapted approach for developing a value-based healthcare delivery model specifically for sarcoma patients [8, 9].

The sustainable healthcare triad

The sustainable healthcare triad emphasises the interconnectedness of clinical care, outcomes and quality measures, and cost efficiency. Currently, the fee-for-service system does not consider the quality or cost control of medical procedures, such as surgeries. However, the new ecosystem-based triad necessitates coordinated, multidisciplinary interventions evaluated for their quality, outcome and costs. This approach integrates key parameters from the patient's perspective and identifies key performance indicators for individual physicians. Aligning patient and physician views on cost efficiency is crucial for establishing a sustainable healthcare system, including also an objective and transparent definition of variable physician salaries.

Transdisciplinary sarcoma surgery

Sarcoma surgery and care are highly transdisciplinary, serving as a model for developing a sustainable healthcare system. The complexity of sarcomas necessitates collaboration across multiple disciplines to achieve optimal tumour removal and local control. The Swiss Sarcoma Network (www.swiss-sarcoma.net) exemplifies the integration of disciplines and institutions, fostering a multi-institutional and transdisciplinary approach rather than a mono-institutional silo system.

Requirement 1: Physician-based metrics: Definition of surgical spectrum including complexity and quality of care

Sarcoma surgery is a highly complex procedure influenced by factors such as anatomical location, tumour size and biology. A senior Swiss Sarcoma Network surgeon conduct-

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ed a 10-year analysis to develop a comprehensive surgical profile that considers all relevant parameters for resections and reconstructions [10]. This spectrum serves as a valuable tool for assessing surgical experience, educating future surgeons and evaluating the complexity and costs of specific interventions. Based on this profile, the Swiss Sarcoma Network introduced the soft-tissue surgery complexity score, which incorporates patient-, tumour biology- and surgery-related factors to determine the complexity of each intervention [11]. This score is particularly important for Porter's geography model of care, which strives to deliver the appropriate treatment in the optimal geographic location, leading to improved outcomes and cost-effectiveness. Beyond surgery, sarcoma care entails multiple aspects that demand attention. To address this, the Swiss Sarcoma Network collaborated with an international advisory board of experts to define six categories of quality indicators for sarcoma care [12]. These categories encompass patient work-up, multidisciplinary team / sarcoma board management, therapy (including surgery, radiation and systemic therapy), complexity of sarcoma therapy, clinical outcomes and patient-reported outcomes. Evaluating these indicators is vital for sustaining a healthcare ecosystem, as it provides a comprehensive view of patient outcomes and the quality of care, as assessed by physicians.

Requirement 2: Patient-reported outcome measures

In value-based healthcare, patient-reported outcome measures (PROMs) play a crucial role in assessing treatment effectiveness and improving outcomes, providing valuable insights beyond clinical metrics [9]. While numerous patient-reported outcome measures exist, only a few have been created for sarcoma surgery [13]. One widely used patient-reported outcome measure is the EQ-5D, which includes five questions on general health dimensions and has been validated for various diseases, including cancer. The Swiss Sarcoma Network has established a reference score of EQ-5D specifically for sarcoma patients and has revealed that the most significant negative predictor of perceived health is the administration of chemotherapy.

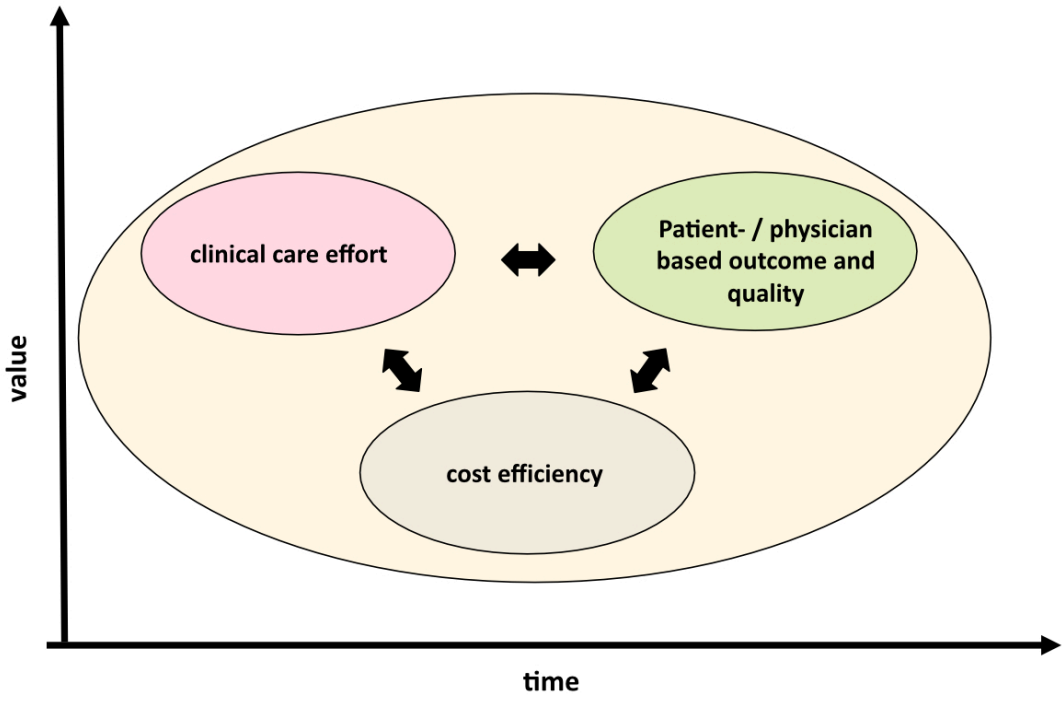
Sarcoma surgery and care present challenges because treatments are individualised and multidimensional. To address these challenges, the Swiss Sarcoma Network has developed a novel health-related quality of life (HRQOL) instrument [13]. This survey instrument utilises over 10 personalised generic patient-reported outcome measure questionnaires, allowing patients to electronically complete questionnaires based on their specific treatments and longitudinal follow-up periods. By incorporating a comprehensive set of patient-reported outcome measures, this approach aims to capture the holistic impact of sarcoma treatment on patients' lives.

Requirement 3: Interoperable digital platform to allow real-world-time data collection and evidence analytics (RWTD/E)

Managing healthcare data is a significant challenge in today's world, but the digital transformation of healthcare practices holds great potential for revolutionising current approaches. Instant access to real-world-time clinical data and automated analyses are crucial, especially in multidisciplinary and multi-institutional settings.

To integrate complex data into daily practice and generate real-world-time evidence, a key strategy is combining the management of multidisciplinary team/sarcoma board conferences (MDT/SB) with the patient registry. By doing so, conflicting issues like surgical margins can be addressed

Figure 1: The sustainable healthcare triad aligns the clinical effort with outcome and quality, as well as cost efficiency. The goal is to benchmark these parameters over time to establish shared value.



and resolved through a multidisciplinary approach, with data recorded directly in the registry without the need for retrospective data collection.

During MDT/SB, the presenting physician and their team provide patient information, which is associated with the registry. Patients with sarcoma recurrence are automatically presented to the MDT/SB, and their data are stored in the registry. Patients without recurrence undergo regular check-ups and provide electronic patient-reported outcome measures. This system enables real-world-time follow-up of all patients.

The platform used incorporates over 500 parameters and facilitates calculations of quality indicators and simple statistics for direct visualisation. With real-world-time data collection and evidence analytics, predictive modelling becomes possible, ultimately leading to the development of a human-sarcoma digital twin and enabling individualised precision care.

Requirement 4: Health services research

Health services research examines the impact of various factors on healthcare access, quality and costs and on patients' well-being. Utilising an interoperable digital platform with descriptive and inferential statistics enables real-world-time research. This interdisciplinary field investigates how social factors, financing systems, organisational structure, health technologies and personal behaviours affect healthcare. A sarcoma study including all patients undergoing biopsy revealed 55% malignancy in suspicious soft tissue and bone neoplasms [14]. This finding has implications for planning and establishing an integrated practice unit (IPU) to streamline diagnostics. Another analysis compared pathology workups from different institutions, emphasising the importance of reference reviews. Incorrect diagnosis impacted treatment in 12.2% of cases [15]. Consulting reference pathologists reduced time to diagnosis. An ongoing project is evaluating the costs of hospitalisations and surgical interventions across three hospitals and is considering the case mix index, complexity score and outcomes.

Embedding health services research within hospitals is crucial. Affiliation with a medical faculty with health-focused research facilitates these analyses. Leveraging digital platforms and data analysis improves healthcare practices and patient outcomes in real time.

Conclusion

Healthcare organisations face numerous challenges, including labour shortages, cost containment and capital contraction. To address these challenges, the development of an integrated, preventive, transparent, outpatient-based and data-driven healthcare system is necessary. The sustainable healthcare triad, comprising clinical care, physician- and patient-based outcomes and quality, and cost efficiency, plays a vital role in this system. Defining the triad enables the establishment of key performance indicators for sarcoma care and aligns patient and physician perspectives on cost efficiency. The transdisciplinary organisation of sarcoma care, involving multiple disciplines and institutions, serves as a model for building a sustainable healthcare system. Defining the surgical spectrum, with its associated complexity, and the quality of care, using physician- and patient-based metrics, is crucial to this process. By adopting these strategies, healthcare organisations can deliver improved care while optimising efficiency and sustainability.

Future directions

The healthcare industry must evolve and adapt to overcome challenges like workforce shortages and capital contraction. Digitalisation and electronic health records will play a crucial role. Defining quality of care with physician-based metrics aligns patient and physician views on cost efficiency for a sustainable healthcare system. Embracing and implementing the sustainable healthcare triad is necessary to define the shared value. Further research is needed to explore how the industry can adapt and achieve sustainable healthcare delivery.

Further literature

A summary of the scientific contributions of the Swiss Sarcoma Network and further literature can be found under this link or QR code:

https://swiss-sarcoma.net/pdf/20230930-SSN_academic_overview.pdf

Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Review

Data-Driven Defragmentation: Achieving Value-Based Sarcoma and Rare Cancer Care Through Integrated Care Pathway Mapping

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Abstract: Sarcomas, a rare and complex group of cancers, require multidisciplinary care across multiple healthcare settings, often leading to delays, redundant testing, and fragmented data. This fragmented care landscape obstructs the implementation of Value-Based Healthcare (VBHC), where care efficiency is tied to measurable patient outcomes.ShapeHub, an interoperable digital platform, aims to streamline sarcoma care by centralizing patient data across providers, akin to a logistics system tracking an item through each stage of delivery. ShapeHub integrates diagnostics, treatment records, and specialist consultations into a unified dataset accessible to all care providers, enabling timely decision-making and reducing diagnostic delays. In a case study within the Swiss Sarcoma Network, ShapeHub has shown substantial impact, improving diagnostic pathways, reducing unplanned surgeries, and optimizing radiotherapy protocols. Through AI-driven natural language processing, Fast Healthcare Interoperability Resources, and Health Information Exchanges, HIEs, the platform transforms unstructured records into real-time, actionable insights, enhancing multidisciplinary collaboration and clinical outcomes. By identifying redundancies, ShapeHub also contributes to cost efficiency, benchmarking treatment costs across institutions and optimizing care pathways. This data-driven approach creates a foundation for precision medicine applications, including digital twin technology, to predict treatment responses and personalize care plans. ShapeHub offers a scalable model for managing rare cancers and complex diseases, harmonizing care pathways, improving precision oncology, and transforming VBHC into a reality. This article outlines the potential of ShapeHub to overcome fragmented data barriers and improve patient-centered care.

Keywords: value-based healthcare; Sarcoma; Artificial Intelligence; data

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1. Introduction

Sarcomas, as a category of rare cancers, present significant clinical and logistical challenges due to their heterogeneous nature and low incidence rates [1]. Diagnosing and managing sarcomas often involves multiple healthcare settings, from primary care and community hospitals to specialized cancer centers [2]. This multi-step process results in fragmented care pathways that not only delay diagnosis but also lead to data being scattered across various institutions [2]. This fragmented data landscape, or "data vortex",

hinders the implementation of personalized medicine and Value-Based Healthcare (VBHC), where efficiency and quality of care are intrinsically linked to measurable patient outcomes.

Our proposed solution is a data-driven defragmentation approach facilitated through an integrated interoperable digital platform called ShapeHub. ShapeHub is designed to organize care around and across specific medical conditions, akin to the logistics system that tracks an item through various stages of delivery. For example, ShapeHub ensures that all relevant patient data—such as diagnostic results, treatment updates, and specialist consultations—are captured and shared across care providers, reducing delays and enhancing continuity of care. This ensures that the patient's journey through different healthcare settings is streamlined and transparent, similar to how logistics systems manage the transport of goods. This platform centralizes and harmonizes patient information across healthcare sites, enabling continuous and cohesive care pathways. By ensuring that every encounter—whether a simple diagnostic procedure or a complex surgical intervention—contributes to a unified dataset, ShapeHub creates a cohesive and comprehensive as well as automatically created record. This transforms the fragmented care model into a streamlined, value-oriented system. This harmonization not only improves workflow efficiency but enables personalized treatment decisions by leveraging artificial intelligence (AI)-powered risk stratification and precision oncology tools. This article explores how this model works in practice, offering a roadmap for optimizing sarcoma care and care for other rare cancers.

2. Theoretical and Practical Background

2.1. Fragmentation as a Systemic Challenge

Fragmentation in sarcoma care is multifaceted. Patients are often first seen by their family or primary care physician, who may initiate initial diagnostics before referring them to specialists [3]. Patients subsequently undergo numerous diagnostics—imaging, biopsies, and lab tests—at different institutions before reaching a definitive diagnosis [3]. Additionally, treatment pathways involve a range of specialists, including oncologists, surgeons, radiologists, and pathologists [4]. Each point of care generates data that remain isolated within the institution's siloed system. This data vortex prevents healthcare providers from having a comprehensive view of the patient's journey, resulting in repeated tests, miscommunications, and delays that negatively impact outcomes.

2.2. Digital Interoperable Platforms as Enablers

Digital interoperable platforms like ShapeHub aim to address these challenges by acting as a centralized hub that will integrate data from all care points, including diagnostic imaging, treatment records, specialist consultations, and follow-up care. First, access to the platform is facilitated through a trackable patient identification system based on World ID, which functions similarly to a logistics tracking system—like those used in supply chain management to ensure items are transported seamlessly [5]. In healthcare, each patient interaction can be efficiently tracked across all care settings, enhancing both transparency and the quality of care.

After access is granted, it is crucial to harmonize data acquisition using the principles of click and collect, talk and capture (i.e., Natural Language Processing (NLP)), and scan and sync. The latter includes an AI ontology algorithm that screens for parameters from PDF documents provided by other institutions [6]. ShapeHub's internal data collection is designed to be directly analyzable, minimizing the need for external standard conversions.

By utilizing interoperability standards such as FHIRs (Fast Healthcare Interoperability Resources) [7] and leveraging technologies like Health Information Exchanges (HIEs) [8,9], blockchain, and a trackable system for patient interactions, ShapeHub is planned to facilitate the seamless transfer of information between healthcare providers, ensuring that every

patient interaction is recorded and accessible for one given medical condition and its associated comorbidities. FHIRs and HIEs are complementary tools that support efficient data exchange, with FHIRs providing the standard for data formats and HIEs facilitating the actual data exchange. Furthermore, the platform will employ AI algorithms and NLP to harmonize and structure data, transforming previously unstructured information into actionable insights.

ShapeHub not only reduces redundancies but also ensures that all healthcare providers involved have access to up-to-date, accurate information, creating a unified patient journey that supports VBHC. This comprehensive access to integrated patient data directly contributes to better clinical decision-making, improved patient outcomes, and enhanced quality of care. Furthermore, ShapeHub facilitates personalized treatment recommendations and dynamic treatment adjustments based on evolving clinical and molecular data and by continuously integrating real-time patient responses.

As the volume of healthcare data continues to grow, AI and machine learning (ML) offer transformative potential for optimizing sarcoma care. By leveraging AI-driven analytics, ShapeHub can enable dynamic risk stratification, predictive modeling, and decision support, enhancing the precision and efficiency of sarcoma management. Through natural language processing (NLP), unstructured radiology, pathology, and clinical reports can be systematically processed, extracting key diagnostic and prognostic insights in real time [10]. Additionally, machine learning models trained on multi-omics data (genomics, proteomics, imaging, and clinical histories) could refine personalized treatment strategies by predicting treatment responses, toxicities, and long-term outcomes [11].

An essential component of AI integration within ShapeHub is the use of federated learning, which allows multi-institutional collaboration without directly sharing patient data [12]. This decentralized approach ensures compliance with data privacy regulations such as GDPR while enabling continuous model refinement across multiple centers. By systematically incorporating real-world-time feedback loops, AI models embedded within ShapeHub can adapt to evolving clinical knowledge, offering tailored treatment recommendations that align with precision oncology principles.

Beyond immediate clinical benefits, AI-powered insights also contribute to long-term outcome tracking and real-world validation. The ability to conduct real-time comparative effectiveness research will allow for the continuous evaluation of treatment pathways [13]. Target trial emulation, a method used within ShapeHub, provides an innovative way to emulate randomized controlled trials (RCTs) by retrospectively comparing different treatment strategies across patient cohorts [14]. This allows for the identification of best practices and the optimization of referral pathways, ultimately reducing unnecessary interventions such as unplanned "whoops" surgeries.

To ensure the sustainable impact of AI-driven decision support, it is crucial to establish standardized validation frameworks that assess ShapeHub's effectiveness across different healthcare settings. By benchmarking patient outcomes and costs over time, we can systematically assess how digital tools improve clinical efficiency, patient experience, and healthcare resource utilization. Future directions should focus on expanding ShapeHub's capabilities to include predictive digital twin technology, wherein virtual patient simulations can help forecast treatment outcomes before interventions are initiated [15]. This will facilitate truly personalized medicine, where therapy adjustments are continuously optimized based on real-time patient data.

The integration of AI and long-term validation methodologies within ShapeHub represents a paradigm shift in rare cancer management. By transforming fragmented, siloed data into actionable insights, ShapeHub lays the foundation for a learning healthcare system that continuously evolves, improving patient care and advancing VBHC principles.

2.3. Related Work: Positioning ShapeHub Among Existing Digital Care Pathways

Several digital platforms and frameworks have attempted to address the problem of care fragmentation and interoperability in oncology and rare disease management. While these initiatives have made progress in standardizing health data or supporting multidisciplinary collaboration, ShapeHub represents a unique synthesis of these efforts, integrating real-time data harmonization, AI-driven analytics, and care pathway mapping within a single platform.

2.3.1. Integrated Practice Units and Value-Based Healthcare

The concept of organizing care around specific medical conditions, as pioneered by Porter and Teisberg's VBHC framework [16], has led to the development of Integrated Practice Units (IPUs) in institutions like the Cleveland Clinic and MD Anderson Cancer Center. These units collocate multidisciplinary teams to streamline decision-making and measure outcomes. However, most IPUs rely on co-location rather than digital infrastructure, limiting their scalability across fragmented systems or networks. ShapeHub expands on the IPU model by enabling virtual integration through data, not geography.

2.3.2. Electronic Health Record (EHR) Enhancements and Learning Health Systems

Platforms such as Epic Cosmos, Flatiron Health, and ASCO's CancerLinQ have attempted to extract structured insights from electronic health records (EHRs) in oncology. For example, Flatiron's oncology-specific EHR offers real-world evidence from de-identified datasets across many US practices. However, these systems often function within a single-vendor ecosystem and are not purpose-built for rare diseases or real-time clinical decision-making [17]. In contrast, ShapeHub prioritizes interoperability across institutions and care settings, and its modular, disease-agnostic design makes it suitable for rare and complex conditions.

2.3.3. National Interoperability Initiatives and Health Information Exchanges (HIEs)

Countries such as France, the UK, and the Netherlands have deployed national health data platforms like the Dossier Médical Partagé (DMP) or MedMij, aiming to standardize longitudinal health records [18,19]. These platforms primarily serve administrative or patient communication functions and often struggle with deep clinical integration, particularly in oncology. Similarly, traditional HIEs facilitate data sharing but do not provide the structured care pathway analytics, AI integration, or decision support features built into ShapeHub.

2.3.4. Rare Disease Networks and European Reference Networks (ERNs)

The European Reference Networks (ERNs) for rare diseases promote cross-border collaboration among centers of expertise. While ERNs focus on knowledge exchange and remote consultation, they currently lack a shared, structured, interoperable data platform tailored to clinical decision-making [20]. ShapeHub can complement these networks by offering a technical solution for harmonized care tracking and pathway optimization across borders.

2.3.5. AI-Driven Clinical Decision Support Systems

Recent efforts to incorporate AI into oncology include IBM Watson for Oncology and several NLP tools for radiology and pathology interpretation [21]. However, such tools are typically siloed, addressing only one modality or clinical question. ShapeHub's integration of AI, natural language processing, and federated learning within a unified care pathway framework enables not just diagnostic support but end-to-end care optimization across diagnostics, surgery, radiotherapy, and follow-up.

In summary, while prior systems have addressed components of data integration, outcome benchmarking, or digital collaboration, ShapeHub uniquely combines them into a real-time, interoperable, and AI-enhanced infrastructure specifically built for rare and complex diseases like sarcoma. It thus serves as a bridge between visionary concepts (VBHC, learning health systems, and digital twins) and practical, implementable solutions.

3. Case Study: ShapeHub's Implementation in the Swiss Sarcoma Network (SSN)

The Swiss Sarcoma Network (SSN) provides an illustrative example of how the current version of ShapeHub has already made significant contributions through harmonized structured data integration. Figure 1 presents an overview of the input and output of ShapeHub. Specifically, ShapeHub has improved diagnostic pathways, reduced unnecessary surgeries, and optimized treatment protocols, leading to better care outcomes. Here, we delve into three specific scenarios that highlight the digital interoperable platform's potential impact.

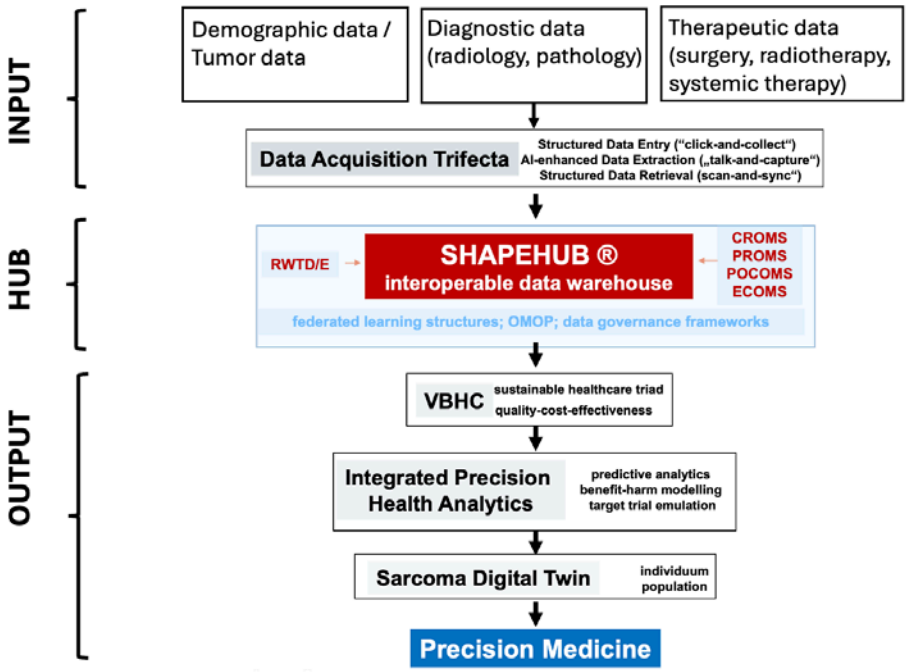


Figure 1. Overview of input and output of ShapeHub. CROM: Clinician Report Outcome Measures; PROM: Patient Reported Outcome Measures; POCOMS: Patient Oriented and Centric Outcome Measures; ECOMS: Economic Outcome Measures; RWTD/E: Real World Time Data/Evidence; VBHC: Valued Based Healthcare.

3.1. Example 1: Refining Diagnostic Pathways

Traditionally, sarcoma patients experience diagnostic delays, often undergoing multiple scans and consultations before a diagnosis is confirmed [3]. Within the SSN, a recent real-world-time analysis included 1028 patients presented to the multidisciplinary tumor board between 2018 and 2021.

The study revealed that the patient interval (a median of 2.3 months) contributed the largest share to the total diagnostic delay, followed closely by the secondary care interval, which represented the most significant component of the diagnostic interval itself. Notably, older patient age, axial tumor localization, and larger tumor size were identified as factors associated with longer intervals and an increased probability of sarcoma.

Specifically, sarcomas localized to the axial skeleton had a statistically significant longer diagnostic delay compared to those in the extremities (median 6.7 vs. 4.1 months). Through ShapeHub's real-time tracking of referral steps and delays, these findings allow

for the dynamic identification of bottlenecks and propose actionable measures, such as reducing secondary care waiting times, to streamline the diagnostic journey and improve early detection rates in sarcoma patients.

3.2. Example 2: Reducing Unplanned "Whoops" Surgeries

Unplanned "whoops" surgeries occur when tumor removal is attempted without full staging or multidisciplinary input and without expecting the diagnosis of sarcoma. ShapeHub aims to minimize this risk by consolidating patient information from local hospitals, imaging centers, and sarcoma specialists into a single view. By providing specialists with comprehensive patient records, we believe that surgical decisions will be based on a complete and accurate understanding of the tumor's characteristics and the patient's overall health. ShapeHub has already contributed significantly to understanding the reasons for "whoops" surgeries and their consequences. Additionally, ShapeHub has enabled target trial emulation (TTE) to compare groups in analogy to randomized controlled trials (RCTs), offering valuable insights into the impact of different referral and treatment pathways [22]. As part of ShapeHub, TTE can be used for any possible comparison of patient groups, providing a flexible tool for evaluating outcomes across various aspects of care. The study demonstrated that 19.6% of all patients experienced an unplanned excision (UE), and these patients had a 2.27-fold increased risk (95% CI, 1.12–4.60) of local recurrence compared to those undergoing planned resections.

Interestingly, despite the increased risk of local failure, no statistically significant differences were observed in metastasis-free survival, cancer-specific survival, or overall survival between the two groups during the follow-up period. Furthermore, the presence of residual tumor after UE was observed in 31% to 74% of cases, which substantially contributed to the observed risk of local recurrence. By offering an integrated patient overview before any surgical intervention, ShapeHub supports the early identification of suspicious lesions, facilitates timely referral to specialized centers, and thus significantly reduces the likelihood of unplanned surgeries and their associated adverse outcomes.

3.3. Example 3: Optimizing Radiotherapy and Surgical Protocols

In sarcoma care, the timing and coordination of treatments, such as radiotherapy and surgery, are critical. We employed a different radiotherapy (RT) schedule, specifically an ultrahypofractionated approach using only 5 fractions of 5 Gy each, compared to the traditional 25 fractions of 2 Gy. The median interval between radiation completion and surgery was 16 days, substantially shorter than traditional approaches, which often recommend waiting periods of 4–8 weeks. Additionally, clear resection margins (R0) were achieved in 92% of patients, and early treatment-related toxicity was limited to grade 0–1 dermatitis. Through real-time data integration and multidisciplinary scheduling enabled by ShapeHub, these outcomes demonstrate how optimized radiotherapy protocols can be safely accelerated, improving patient experience while maintaining excellent oncologic results. Using ShapeHub, we were able to analyze and compare the outcomes, demonstrating that the shorter schedule provides the same local control rate after 2 years and, importantly, similar low wound healing complication rates as the normofractionated schedule [23]. This highlights the strength of our ShapeHub system, which allows for a real-world-time assessment and comparison of treatment protocols, including the ability to compare results from different institutions and settings prospectively, as well as comparisons across different care groups such as surgical groups, chemotherapy groups, and other care modalities, providing a consistent and standardized approach to evaluating outcomes. The ability to implement an RT schedule that reduces the treatment effort by 80%, while maintaining

clinical benefits, significantly lowers operational costs and reduces the burden on patients, who only need to attend 5 sessions instead of 25.

4. Addressing Fragmentation: Care Pathway Mapping as a Solution to the Data Vortex

4.1. Care Pathway Mapping

ShapeHub's core function is to map and organize patient journeys from the initial point of care to follow-up. The platform captures each patient encounter—whether at a community hospital, imaging center, or specialist clinic—and integrates it into the central system using a structured data capture approach right from the beginning, ensuring that all data collected are consistent and directly analyzable. This internal data structure minimizes the need for external standard conversions such as FHIRs [7] or OMOP for internal use. However, to ensure collaboration with external systems and institutions, ShapeHub utilizes FHIRs [7] for standardized data formats and HIEs [8,24] to facilitate the actual data exchange, alongside middleware solutions that facilitate communication and data management between healthcare systems. Middleware solutions, analogous to logistics tracking technologies like GS1, facilitate seamless communication between different healthcare systems, ensuring that the data move accurately and efficiently between institutions, just as logistics systems manage the flow of items through complex networks. This ensures that all data related to the patient's sarcoma care are structured and harmonized, creating a cohesive, real-world-time view of the patient's health status.

4.2. Implementing Solutions to the Data Vortex

- HIE Integration: Through HIEs [8,9], ShapeHub aims to standardize patient information exchange, ensuring that data are consolidated under a single patient record. This integration is expected to eliminate inconsistencies, reduce the duplication of tests, and improve overall care efficiency.
- AI and Blockchain Technologies: AI algorithms will structure data into actionable formats, while blockchain technology is planned to secure and authenticate each data entry, ensuring that information integrity is maintained across all points of care. Patient identification will be managed through systems like World ID [5], functioning as a trackable identification system that securely links patient data across institutions, ensuring that information is accessible to authorized healthcare providers and allowing for efficient tracking throughout the care pathway.

By employing these methods, ShapeHub seeks to dismantle the data vortex, transforming fragmented records into a unified dataset that healthcare providers can rely on for accurate, evidence-based decision-making.

5. Transdisciplinary Collaboration: The Key to Overcoming the Data Vortex

5.1. Unified Protocols and Shared Data

One of the most significant goals of ShapeHub is to facilitate transdisciplinary collaboration. Sarcoma care inherently involves multiple specialties, and without a system that integrates and shares data efficiently, care teams often operate in silos. ShapeHub is designed to unify these teams by providing access to a centralized patient record that is updated in real-world time, ensuring that each specialist—whether an oncologist, surgeon, or radiologist—has the most current and complete information.

5.2. Impact on Clinical Decision-Making

We demonstrated ShapeHub's ability to enhance multidisciplinary meetings within SSNs. Specialists are able to review and discuss the same comprehensive dataset, leading to improved treatment planning and coordination. Our approach showed better outcomes in various aspects, reducing variation and improving consistency in care delivery, as evidenced by recent publications.

6. Economic Impact and Cost Efficiency

6.1. Comprehensive Cost Mapping

One of the key objectives of VBHC is aligning patient outcomes with costs, where cost mapping is synonymous with aligning reimbursement with value [25]. ShapeHub is being designed to enable cost mapping by integrating financial data with clinical outcomes across the patient's care pathway. We are currently in the stage of defining cost drivers to generate a comprehensive view of treatment costs, distinguishing between cost expenses and cost revenues, while aligning these metrics with the overall value provided to patients.

6.2. Benchmarking and Efficiency Gains

Preliminary analyses are exploring how ShapeHub can be used to benchmark costs across different hospitals and treatment modalities. Our focus is on mapping cost expenses per discipline. We have found that the costs of surgeries themselves are consistent across hospitals; however, the overhead costs associated with hospitalization differ significantly. It is not the surgery itself but rather the overhead costs in the context of hospitalization that surpass the expenses of surgery alone. By minimizing duplicate imaging and aligning diagnostic timelines, ShapeHub could help identify these discrepancies and create opportunities for substantial cost savings while maintaining high-quality outcomes.

7. Future Vision: Precision Medicine and Digital Twins

7.1. The Role of Digital Twins

As ShapeHub consolidates and harmonizes care pathways, it lays the groundwork for advanced care models like digital twins—virtual representations of patient health [26]. These models require high-quality, structured data, which ShapeHub aims to provide through its integrated approach. We are developing the infrastructure needed to simulate digital twins for sarcoma patients, with the goal of predicting treatment responses and optimizing care plans.

7.2. Scalability Beyond Sarcoma

The architecture of ShapeHub is designed to be scalable to other rare and complex cancers. Although currently focused on sarcoma care, the platform's algorithms and data modules are being developed to support a broader range of conditions. We expect that the success seen in sarcoma care can be expanded to other disease areas in the future.

8. Implications

The development and implementation of ShapeHub carry significant implications beyond sarcoma care, offering a model for transforming how rare and complex diseases are managed in modern healthcare systems.

8.1. Health System Integration and Learning Health Systems

By structuring and harmonizing patient data across institutions, ShapeHub aligns closely with the vision of a learning health system—a healthcare model where data and experience are continuously analyzed and fed back to improve care quality and efficiency

in real time [27]. The ability to incorporate real-world-time patient feedback, perform target trial emulation, and continuously update clinical pathways supports adaptive care models that can evolve with emerging evidence.

8.2. Policy and Reimbursement Models Aligned with VBHC

The integration of clinical and financial data enables precise cost–outcome mapping, an essential requirement for implementing Value-Based Healthcare (VBHC) at scale. This supports a transition away from fee-for-service models toward outcome-based reimbursement structures, as championed by policymakers in the EU and the U.S. Centers for Medicare & Medicaid Services (CMS) [25]. ShapeHub's transparent data architecture may also facilitate performance-based contracts and bundled payments for rare cancers.

8.3. Clinical Standardization Across Decentralized Networks

Rare cancer management often suffers from variability in care quality across centers. ShapeHub's structured data architecture enables protocol standardization and benchmarking, reducing unwarranted variation—a key aim in complex oncology pathways [2]. It thus supports networks like European Reference Networks (ERNs) for rare diseases, which rely heavily on shared decision-making and real-time data sharing across national borders [20].

8.4. Enhancing Patient Empowerment and Safety

Access to integrated and up-to-date records empowers patients by reducing redundant procedures and ensuring transparency across transitions of care. In addition, by proactively identifying risk factors for adverse events (e.g., "whoops" surgeries), ShapeHub improves safety and minimizes preventable harm, aligning with global patient safety strategies [28].

8.5. Scalable Infrastructure for Digital Twin and Precision Medicine

As digital twins and AI-based precision tools advance, they require structured, longitudinal, and harmonized datasets—precisely the kind of data environment ShapeHub facilitates. This positions it as foundational infrastructure for future-ready, simulation-based treatment planning [15]. Moreover, its modular architecture can be scaled to support other rare and complex diseases, offering a reusable blueprint for digital transformation.

9. Conclusions: Call to Action

To implement VBHC effectively in sarcoma care and beyond, healthcare systems must adopt data harmonization strategies to defragment care. ShapeHub demonstrates this by creating a unified, interoperable, and patient-centered platform; care pathways can be transformed, leading to improved outcomes, cost efficiency, and the elimination of data silos. Moreover, the dynamic personalization of therapy and care pathways can be achieved by allowing for the continuous response feedback of clinical data.

We call on healthcare institutions, technology providers, and policymakers to collaborate in developing and scaling such systems. By doing so, we can build a cohesive and sustainable healthcare ecosystem that supports not only sarcoma care but also a wide range of rare and complex diseases.

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REVIEW

Beyond the sarcoma center: establishing the Sarcoma HASM network—a Hub and Spoke Model network for global integrated and precision care

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The landscape of sarcoma treatment has evolved significantly, transitioning from amputations to limb-sparing surgeries, underpinned by advancements in multidisciplinary strategies. The establishment of specialized sarcoma centers has been pivotal, though challenges in accessibility and expertise persist. This manuscript proposes the Sarcoma Hub and Spoke Model (HASM) network to address these issues, enhancing coordination and expanding access to specialized care. The HASM network centralizes complex case management at hubs while peripheral spokes manage routine diagnostics and treatments, optimizing resource use and ensuring patient-centered care. Integration with digital interoperable platforms facilitates real-time/real-world data exchange, supports multidisciplinary team meetings, and enables advanced predictive analytics such as Sarcoma Digital Twins and causal machine learning for personalized treatment. The Sarcoma Care Data Warehouse further enhances this model by aggregating comprehensive patient data, supporting quality assessment and continuous improvement. This innovative approach aims to set a new standard for sarcoma care, leveraging technology and collaborative expertise to improve outcomes globally.

Key words: sarcoma, Hub and Spoke Model (HASM), multidisciplinary, digital interoperable platforms, predictive analytics, Sarcoma Digital Twins, quality assessment

INTRODUCTION

Over recent decades, the landscape of sarcoma treatment has been profoundly transformed. The evolution from traditional methods to highly specialized, multidisciplinary strategies has significantly enhanced patient outcomes. Initially dominated by amputations, the field has shifted toward limb-sparing surgeries, enabled by pioneering advancements in surgical techniques and the integration of both local and systemic therapies. Today, limb salvage is the preferred approach in >95% of sarcoma cases, demonstrating a major commitment to preserving quality of life while aggressively managing the disease.[1,2] These advancements highlight a paradigm shift from reactive to proactive patient care, where the goal is not just survival but maintaining life quality. Alongside these therapeutic advancements, the establishment of sarcoma centers has emerged as a cornerstone in modern sarcoma care, underscoring the importance of a cohesive approach through multidisciplinary teams (MDTs).[3-6]

Definition, role, and structure of a sarcoma center

The definition of a sarcoma center is at least problematic; the primary requirements are weekly MDT meetings and case volume. However, these criteria alone do not ensure the center's effectiveness. Sarcoma centers are specialized facilities dedicated to the comprehensive care of patients with sarcomas, characterized by their use of MDTs.[6-8] These teams, typically comprising experts such as pathologists, radiologists, sarcoma surgeons, radiation oncologists, and medical oncologists, are foundational to the centers' operations.[9,10] They convene regularly at MDT meetings to collaboratively assess each patient's case, ensuring that treatment decisions are not only based on the collective expertise of various specialties but are also deeply rooted in evidence and a thorough understanding of sarcoma biology.

However, it is crucial to note that the true measure of a center's capability goes beyond mere numbers; while case volume is often thought to be indicative of a center's

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efficacy, the main requirements are not just the case volume and regular MDT meetings: it requires a nuanced approach that includes the ability to manage complex cases effectively.[11-17] This involves not just surgical expertise but also the strategic composition of treatment teams that can adapt to the unique challenges posed by different sarcoma types. The lack of formal training of sarcoma specialists means that an MDT with little experience cannot compensate for the lack of expertise of a single specialist. Furthermore, even in centers where specialists are available, the relationship between volume and outcome may vary depending on the resources and staff that the center is given.

In addition to clinical care, sarcoma centers function as hubs for advanced training and research, hosting specialized education programs for medical professionals. These programs typically include opportunities for international collaboration, fellowships, and other forms of professional development, crucial for nurturing a new generation of sarcoma specialists. Moreover, sarcoma centers provide all contemporary therapeutic options available in the field, including cutting-edge surgical methods, interventional radiology, and advanced radiation therapies. They also ensure access to clinical trials and maintain comprehensive prospective databases, instrumental in refining treatment protocols and advancing sarcoma care.[18-22]

The role of a sarcoma center extends beyond mere treatment of the disease; it encompasses a holistic approach to care that integrates workup, biopsy, and initial diagnosis, comprehensive treatment planning, and follow-up care under one roof, ensuring a seamless patient journey. In this context, it is crucial that each sarcoma center functions as both a Diagnostic Coordination Hub and a Therapeutic Integration Hub:

The Diagnostic Coordination Hub is where the radiologist, pathologist, and sarcoma surgeon convene to review referral consultations and jointly determine the appropriate course of action for patients with suspected sarcoma (Figure 1). This may involve deciding whether a biopsy is necessary, or if the patient should be referred directly for further treatment. This hub serves as a critical point of convergence where specialists analyze and discuss the submitted queries from referring physicians who seek guidance on whether to refer a patient, what further steps to take, or how to proceed with treatment. By centralizing this expertise, the center ensures that all patients receive a thoroughly considered and unified approach to their diagnosis and care plan.

The Therapeutic Integration Hub coordinates the actual treatment of patients, managing and integrating various modalities such as surgery, chemotherapy, and radiotherapy to ensure personalized and continuous care (Figure 1). This hub facilitates the implementation of treatment plans, ensuring that each patient's therapy is optimized for the best possible outcomes. It serves as a central point for executing complex treatment strategies, closely monitoring patients' progress and adjusting therapies as necessary based on real-time evaluations.

CHALLENGES FACING SARCOMA CENTERS

Sarcoma centers are essential for advancing treatment standards but face significant challenges that limit their reach and effectiveness. The centralized nature of these centers often necessitates long-distance travel for care, creating significant accessibility issues. This geographic barrier results in ∼50% of patients with sarcoma receiving care outside specialized centers, often not adhering to established guidelines.[18] These challenges are particularly pronounced during the initial workup and biopsy of patients suspected of having sarcoma, where strict adherence to guidelines is crucial for accurate diagnosis and management.[23-27]

Furthermore, many sarcoma centers struggle with shortages of skilled experts, exacerbated by an aging workforce and ongoing financial pressures.[9,17,28] These shortages critically impact the center's ability to maintain high-quality, patient-centric care. Healthcare models that prioritize patient volume over quality further compound these issues, diluting the focus on patient-centric outcomes and stifling opportunities for essential collaboration and knowledge sharing.

To effectively address these multifaceted challenges, a rethinking of the organizational model of sarcoma care is crucial. Transitioning from isolated centers to a cohesive Hub and Spoke Model (HASM) network could enhance coordination, optimize resource use, and expand access to specialized care.[29-32] This model not only promises to streamline care delivery but also empowers peripheral physicians to effectively triage patients, taking into account local capabilities and specific patient needs. This strategic shift aims to integrate care locations into a unified system that enhances both the reach and quality of sarcoma treatment, thereby establishing a new standard of care that is inclusive and effective.

PATIENT-CENTRIC MODEL OF CARE

Effective sarcoma treatment necessitates a clear definition of the roles between centralized sarcoma centers and peripheral healthcare facilities in both the workup, including biopsy, and therapy of patients.[9] This balance of centralization and decentralization is essential to cater to the unique needs and circumstances of each patient, considering both the complexity of the disease presentation and the capabilities of the available medical team. Typically, centralization is favored for managing complex sarcomas due to the specialized resources and expertise required; however, there may be exceptions where decentralized care may be appropriate and effective, particularly when local conditions permit.[33-38]

The question of what can be decentralized has to be customized to each sarcoma center and depends on various parameters such as case volume on the one hand, but also the teaching and education of future sarcoma experts at lower-volume sarcoma centers on the other. Decentralization may involve not only the diagnostic workup, including imaging or biopsy, but also parts of the therapy, always in

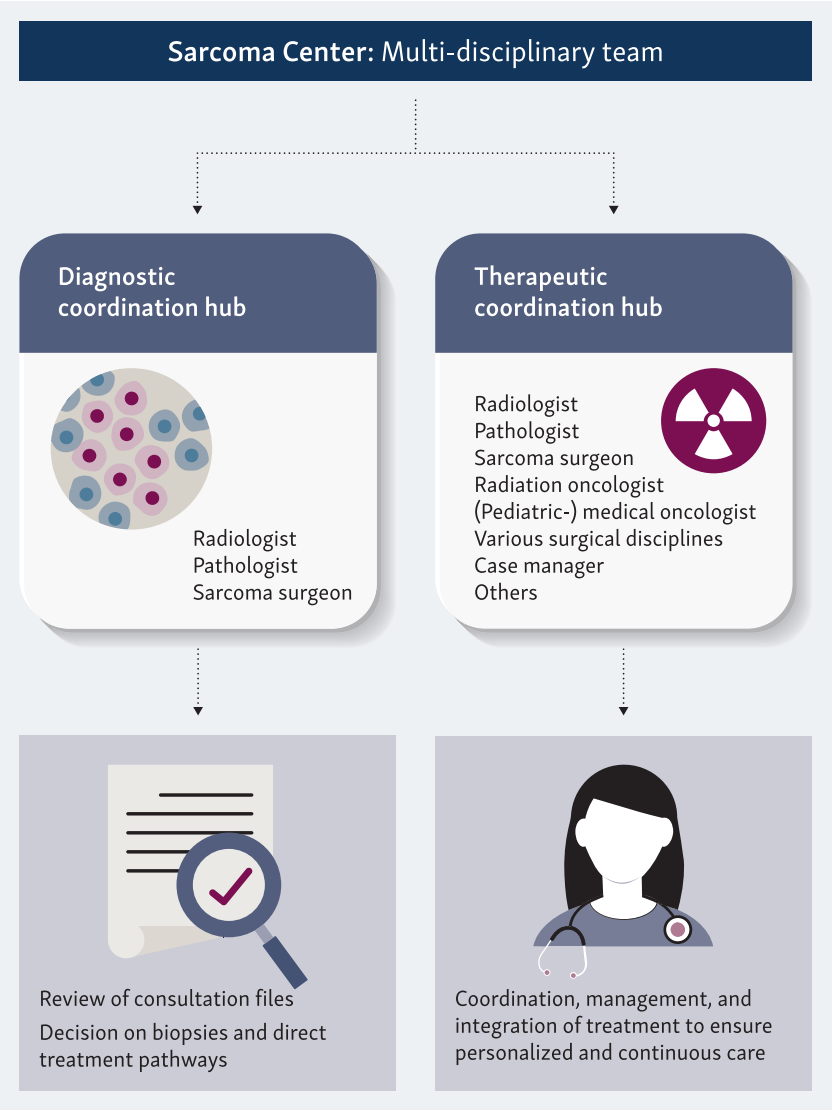


Figure 1. This figure depicts the Sarcoma Center, structured into two main components: the Diagnostic Coordination Hub and the Therapeutic Integration Hub. The Diagnostic Coordination Hub focuses on the initial assessment and diagnosis, where specialists such as radiologists, pathologists, and sarcoma surgeons review referrals and determine the need for biopsies and direct treatment pathways. The Therapeutic Integration Hub coordinates patient treatment, managing and integrating various modalities such as surgery, chemotherapy, and radiotherapy to ensure personalized and continuous care. Together, these hubs streamline the patient journey from diagnosis to treatment, highlighting the center's commitment to comprehensive and coordinated care.

tight consultation with the sarcoma center and its specialists. For example, straightforward cases such as a dedifferentiated liposarcoma of the retroperitoneum, which shows clear clinical—imaging—pathological concordance, might not necessitate a centralized review of the diagnosis. Conversely, more complex conditions, such as extraskeletal myxoid chondrosarcoma, generally require a centralized pathologic review to properly diagnose it and treat it accordingly.

The balance of what might possibly be decentralized can be discussed per discipline as follows:

- Pathology: Diagnostic work for straightforward cases, where the clinical presentation aligns well with common pathologic expectations, can often be handled at local centers. However, complex pathological analyses that are critical for accurate diagnosis should typically be centralized.
- Surgery: Procedures that are technically simple and carry lower risks, such as the removal of atypical lipomatous tumors, skin sarcoma such as skin leiomyosarcoma or some dermatofibrosarcoma protuberans, or simple gastrointestinal tumor or simple lung metastasectomies, can often be carried out effectively at local centers. High-volume centers might prefer these surgeries to be performed peripherally to focus resources on more complex cases, while smaller sarcoma centers might use them as valuable training for surgeons in training. Complex cases, such as large (>5 cm) superficial or deep soft tissue sarcomas of any size in the extremities or trunk wall, as well as retroperitoneal or pelvic sarcomas, should always be centralized, as their management requires specialized expertise.
- Radiotherapy: While routine post-operative radiotherapy for extremity and trunk wall sarcomas—although rare in current treatment algorithms—and palliative treatments

can be administered locally, more complex scenarios requiring precise coordination and planning, such as preoperative radiotherapy for large extremity/trunk wall sarcomas or retroperitoneal tumors, should generally be centralized.
- Chemotherapy: Standard chemotherapy protocols, such as anthracycline-based regimens in the advanced or adjuvant setting, can often be administered locally. By contrast, intricate chemotherapy protocols, especially those involving neoadjuvant therapies for localized disease, concurrent chemoradiotherapy, or multidrug regimens for aggressive sarcomas such as Ewing's or rhabdomyosarcoma, require the specialized capabilities of high-volume centers.

Decentralizing follow-up care and treatments with established, lower-complexity protocols and telehealth support may enhance accessibility and reduce the travel burden for patients, allowing more frequent monitoring within their community. The decision to centralize or decentralize sarcoma care, especially in large countries, reflects a complex balance of multiple factors. Developing a flexible, reproducible, and transparent model that integrates various levels of care is crucial, with imperative access to the respective data by all providers at any time (e.g. via an interoperable digital platform). This model tailors treatment plans based on the complexity of each case and the local resources available, ensuring that patients receive timely, expert, and personalized care at every stage of their treatment.

ESTABLISHING THE HUB AND SPOKE MODEL NETWORK

In the Sarcoma HASM network, all strategic decisions are centralized to ensure optimal care tailored to the complexity of each patient's condition.[39] The hub, equipped with advanced medical technology and specialized staff, handles the most complex cases, while spokes—regional centers connected to the hub—manage standard diagnostics and, if necessary, treatments, referring more complex cases to the hub.[29-32] This configuration not only enhances the effectiveness of the Sarcoma HASM network by ensuring appropriate escalation of care and resource utilization but also maintains a focus on patient-centered approaches at local levels.

The hub's role extends beyond just providing diagnostic workups and treatments. It acts as a center for research and development, pushing forward the boundaries of sarcoma treatment and serving as a training ground for medical professionals. This enhances the overall quality of care by disseminating advanced knowledge and practices.[40] In addition, hubs orchestrate the clinical strategies and protocols across the network, ensuring uniformity in care standards and methodologies.

Spokes often act as the first line of interaction for patients, offering diagnostics and treatment for less complex conditions. They play a crucial role in the continuity of care, managing ongoing treatments and follow-ups, which alleviates the demand on hub facilities. Spokes ensure that care is accessible and timely, providing a critical local presence that supports the broader health system's efficiency.

The success of this model is contingent upon its integration into the specific healthcare framework of each country, tailored to accommodate local nuances such as financial systems, staffing of experts, and the geographical distribution of medical facilities. For instance, European examples such as NETSARC in France, and models in the UK, Germany, Poland, and Italy each demonstrate adaptations to their respective national healthcare environments. The European Reference Network on Rare Adult Solid Cancers (EURACAN), the European Union-wide initiative, exemplifies regional collaboration across Europe, aiming to standardize care and improve outcomes across member states.[41,42]

Such adaptations ensure that the HASM network provides high-quality care efficiently and sustainably. By matching the number of hubs and spokes to the needs and resources of each country, the model supports extensive and equitable access to specialized sarcoma care. The HASM network represents a practical solution to the challenges of delivering high-quality sarcoma care across diverse geographic and systemic landscapes. By centralizing complex decision-making and treatment strategies rather than all-patient care, this model ensures that expertise is utilized effectively while maintaining patient-centered care at local levels. This approach not only maximizes resource utilization but also supports the overarching goal of improving health outcomes for patients with sarcoma throughout various healthcare systems.

INTEGRATION WITH DIGITAL INTEROPERABLE PLATFORMS

For the effective function of a Hub and Spoke Model in sarcoma care, a robust and dedicated digital data infrastructure is crucial, enabling seamless exchange of information and supporting comprehensive management of patient care across various settings. The digital platform facilitates real-time/real-world access to patient records, imaging, and test results, ensuring that all healthcare providers, regardless of location, have up-to-date information to inform patient care decisions.[43,44]

The integration of real-time/real-world data into the network's digital platform enhances patient care by allowing immediate updates to patient records. This capability ensures that any changes in a patient's condition or treatment response are promptly reflected in their records, accessible during consultations or treatments across the network. This level of immediacy in data updating is crucial for maintaining continuous monitoring and adjusting treatment protocols as needed swiftly.

This digital interoperable platform supports the logistics of MDT meetings, which are essential for discussing complex cases.[44] These meetings are supported technologically to ensure that all team members—whether they are at the hub or any of the spokes—have access to comprehensive, real-time patient data. The platform also enables telemedicine capabilities, allowing participants from all spokes to

log in and actively participate in these critical discussions. This inclusivity ensures that expert opinions are leveraged during decision-making processes, enhancing the quality of care provided.

The platform is also instrumental in collecting and managing patient-reported outcome measures (PROMs). Patients are regularly asked to fill out PROMs during their follow-up visits to immediately update the disease status in the platform, and any local or systemic recurrence is immediately flagged for discussion at the next MDT meeting, while regular and uneventful follow-up is also recorded.[45] This process guarantees that all significant patient health events are captured and reviewed by the full team, facilitating timely and appropriate clinical responses.

To fully harness the potential of a hub and spoke network in sarcoma care, the digital interoperable platform must be designed to support comprehensive data analysis. This interoperable platform should facilitate not just the collection and relay of data but also the sophisticated analysis of critical parameters. Such capabilities are essential for enabling informed decision-making processes such as triage between the hub and the spoke, ensuring that every patient receives the most appropriate level of care. By integrating these technological advancements, the network can maintain cohesive and integrated operations, essential for delivering high-quality, patient-centered care across various settings.

THE SARCOMA CARE DATA WAREHOUSE: REGISTRY WITH INTEGRATED AUTOMATED ANALYSIS

The Sarcoma Care Data Warehouse (e.g. Sarconnector) extends beyond mere data aggregation to actively contribute to clinical decision making and healthcare management.[44] This sophisticated data repository and processing center aggregates comprehensive patient data, including detailed patient demographics, specific treatment protocols used, immediate treatment outcomes, and long-term follow-up data.[46] With the integration of clinical-reported outcome measures, PROMs, patient-centric omics measures, and economic measures, the data warehouse supports a holistic approach to care quality assessment and enables value-based healthcare.[47] This structured approach allows for continuous improvement and benchmarking, ensuring that each Sarcoma HASM network contributes to the global effort of improving outcomes for patients with sarcoma.

The data warehouse aggregates a wide array of patient data, including treatment histories, outcome metrics, and patient-reported outcomes. Specific metrics critical for sarcoma care such as time and accuracy to establish a diagnosis, the thoroughness of pathological analysis, and whether a reference review has occurred, which are collectively summarized with the definition of quality indicators of sarcoma care, are meticulously tracked.[48-52] This information is crucial in assessing the efficiency and quality of the diagnostic pathway and allows comparison and benchmarking with other Sarcoma HASM networks.

By applying sophisticated and automated data analytics, the system identifies patterns and trends that can inform treatment protocols and patient management strategies. For instance, analysis of time to treatment initiation, 30/90-day morbidity and mortality after surgery, and the complexity of tumor resections (soft tissue versus bone) provide insights that assist in deciding whether a case should be centralized for more specialized care or can be managed locally, not only within one given Sarcoma HASM network, but also among hubs of the wider geography, using federated data structures.[53] Automated analysis within the warehouse includes algorithms designed to support real-time/real-world decision making, such as triaging patients based on the complexity of surgery needed, as well as benchmarking. This dynamic approach to data handling helps optimize resource allocation across the hub and spoke network.

Regularly updated analytics dashboards provide clinicians and policymakers visibility into both hub and spoke facilities' performance.[52] This facilitates quality improvement initiatives and ensures that standards of care are uniformly high across all locations. Metrics such as the accuracy and type of biopsies performed are crucial for evaluating diagnostic precision and ensuring that sarcoma diagnoses are timely and accurate.[54]

The data warehouse is an invaluable resource for research, enabling the study of long-term treatment efficacy and outcomes across a diverse patient population. It also supports participation in clinical trials by quickly identifying eligible patients and efficiently monitoring trial outcomes, thus enhancing the network's contribution to global sarcoma research efforts. An emphasis on developing and refining sarcoma-specific instruments to follow the longitudinal outcomes of patients ensures continuous improvement in the accuracy of treatment responses and long-term patient care.

This advanced data warehouse, integral to our digital interoperable platform, ensures that every piece of data collected serves a purpose beyond mere recordkeeping.[55] It transforms raw data into a cornerstone of high-quality sarcoma care, facilitating a proactive, predictive, and patient-centered approach that is essential for modern healthcare. By leveraging real-time/real-world data and automated analytics, the network can continuously improve care processes and outcomes, aligning with the broader goals of precision medicine and integrated care. This strategic use of data not only streamlines the clinical patient pathways but also strengthens the decision-making process regarding the centralization versus decentralization of patient care based on detailed, real-time analyses.

STANDARDIZING DATA FOR QUALITY ASSESSMENT

In the evolving landscape of sarcoma care and as a prerequisite, standardizing prospective data collection across Sarcoma HASM networks is crucial for ensuring consistent and high-quality treatment across different regions and countries. A harmonized prospective minimal dataset is foundational for evaluating and comparing the quality of care provided by these networks. This set includes patient demographics (essential for understanding the diverse

impacts of treatments across different population groups), treatment protocols used (details of surgical interventions, chemotherapy regimens, radiotherapy, and other relevant treatments), immediate treatment outcomes (early results of treatments which include surgical success and initial response to other therapies), and long-term follow-up data (critical for assessing outcomes such as local recurrence rates and metastasis-free survival), which are pivotal for evaluating the long-term efficacy of the treatments administered (Table 1).

These elements ensure a baseline from which each Sarcoma HASM network can assess and compare its performance. For instance, standardized metrics on local recurrence and metastasis-free survival provide clear indicators of treatment success or need for improvement. The initial set of quality indicators includes basic yet critical metrics such as treatment efficacy, patient survival rates, and complication rates. These indicators provide immediate feedback on the direct impacts of the care processes implemented.

To foster a more holistic assessment of care quality, this dataset will be expanded to include granular data such as patient satisfaction and quality of life metrics. These aspects are vital for comprehensive care assessments, going beyond clinical outcomes to encompass the overall well-being of patients. Expanding this minimal dataset aligns with the vision recently articulated, aiming to provide a holistic assessment of quality indicators across Sarcoma HASM networks.[52] This approach not only facilitates large-scale quality comparisons within and between countries but also highlights the model's efficacy in delivering specialized sarcoma care.

A recent benchmarking study illustrates that benchmarking is not only feasible but also instrumental in identifying unexpected variations in care quality.[44] By identifying key parameters of strengths and areas for improvement, Sarcoma HASM networks can implement targeted interventions to elevate the standard of care. This benchmarking process underpins the continuous improvement ethos of the network, ensuring that each Sarcoma HASM network not only meets but also exceeds the standards of sarcoma treatment and patient care.

By standardizing data and expanding quality indicators, Sarcoma HASM networks can achieve a detailed and actionable understanding of their performance. This structured approach to data enables a continuous cycle of assessment, benchmarking, and improvement, ensuring that each Sarcoma HASM network is a beacon of excellence in sarcoma care. The ultimate goal is to create a robust, data-driven environment where every Sarcoma HASM network contributes to the global effort of improving outcomes for patients with sarcoma, making high-quality care a universal standard.

Table 1. Patient data and clinical outcomes at the Sarcoma Center/Integrated Practice Unit

Parameter	Description
Patient ID	Unique identifier for each patient
Gender	Male (M) or female (F)
Date of birth	Patient's birthdate
Tumor site	Anatomical location of the tumor
Tumor depth	Superficial or deep
Histological diagnosis date	Date when the tumor was histologically diagnosed
Surgery date	Date when the patient underwent surgery
Surgery type	Primary surgery, re-excision, etc.
Margin status	Surgical margin status (R0, R1, or R2)
Maximal tumor size (mm)	Size of the tumor in millimeters
Histology	Histological type of the tumor
Grading	Grading of the tumor
Chemotherapy	Details about chemotherapy
Radiotherapy	Details about radiotherapy
First local recurrence date	Date of the first local recurrence
First local recurrence treatment	Treatment administered for the first local recurrence
Second local recurrence date	Date of the second local recurrence
Second local recurrence treatment	Treatment administered for the second local recurrence
Pulmonary metastasis date	Date when pulmonary metastases were detected
Extrapulmonary metastasis date	Date when extrapulmonary metastases were detected
Metastasis site	Anatomical site of extrapulmonary metastases
Metastasis treatment	Treatment details for metastases
Current status	Patient's current health status
Last follow-up date	Most recent follow-up date

ADVANCING SARCOMA TREATMENT: PREDICTIVE ANALYTICS AND PERSONALIZED CARE MODELS

As we continue to standardize and expand the dataset within Sarcoma Hub and Spoke Models (Sarcoma HASM networks), the foundation is set for leveraging these robust datasets to drive advancements in predictive analytics and personalized care.[56,57] The integration of comprehensive quality indicators with structured data provides an ideal basis for developing advanced predictive tools such as Sarcoma Digital Twins and using causal machine learning (CML) to enhance treatment precision.[58-60]

A Sarcoma Digital Twin is a virtual model that represents an individual patient with sarcoma in a detailed and dynamic manner. This digital counterpart is continuously updated with real-time/real-world data from the patient's ongoing treatments and responses. By simulating various treatment scenarios, the digital twin predicts potential outcomes, allowing oncologists to visualize the effects of different treatment paths before they are implemented in the real world.

The creation of a digital twin involves integrating diverse data types, including genetic information, clinical data, and real-time/real-world health monitoring. This model uses predictive algorithms to assess how a patient might respond to different treatment options, considering their unique medical history and current health status. This technology enables healthcare providers to simulate treatment outcomes under various scenarios, providing a risk—benefit analysis that helps in making informed, personalized treatment decisions. This approach is particularly valuable in

planning complex interventions where multiple treatment options are viable.

CML represents a significant evolution from traditional predictive analytics.[61] Unlike standard models that only forecast outcomes based on historical data correlations, CML identifies and understands the causal relationships between treatment actions and outcomes. CML analyzes the potential outcomes of different treatment strategies, weighing the expected benefits against possible adverse effects. For patients with sarcoma, this means that treatment plans can be tailored not just to maximize efficacy but also to minimize side effects, enhancing the overall treatment experience and outcomes.

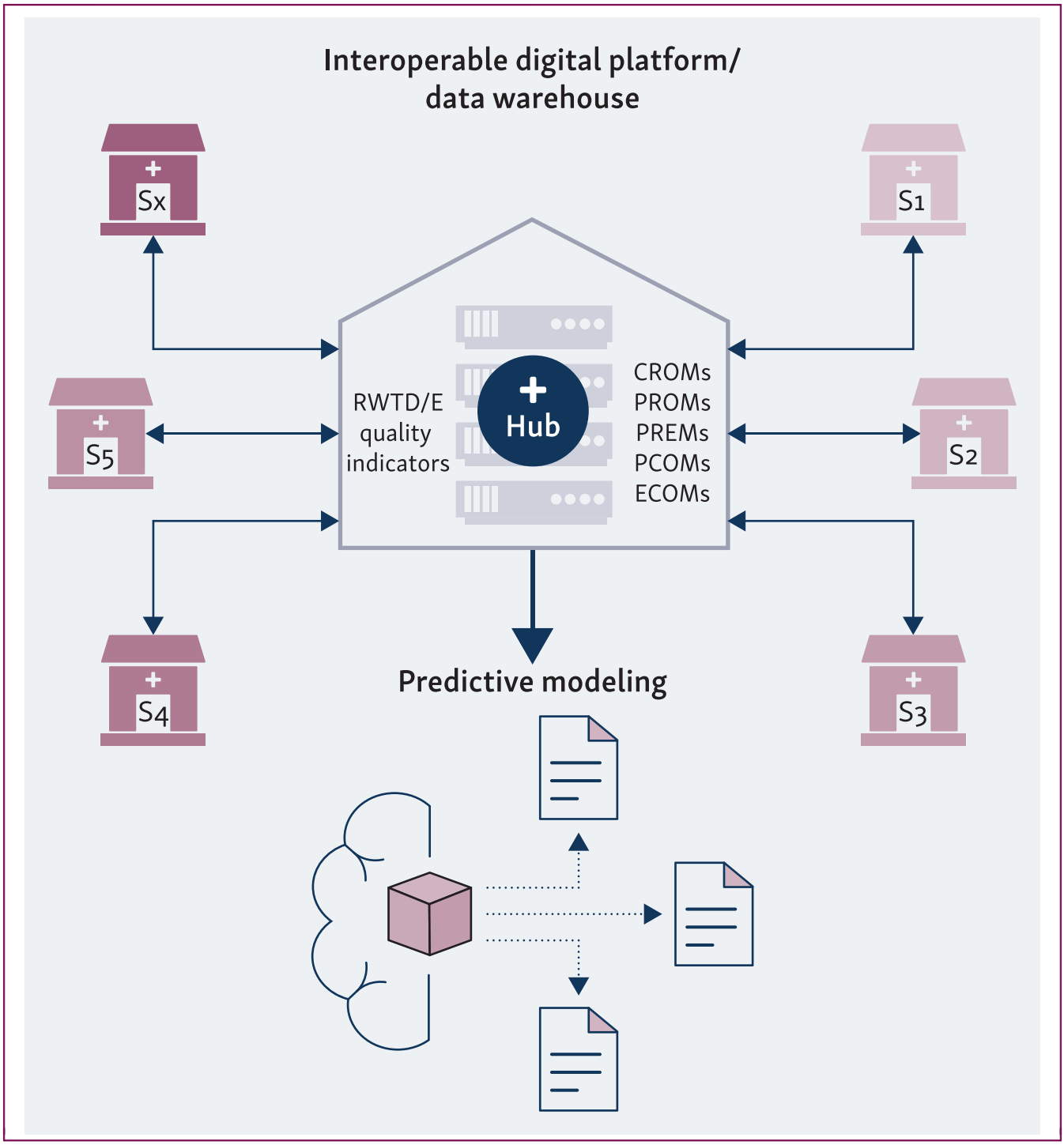


Figure 2. This figure illustrates an interconnected Hub and Spoke Model for sarcoma care, where a central hub coordinates complex case management and predictive modeling, linked to multiple spokes representing regional healthcare centers handling routine diagnostics and treatments. The central interoperable digital platform/data warehouse aggregates and analyzes real-time data from these nodes, integrating clinical-reported outcome measures (CROMs), patient-reported outcome measures (PROMs), patient-reported experience measures (PREMs), economic measures (ECOMs), and patient-centric omics measures (PCOMs) to optimize treatment and resource allocation. This setup facilitates multihub collaboration across geographic locations and continents, enhancing the generation of expansive population data to inform quality metrics and establish global sarcoma care standards. RWTD/E, real-world-time data and evidence.

In sarcoma care, CML can predict the balance between positive outcomes (such as gain in life years) and potential side-effects or toxicities. This predictive capability is crucial in decision-making processes where the trade-offs between aggressive treatment and quality of life are complex and critical.

The future of sarcoma care lies in the ability to not only react to conditions as they occur but also to anticipate and plan treatments in a manner that is precisely tailored to each patient's specific situation. As Sarcoma HASM networks evolve, the integration of Sarcoma Digital Twins and CML will revolutionize how care is delivered, moving toward a truly personalized approach that is predictive, proactive, and patient-centered. The potential to significantly improve patient outcomes by precisely balancing treatment efficacy against side-effects represents a transformative step forward in oncology (Figure 2).

CONCLUSION

The transformation of sarcoma care through the adoption of the Hub and Spoke Model marks a pivotal shift in how we approach complex and rare diseases. This model promises a future where integrated care is the standard, supported by advanced digital platforms that ensure all patients, regardless of geographic location, have access to the best possible treatments and outcomes. Through continued collaboration and innovation, this model aims to improve global health outcomes, leveraging cutting-edge technology and collaborative expertise to create a health system that is adaptable, responsive, and just.

The Sarcoma HASM network not only streamlines resource utilization but also enhances patient care and bolsters research capabilities. By centralizing strategic decision-making and expertise while decentralizing routine care, we can achieve a more efficient, effective, and patient-centered healthcare system. Healthcare providers, policymakers, and stakeholders are urged to support the integration of this model into their national health systems. This integration will facilitate the optimal use of technological innovations such as digital twins and CML, enhancing the ability to deliver personalized care based on predictive analytics.

Looking forward, the Sarcoma HASM network sets a template that could be adapted for all rare and complex diseases, potentially redefining healthcare practices worldwide. This model promises a future where integrated care is the standard, supported by advanced digital platforms that ensure all patients, regardless of geographic location, have access to the best possible treatments and outcomes. Through continued collaboration and innovation, we can expand this model to create a global health network that not only addresses the needs of patients with sarcoma but also serves as a beacon for treating various rare conditions.

Our vision extends beyond immediate clinical needs to encompass a healthcare ecosystem that leverages cutting-edge technology and collaborative expertise to improve global health outcomes. By embracing this model, we can ensure that every patient receives care that is not only timely and effective but also tailored to their unique health context.

As we move forward, let us commit to a future where technology and human expertise converge to create a health system that is more adaptable, responsive, and just. The Sarcoma HASM network exemplifies how structured, data-driven approaches can revolutionize medical treatment, making the promise of precision medicine a reality for sarcoma and beyond.

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Swiss Sarcoma Network (SSN)

Wie stellen wir die Behandlungsqualität für unsere Sarkompatienten sicher?

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Sarkome sind seltene Tumore, die biologisch durch mehr als 100 verschiedene Entitäten und deren Varianten definiert werden. Sie erfordern eine multidisziplinäre Abklärung und Behandlung. Der Behandlungserfolg wird beeinträchtigt durch ungeplante Resektionen, mangelnde Koordination im Management der Patienten bzw. im weiteren Verlauf durch die Entwicklung von Metastasen.

Eine Hauptursache für die eingeschränkten Erfolgsaussichten liegt in der heutigen Art unserer Medizin, die mit zunehmender Spezialisierung immer mehr Disziplinen-orientiert, weniger Problem-fokussiert agiert. Jede Disziplin oder Fachperson beschränkt sich vornehmlich auf den eigenen Fachbereich, wobei der entsprechende Beitrag ohne interdisziplinäre Vorabsprachen (Tumorkonferenzen) nicht Teil einer komplexen Strategie wird. Dies mag erklären, weshalb wir uns schwertun, interdisziplinäre Daten auch zu erfassen. Hierfür müssten wir eine gemeinsame, Disziplinen-unabhängige Sprache entwickeln und definieren. Ohne ein solches Vorgehen werden wir auch weiterhin keine zuverlässigen Vergleiche anstellen können, weder auf nationaler noch auf internationaler Ebene, weiterhin nicht wissen, wie viele Sarkompatienten wie und wo mit welchem Resultat behandelt werden. In dieser Situation ist nun der HSM-Entscheid anstehend. Die Gefahr diesbezüglich besteht darin, dass durch den Kampf um Fall-Zahlen einzelner Institutionen – statt durch interdisziplinäre Konzepte/Prozesse und Quantifizierung von Resultaten – Konkurrenz, monopolistisches und monodisziplinäres Denken noch mehr gefördert werden.

Ausgangslage

Die Grundlage des Erfolges liegt in der gelebten Interdisziplinarität, sowohl innerhalb einer Institution als auch zwischen den Institutionen, mit einem Austausch auf Augenhöhe, bestimmt durch das Experten-Wissen und nicht durch blosses Zahlen-Denken. Die Organisation nimmt dabei eine kritische Rolle ein. Grundsätzlich stehen alternativ das «Netzwerk of Excellence» oder aber das «Center of Excellence» zur Diskussion, wobei man über die jeweiligen Vor- und Nachteile sicher geteilter Meinung sein kann. Weil im Rahmen der Abklärung das Verhältnis von Sarkomverdacht zu Sarkomdiagnose 5:1 beträgt, und weil ungeplante Resektionen ((20% aller Sarkomdiagnosen werden durch die sogenannten whoops! («unintended resections»)-Operationen gestellt)) weiterhin ein ungelöstes Problem darstellen, wird es illusorisch sein, alle Patienten mit einem Verdacht auf ein Sarkom an einem geografischen Ort zu zentralisieren. Abgesehen von der fehlenden Infrastruktur, die eine solche Patientenmenge z. B. für die Deutschschweiz aufnehmen könnte, und abgesehen davon, dass die wenigsten Patienten gewillt sind, nur schon für eine Biopsie die Stadt zu wechseln. Auch deshalb ist in der Schweiz ein starkes Netzwerk von grosser Bedeutung.

Das Ziel des Swiss Sarcoma Networks (SSN) ist es, Sarkom-Experten aller Disziplinen und aller Institutionen zusammenzubringen, um eine gemeinsame Sprache zu definieren, das diagnostische und therapeutische Vorgehen aller Patienten initial gemeinsam zu besprechen und die Daten nach definierten Qualitätskriterien in einer gemeinsamen Datenbank zu erfassen. Hierbei kann sich jede Institution beteiligen, sofern sie bereit ist, die Patienten mit muskuloskelettalen Tumoren im Rahmen des gemeinsamen Sarkomboardes zu besprechen und die Patientendaten zu registrieren.

Definition interdisziplinärer Qualitätsindikatoren

Das SSN hat in seiner Inaugurationssitzung 2018 diese Qualitätsindikatoren definiert. Sie basieren auf genauen histopathologischen Diagnosen mit Aufschlüsselung, wie viele Tumore gutartig, intermediär oder bösartig sind. Es wird erfasst, wie viele primäre Fälle mit oder ohne Vorbehandlung besprochen werden, bei wie vielen Patienten ungeplante Operationen stattgefunden haben, wie hoch die Lokalrezidiv- und Metastasierungsraten sind, ob die Biopsie durch ein multidisziplinäres Team erfolgte, ob die Gewebe-Analyse durch einen Pathologie-Experten erfolgte und zu welchem Zeitpunkt im Krankheitsverlauf die Vorstellung am Sarkomboard stattfand. Zu jedem Abklärungs- und Behandlungsschritt werden die Disziplin, Art der Ausführung und allfällige Komplikationen erfasst. Selbstverständlich ist diese Liste bei Bedarf beliebig erweiterbar.

Gemeinsames inter-institutionelles telemedizinisches Sarkomboard

Das SSN organisiert jeden Dienstag um 17 Uhr ein interdisziplinäres Sarkomboard, welches telemedizinisch via ActVisual® übertragen wird. Dabei werden alle konsekutiven Patienten aller teilnehmenden Institutionen vorgestellt und diskutiert. Gäste können sich leicht via Computer oder Smartphone selber einloggen und so persönlich teilnehmen. Patienten-Vorstellungen auch anderer, derzeit nicht beteiligter Spitäler sind willkommen. Der grösste Vorteil dieser überregionalen Strategie liegt darin, dass durch dieses telemedizinisch übertragene Sarkomboard die Exposition von Experten zu Sarkomdiagnosen und Herausforderungen des Patienten-Managements maximiert werden kann, wodurch die Expertise jedes einzelnen gesteigert wird, unabhängig von der einzelnen Institution.

Pathologie-Review

Die korrekte histopathologische Diagnose durch die Pathologie ist die Basis, um einem Patienten die optimalen Voraussetzungen für die Behandlung und damit die optimale Überlebensrate zu ermöglichen. Das Pathologie-Expertenwissen ist abhängig vom Fallumfang. Das SSN fördert durch den Austausch unter den Pathologen nicht nur die Exposition, sondern auch die Qualität der Diagnosestellung. Im Rahmen der «Swiss Working Group on Sarcomas» der Schweizerischen Gesellschaft für Pathologie unter der Leitung von Prof. Beata Bode werden die Sarkomdiagnosen in einem consensus-read-out reviewed. Wird keine Einigung erzielt, werden internationale Experten beigezogen. So wird einerseits sichergestellt, dass alle Sarkomdiagnosen einem Expertenreview unterzogen werden, zugleich aber wird auch das Expertenwissen unter den Pathologen gefördert.

Etablierung eines Quality Management Systems (QMS)

Die richtige Diagnose und das korrekte Durchführen einer oft multimodalen Therapie bzw. deren bestmögliche Sequenz für den einzelnen Patienten sind zentrale Pfeiler in jeder Sarkombehandlung. Der zeitlich zielgerichtete Ablauf wird häufig durch infrastrukturelle und logistische Gegebenheiten ungünstig beeinflusst – ein im Alltag oft gesehenes Problem, bislang ohne Quantifizierung/Datenerfassung für die Schweiz. Die zeitlich effiziente Abfolge der Teilschritte ist zentral für den Patienten bzw. seine Prognose. Die zeitlichen Kenndaten gehören genauso wie die vorgenannten Parameter zu den Qualitäts-definierenden Grössen einer Sarkombehandlung.

Register

Wenn die Qualität in Diagnostik und Therapie von Sarkompatienten verbessert werden soll, ist die Datenerfassung die Basis im Sinne einer conditio sine qua non. Register haben häufig den Nachteil, dass sie nicht koordiniert und abgestimmt sind, dass zu viel oder zu wenig Parameter erfasst werden und vor allem, dass systematisch inkorrekte Daten erfasst werden. So erlaubt die ICD-Kodierung keine korrekte Abbildung aller Sarkomdiagnosen, wodurch sich viele Register bereits selber limitieren. Zudem werden die Daten häufig von Datenmanagern eingegeben, die an der Sarkombehandlung unbeteiligt sind und Details nicht verstehen können. Wenn z. B. die Diagnose oder der chirurgische Margin Status nicht sauber definiert werden, kann ein Datenmanager nur inkorrekte Daten eingeben, wodurch ein solches Register die eigentlichen Ansprüche nicht erfüllen wird. Das SSN koppelt deswegen die Informationen des Registers (SwissSarcomaRegistry) mit jenen der Anmeldung für das Sarkomboard, bei welcher alle relevanten Informationen zusammengefasst werden. Eine erste Qualitätskontrolle der Daten kann so bereits am Sarkomboard erfolgen. Das SwissSarcomaRegistry wird von Adjumed bereitgestellt, eine Firma mit 25-jähriger Erfahrung für Qualitätserfassung im Medizinbereich. Das Register ist international abgestimmt mit dem aktuell grössten existierenden Register weltweit. Die französischen Kollegen erstellten ihr Register 2010, haben seither > 60000 Sarkompatienten erfasst. Durch den Abgleich mit diesem französischen Register wird es uns möglich, Daten aus der Schweiz direkt mit jenen aus Frankreich auf internationaler Ebene zu vergleichen.

Internationaler Austausch

Die Rarität der Sarkomdiagnosen in der Schweiz erlaubt es uns nicht, unseren eigenen Weg unabhängig von internationalem Expertenwissen (Internationales Advisory Board) zu gehen, wenn wir optimale Qualität für unsere Patienten anbieten wollen. Zu diesem Zweck baut das SSN auf internationale Kollaborationen, vornehmlich mit den Experten aus Frankreich, Spanien und Italien, welche alle dieselbe Absicht verfolgen: Qualität zu definieren, zu dokumentieren und zu analysieren. Somit wird sichergestellt, dass die Sarkombehandlung in der Schweiz nach internationalem Top-Standard erfolgt und weiter ausgebaut werden kann. Im Rahmen eines solchen International Advisory Boards stehen internationale Experten jederzeit zur Verfügung für Diskussionen anspruchsvoller Situationen in der täglichen Patientenbehandlung, unterstützen mit ihrer Expertise Aufbau und Analyse des Registers und stehen uns für die Aus- und Weiterbildung zur Verfügung.

Weiter- und Fortbildung

Damit sich das SSN mit seinem Hauptziel, Qualität zu fördern, weiter entwickeln kann, sind Lehre, Weiter- und Fortbildung und damit der internationale Austausch unabdingbar. Das SSN organisiert viermal jährlich eine Fortbildungsveranstaltung (jeweils Freitagnachmittag am Ende jedes Quartals, Gliederung in Übersichtsvortrag mit Information zum aktuellen Status der nationalen Register, Fallvorstellungen, und es sollen Themata aus dem Bereich «ungelöste Probleme» (zum Beispiel: Wie wird ein chirurgischer Margin definiert?) adressiert werden, wobei im Anschluss an die Einführung ins Thema ein Consensus erarbeitet wird.

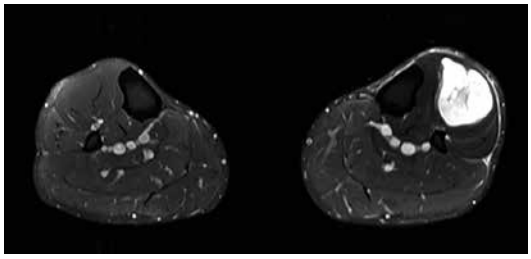
Des Weiteren wird im Mai 2020 das nächste SwissSarcomaSymposium in Luzern stattfinden nebst Exponenten des Internationalen Advisory Board des SSN im Beisein auch von Sarkomexperten aus der Mayo Clinic, USA sowie der IVINS society.

Schlussfolgerungen:

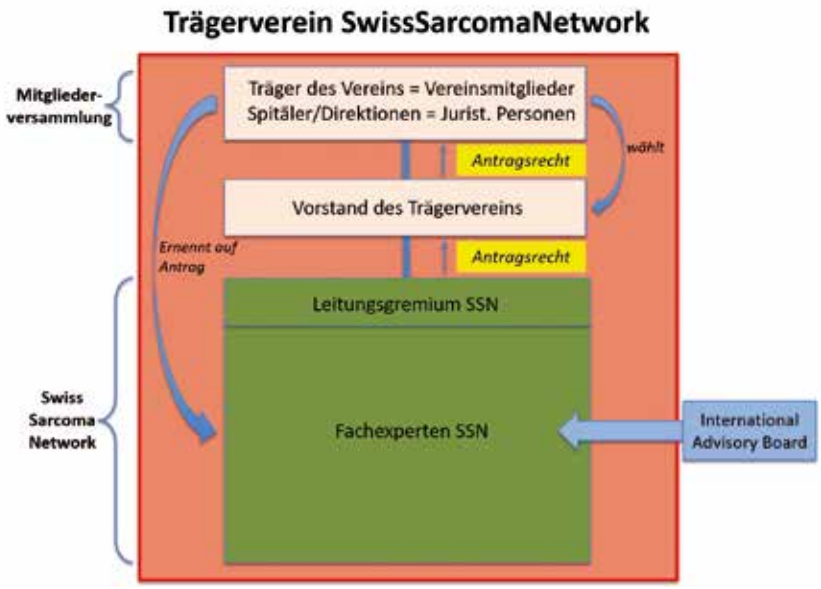
Wir müssen uns lösen von herkömmlichen Fach- und Institutions-zentrierten Dogmen und Verhaltensweisen und alles daransetzen, die interdisziplinäre und interinstitutionelle Zusammenarbeit maximal zu fördern. Die erforderliche Interdisziplinarität wird vor allem durch einen aktiven Austausch zwischen den Experten in verschiedenen Institutionen gefördert, basierend auf gemeinsam definierten inhaltlichen Verbindlichkeiten. Es müssen Strukturen geschaffen werden, die eine interdisziplinäre und interinstitutionelle Gemeinsamkeit fördern, mit gemeinsamen Kriterien. Es muss bewusst(er) werden, dass nicht allein Operations- bzw. Fall-Zahlen Qualität garantieren, da der Schweregrad einer Operation diametral unterschiedlich sein kann und derzeit nicht definiert ist. Die alleinige Orientierung an Operationszahlen kann suboptimale Behandlungen fördern und interdisziplinäre Ansätze verhindern. Die Erfassung interdisziplinär definierter Qualitätsparameter in einem Register mit internationalem Abgleich dürfte wegweisend bzw. zukunftsfähig sein. Es wäre für alle Beteiligten sehr erstrebenswert, wenn das HSM-Fachorgan die Entscheide betreffend Organisation und Management der Sarkome in Zukunft auf sachbasierten, transparenten und einheitlich erfassten Qualitätsindikatoren treffen könnte.

Das SSN stellt eine solche gemeinsame transparente Basis dar, bei der jede Institution und jeder Sarkomexperte in der Schweiz teilnehmen und beitragen kann, sofern die Bereitschaft für die verbindlichen Qualitätsparameter (initiale Sarkomboard-Präsentation aller Primärfälle, Dateneingabe im gemeinsamen Register) besteht.

Weitergehende Informationen unter www.swiss-sarcoma.net



MRI eines Patienten mit Weichteilsarkom im Bereich des Oberschenkels.



Struktur Trägerverein SwissSarcomaNetwork. Die Vereinsmitglieder sind Spitäler/Institutionen, welche Sarkomexperten aus verschiedenen Fachrichtungen ins SwissSarcomaNetwork delegieren.

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Qualitätssicherung in der Behandlung von Sarkomen: Eine interdisziplinäre und interinstitutionelle Herausforderung

Seit jüngerer Zeit rückt die Behandlungsqualität richtigerweise immer mehr in den Fokus des öffentlichen Interesses, obwohl sie für jeden Mediziner spätestens nach der Ausbildung eigentlich die grösste Selbstverständlichkeit darstellt. Eine mögliche Erklärung für diese erhöhte Aufmerksamkeit liegt unter anderem auch darin, dass wir uns der Qualität zwar verpflichtet fühlen, uns aber schwer tun, diese zu definieren und strukturiert zu erfassen. Dies wird besonders offensichtlich bei selteneren Krankheiten wie den Sarkomen, deren Behandlung den Einbezug diverser Disziplinen und Spezialisten oft auch inter-institutionell erfordert, bzw. bei deren Behandlung Expertenwissen und infrastrukturelle Gegebenheiten eine zentrale Rolle spielen.

In den letzten Jahren widmete sich eine Vielzahl von Publikationen den Fragen, welche rund um das Thema Behandlungsqualität und Spezialisierung auftraten (www.sarcoma.surgery → wie finde ich den richtigen Spezialisten?). Insbesondere wird die Definition der Qualität in den Vordergrund gestellt. Basierend auf diversen Studien ist bei Sarkompatienten, die an einem Hochvolumenzentrum/-Netzwerk behandelt wurden, ein besseres Outcome nachgewiesen, auch wenn Letzteres lediglich mit 20 Patienten pro Jahr als Cutoff definiert wird [1-4]. Eine detaillierte Analyse mit grösserem Volumen und demzufolge aussagekräftigen Aussagen existiert in der Sarkomliteratur aber nicht. Zumal das Volumen nur einen von vielen Parametern darstellt. Mindestens so wichtig erscheint die Entwicklung weg vom Disziplinendenken hin zum problemzentrierten Denken. Da die Chirurgie als Hauptpfeiler in der Sarkom-Behandlung für das Outcome zentral ist, steht der Sarkomchirurge im Fokus. In Amerika führen 83% der Sarkomchirurgen 10-30 Operationen für Knochensarkome und 69% 10-50 Operationen für Weichteilsarkome pro Jahr durch [5]. Bezeichnenderweise definieren die Editoren des Annals of Surgical Oncology den Surgical Oncologist nicht über Operationszahlen, sondern über dessen – nebst natürlich technischem – onkologisches Verständnis, dargelegt durch entsprechende Aus- und Weiterbildungen [6]. Es wurde auch gezeigt, dass nicht die Anzahl Operationen für die Qualität entscheidend ist, sondern vielmehr, ob nach den Richtlinien der Sarkomchirurgie operiert wird, was wiederum mit entsprechender Aus- und Weiterbildungen einhergeht [7].

Die Schweiz mit zurzeit zirka 8.4 Millionen Einwohnern würde nach internationalen Massstäben das Volumen für ein einziges, landesweites Sarkomzentrum bieten. Da dies aus diversen Gründen schwierig umzusetzen ist, stehen wir vor der Frage, ob es zielführend ist, mehrere solche Zentren zu unterhalten, die unabhängig voneinander mit entsprechend kleinen Volumina agieren oder ob eine gemeinsame Basis im Sinne eines überregionalen Netzwerkes auf nationaler Ebene angestrebt werden soll, in dem alle relevanten Informationen zentralisiert erfasst werden. Auch diesbezüglich gibt es interessante Hinweise aus der Literatur: traditionellerweise wurde empfohlen, seltene Erkrankungen in dedizierten Referenzzentren zu zentralisieren, um die Multidisziplinarität, Expertise und den Zugang zu Innovation sicherzustellen [8]. Umgekehrt erfordert aber die Zentralisierung sogenannte «*Health Migration*» seitens der Patienten, Ressourcen-Aufbau und potentielle Qualitätseinbussen bei Routine-Arbeiten. Für diese Autoren ist die Netzwerkbildung die logische Antwort [9]. Gerade bei Sarkomen, bei denen ungeplante Resektionen vorgängig nicht histopathologisch diagnostizierter Tumore (sogenannte «Whoops!-Operationen») in der Schweiz 2018 noch immer inakzeptable 20% und mehr beträgt, wird es absolut entscheidend sein, dass Patienten möglichst rasch bei Sarkomverdacht in ein wohnortnah zugängliches Netzwerk eingebunden werden, damit durch die potentielle Health Migration an ein geografisches Zentrum keine Verzögerung auftritt, respektive die ungünstigen Folgen für Qualität und Outcome einer falschen Behandlung minimiert werden können. Deswegen sollte idealerweise ein Netzwerk

mit einem Qualitäts-Management-System (QMS) etabliert werden, das eine zeitnahe Abklärung ermöglicht, das entsprechende Volumen verzeichnet, das die Komplexität von Diagnostik, Therapie und Nachbehandlung berücksichtigt und die Multidisziplinarität gewährleistet [10]. Ein solches QMS sollte zwingend die Transparenz aller Aktivitäten seitens der Behandelnden beinhalten, mit Onlinezugang zu Fallzahlen, Behandlungen und Qualitätsindikatoren.

Das *Swiss Sarcoma Network* (*www.swiss-sarcoma.net*; SSN) entspricht einem solchen überregionalen Netzwerkkonzept wie oben beschrieben. Das SSN wurde 2018 gegründet, wird von einem Trägerverein gebildet und von nationalen Institutionen geführt. Diese Institutionen haben sich vertraglich verpflichtet, die Daten aller konsekutiven Sarkompatienten gemäss festgelegten Qualitätsindikatoren zu erfassen und transparent darzustellen. Der Verein steht grundsätzlich für alle Institutionen offen, die sich diesen Prinzipien ebenfalls verpflichten möchten. Den Hauptpfeiler des SSN bildet das Datenregister der etablierten Firma Adjumed (*www.adjumed.ch*). Adjumed stellt sicher, dass jegliche Daten in Echtzeit analysiert und dargestellt werden. Eine Besonderheit der Datenbank stellt die Kopplung des Registers an das Management des wöchentlich stattfindenden überregionalen Sarkomboardes dar. So müssen zum einen die sowohl für das Register wie für das wöchentliche überregionale Sarkomboard erforderlichen Informationen nicht zusätzlich im Register eingegeben werden, zum andern kann bereits eine Prüfung der Datenqualität am Sarkomboard stattfinden, drittens ist dadurch sichergestellt, dass jegliche Veränderung im Krankheitsverlauf eines Sarkompatienten, die im Rahmen des Tumorboardes diskutiert werden muss, und jede Followup-Information ebenfalls im Register enthalten sind. Am Sarkomboard, das telemedizinisch stattfindet, können sich Experten aus verschiedenen Institutionen direkt miteinander austauschen, so dass eine Diskussion sach- und weniger institutionszentriert oder hierarchiebasiert stattfinden kann. Das SSN definiert SOP's and GCP's nach international gültigen Richtlinien, organisiert Aus- und Weiterbildungs-Curricula inkl. entsprechende Weiterbildungssymposien. Ein weiterer Pfeiler des SSN stellt das «International Advisory Board» dar. Es wird von international anerkannten Sarkom-Experten gebildet, die die Multidisziplinarität abbilden und sich der Qualität und Transparenz verpflichten. Diese internationalen Fachexperten stehen dem SSN für Zweitmeinungen zur Verfügung, was die maximal mögliche Qualität der Therapieentscheidungen für unsere Patienten garantiert. Zusätzlich werden sie für Instructional Course Lectures, der Etablierung eines E-Learning Tools sowie zur Über- und Ausarbeitung der Therapie- und Abklärungsguidelines zur Verfügung stehen. Durch diese Massnahmen wird gewährleistet, dass Qualität nicht nur in Echtzeit erfasst und dargestellt, sondern auch auf internationaler Basis weiterentwickelt wird.

Qualität beinhaltet, unsere Behandlungen und deren Erfolg a) zu definieren, b) zu erfassen und c) auszuwerten, speziell bei seltenen Krankheiten. Unsere aktuelle Realität ist, dass wir noch nicht einmal wissen, wie viele Sarkompatienten in der Schweiz pro Jahr diagnostiziert werden. Dies ist vom medizinisch-ethischen Gesichtspunkt her inakzeptabel. Bezieht man die Tatsache ein, dass Unsummen für die personalisierte Medizin aufgebracht werden, so ist das fast schon skurril. Bislang haben wir kein System, dass es uns erlauben würde, die nach WHO definierten Sarkomentitäten zu erfassen (die ICD10-Codierung erlaubt das nicht) oder deren Behandlungen zu evaluieren und zu vergleichen. Solange wir nicht bereit sind, unsere herkömmlichen Verhaltensweisen zu ändern und einen nächsten Schritt zu tun, wird es konsequenterweise weiterhin nicht möglich sein, die Qualität im wie beschriebenen erforderlichen Sinne zu definieren, und Diskussionen betreffend Sarkommanagement können weiterhin nicht sachbasiert erfolgen. Es wäre selbstverständlich für alle, vor allem aber für unsere Patienten sehr wünschenswert,

vorteilhaft und vor allem einfacher, wenn das HSM-Fachorgan die Entscheide betreffend Organisation und Management der Sarkome in Zukunft auf sachbasierten, transparenten und einheitlich erfassten Qualitätsindikatoren treffen könnte.

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Schweizerisches Sarkom-Netzwerk – Aktivitäten und erste Resultate

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1. Einleitung

Die optimale Abklärung und Behandlung von sarkomatösen Erkrankungen ist grundsätzlich multidisziplinär und erfordert eine ab initio prä-festum abgesprochene Abfolge der einzelnen Schritte. Jeder Schritt beeinflusst und/oder bedingt den nächsten – der Folgeschritt kann nur so gut sein wie der vorangegangene (z.B. keine bestmöglich konformierende präoperative Radiatio ohne rezente und sachkundig durchgeführte MRI/-Befundung; keine ideale Chirurgie bei ungünstig durchgeführter Biopsie... usw.). Deshalb erfolgt bei Verdacht auf eine sarkomatöse Erkrankung die weitere Abklärung/Diagnosesicherung optimalerweise in einem multidisziplinären Team (MDT), das vertraut ist mit den Abläufen, Folgeschritten und Entität-bezogenen pitfalls. Ein Beispiel für die Effektivität dieses ab initio multimodalen/multidisziplinären Vorgehens kann u.a. den Daten des Französischen Sarkom-Netzwerks NETSARC+ entnommen werden [1] (2022): Seit 2010 wurden 26 national designierte Sarkom-Referenz-Zentren installiert mit jeweils multidisziplinären Boards. Seither ist es gesetzlich erforderlich (‹mandatory by law›), dass der erstbetraute Pathologe jeden Fall mit Verdacht auf Sarkom oder intermediäre Malignität an die Pathologie eines Referenz-Zentrums überweist. Die Schlüssel-Parameter 1) Fall-Präsentation an einem Multidisziplinären Sarkom-Board VOR Behandlung, 2) Biopsie VOR Behandlung, und 3) Bildgebung VOR Behandlung wurden analysiert. Es fand sich eine deutliche Verbesserung in der Umsetzung der drei Parameter über die letzten 10 Jahre, mit einer dadurch substanziellen nationalen Qualitätsverbesserung des Managements von Sarkom-Patienten. Auch die Spanische Sarkom-Research-Gruppe GEIS konnte den Effizienz-Effekt des Managements von Sarkom-Erkrankungen durch Multidisziplinäre Teams eindrücklich belegen [2] (2019): So zeigte sich ein um annähernd 25% besseres rückfallfreies 5-Jahres-Überleben, wenn die Biopsie an einem Referenz-Zentrum versus an einem Lokalspital durchgeführt wurde, und ein ca. 15% besseres 5-Jahres-Gesamtüberleben von Sarkom-Patienten mit Management an Referenz-Zentren gegenüber Patienten an Lokalspitälern.

Primäres Ziel und Aufgabe des überregionalen Schweizerischen Sarkom-Netzwerks (SSN) ist deshalb die ab initio interdisziplinär orchestrierte, zeitnahe «state-of-the-art»-Abklärung, Behandlung, Betreuung und Verlaufsbeobachtung von Patienten mit sarkomatösen Erkrankungen. Dies erfolgt im nationalen und internationalen Austausch, im Sinne eines überregionalen krankheitsbezogenen Services, der sich nicht auf geographisch-politisch definierte Institutionen/Grenzen beschränkt.

Vertragliche SSN Mitglieder sind derzeit folgende Institutionen: die Kantonsspitäler Winterthur (KSW), Chur (KSGR), Bellinzona (EOC), Luzern (LUKS), Stadt-Spital Triemli/Waid, die Klinik Hirslanden Zürich, sowie das Pathologie-Institut Enge Zürich, mit Affiliation der Sarkom-Referenzpathologin.

Fallbasierte Kooperationen bestehen mit zahlreichen weiteren Institutionen und Praxen.

In früheren Artikeln wurde das SSN vorgestellt ([3,4] 2018), beziehungsweise die Kennzahlen der bis damals erfassten/behandelten PatientInnen gezeigt ([5] 2020).

Mit dem vorliegenden Beitrag sollen die Kennzahlen der letzten 4 Jahre – basierend auf der SSN Sarkomboard-Register-Dokumentation – aktualisiert, und erste Resultate (‹outcome›-Daten) präsentiert werden.

2. SSN-Resultate (Abbildungen 1–14) aus dem Zeitraum vom 01.01.2018 bis 31.12.2021

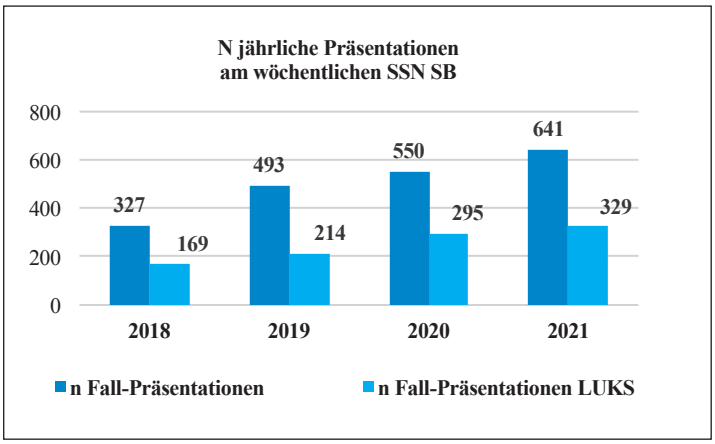


Abb. 1: alle Fallpräsentationen (1.-Präsentationen und Follow-Up-Präsentationen) am wöchentlichen SSN-Sarkomboard (SB) (LUKS-Präsentationen Teilmenge aller Fall-Präsentationen) im Zeitraum 2018–2021

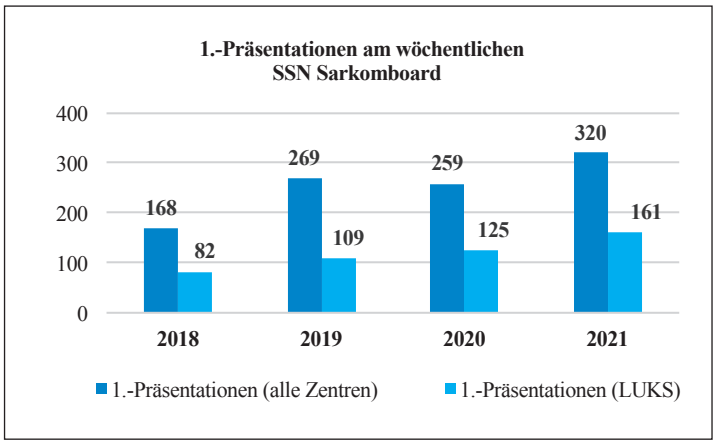


Abb. 2: 1.-Präsentationen am wöchentlichen SSN-Sarkomboard (LUKS-Präsentationen Teilmenge aller Fall-Präsentationen) im Zeitraum 2018–2021

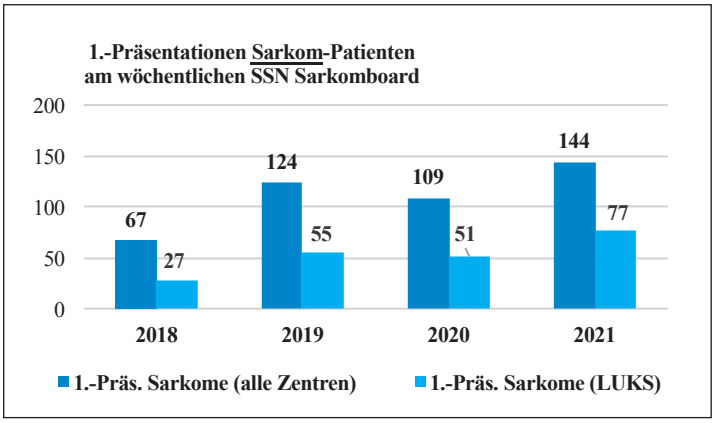


Abb. 3: *1.-Präsentationen von Patienten mit Sarkom-Diagnose (LUKS-Präsentationen Teilmenge aller Fall-Präsentationen) im Zeitraum 2018–2021*

1.-Präsentationen	2018	2019	2020	2021	gesamt
benigne	58	79	75	86	298
SARKOME	67	124	109	144	444
Simulatoren	17	31	23	21	92
Metastasen	5	10	7	13	35
andere	35	28	47	49	159
alle	**182**	**272**	**261**	**313**	**1028**

Abb. 4: *alle SSN-Erstpräsentationen im Zeitraum 2018–2021, gelistet nach Diagnosen*
(Simulator: bildgebend muss der Verdacht eines Sarkoms in Betracht gezogen werden. Eine bioptische Aufarbeitung zeigt aber, dass es sich um eine Läsion handelt, die nicht einem durch die WHO definierten Tumor entspricht, z.B. Infektion, altes organisiertes Hämatom, Metallabrieb bei liegender Prothese usw.)

Indikationen für FU-Präsentation	n	%
im Zusammenhang mit der Initialbehandlung	631	70
1. Lokalrezidiv	47	5
1. systemisches Rezidiv	40	4.5
wichtige FU-Information	24	2.5
andere	162	18
gesamt	**904**	**100**

Abb. 5: *Follow-Up (FU) Präsentationen im Zeitraum 2018–2021, analysiert nach dem Grund der Vorstellung*

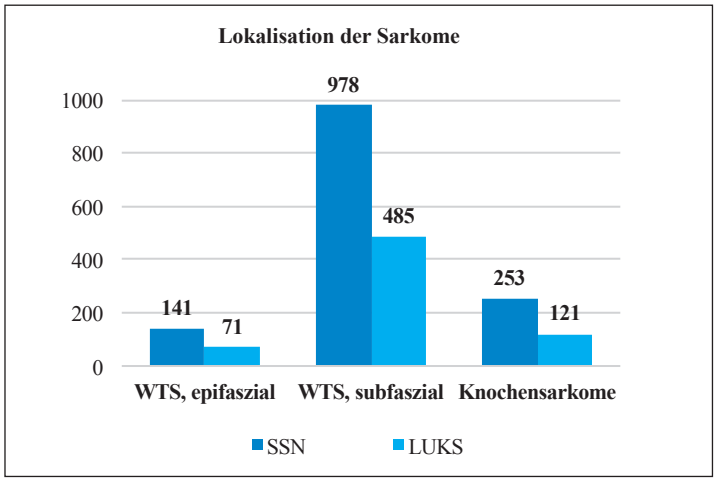


Abb. 6: *Sarkom-Lokalisationen präsentiert im Zeitraum 2018–2021 (LUKS-Präsentationen als Teilmenge aller Fall-Präsentationen)*

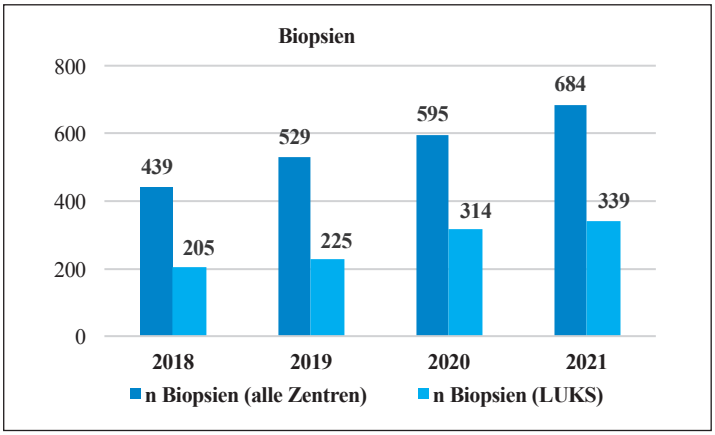


Abb. 7: *Anzahl erfolgter Biopsien zur Diagnosesicherung im Zeitraum 2018–2021 (LUKS-Präsentationen Teilmenge aller Fall-Präsentationen)*

Häufigste Diagnosen	N	%
Lipome	180	9.3
undifferenziertes/unklassifiziertes Sarkom	141	7.3
Dedifferenziertes Liposarkom	125	6.5
nicht-neoplastisch/Tumor-Simulator	118	6.1
Leiomyosarkom	96	5
atypischer lipomatöser Tumor / gut diff. Liposarkom	92	4.8
Myxofibrosarkom	54	2.8
Desmoid-Typ Fibromatosis	53	2.7
Total	**859**	**44.40%**

Abb. 8: *Häufigst gestellte histopathologische Diagnosen aller SSN-Fälle im Zeitraum 2018–2021*

OP-Indikation	N	%
1.-OP	377	83.5
OP nach WHOOPS	31	7
OP Lokalrezidiv	21	4.5
OP pathol. Fraktur	7	1.5
andere	16	3.5
gesamt	**452**	**100**

Abb. 9: *Indikationen für Operationen der SSN-Sarkom-PatientInnen im Zeitraum 2018–2021*

Strahlentherapie	N	%
kurativ präoperativ	122	86
kurativ postoperativ	7	5
definitiv	6	4
palliativ	6	4
gesamt	**141**	**100%**

Abb. 10: *Anzahl erfolgter Radiotherapien der SSN-Sarkom-Patienten im Zeitraum 2018–2021*
(Basierend auf den Daten des prosp. rand. Canadian Trials (2002) soll bei indizierter Kombination der Operation mit einer Strahlentherapie das **präoperative** Vorgehen gewählt werden [6,7].

Systemtherapie	N	%
Kurativ neoadjuvant	34	49
Kurativ adjuvant	13	19
palliativ	23	32
gesamt	**70**	**100%**

Abb. 11: *erfolgte Systemtherapien bei SSN-Sarkom-PatientInnen im Zeitraum 2018–2021, gelistet nach der Intention*

Qualitäts-Indikatoren für die Lokaltherapie	%
1) Radikalität der Operationen	>95% R0 <5% R1 0% R2
2) Wundkomplikationsrate nach kurativer RT&OP	<5%
3) Lokalkontrolle	>95%

Abb. 12: *Qualitäts-Indikatoren zum lokalen Outcome nach Sarkom-Behandlungen im Zeitraum 2018–2021:*

- *Radikalität der Operation*
- *Wundkomplikationsrate nach Kombinationstherapie mit präoperativer Radiatio*
- *Lokalkontrolle*

	2018	2019	2020	2021
n WHOOPS Läsionen/Jahr	19	48	27	28
n 1.-Präsentationen/Jahr	168	269	259	320
% WHOOPS der 1.-Präsentationen	**~11%**	**~28%**	**~10%**	**~9%**
n Sarkom1.-Präsentationen/Jahr	67	124	109	144
% WHOOPS der Sarkom-1.-Präsentationen	**28%**	**39%**	**25%**	**19%**

Abb. 13: *Entwicklung der Anzahl WHOOPS-Eingriffe im SSN-Einzugsgebiet (aktuell wird noch jeder 5. Patient im SSN-Einzugsgebiet initial nicht unter den erforderlichen onkologischen Gesichtspunkten, ausserhalb eines Sarkomboards, anbehandelt).*

‹Whoops lesion› = ungeplante Exzisionen von Weichteilsarkomen ohne vorangehende Diagnostik resp. Bildgebung. Whoops-Läsionen kommen bei 20–50% aller Patienten mit Weichteilsarkomen vor. Whoops-lesions' sind assoziiert mit einer erhöhten Rate an Lokal-Rezidiven und schlechterer Prognose.
Hierzu liegen u.a. Daten des Kanadischen Sarkom-Zentrums in Toronto vor, die den prognostisch ungünstigen Einfluss nach Whoops-Eingriffen deutlich machen [8] (2018): Die 5-Jahres-Lokalkontrollrate nach Operationen mit tumorfreien Rändern betrug 96%, nach geplant positiven Rändern noch immer 90%, bei whoops lesions 82%, nur nach versehentlich positiven Resektions-Rändern noch tiefer mit 72% (p<0.001).

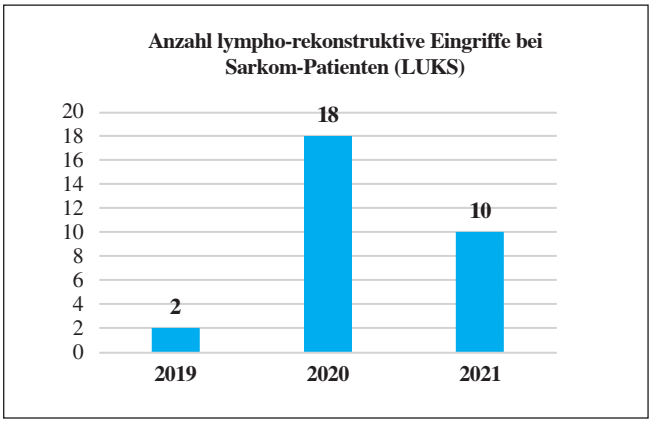


Abb. 14: *durchgeführte lympho-rekonstruktive Chirurgie im Rahmen der Erst-Operation bei Sarkom-PatientInnen (durch Koautor MS, der das Vorgehen bei Sarkom-Operationen eingeführt hat) [9-12] – mit dem Ziel der Verhinderung oder Behandlung eines distalen Oedems bei Sarkom-Therapien v.a. von Extremitäten/Becken*

3. Kontaktaufnahme mit dem SSN

Ich möchte einen Fall präsentieren am SSN Sarkom-Board LUKS:

– Informationen unter:
www. swiss-sarcoma.net

– Anmeldungen für Fallpräsentationen am wöchentlichen Sarkomboard:
office@sarcoma.surgery

Kontaktierung bei Verdacht auf / bei bereits gesicherter Sarkom-Diagnose:

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info@sarkom-schweiz.ch

Websites:
swiss-sarcoma.net | www.sarcoma.surgery | www.sarcoma.academy

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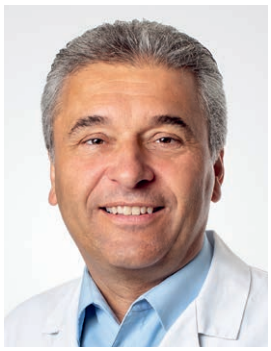
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Development of a value-based healthcare delivery model for sarcoma patients

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Summary

The urgent need to restructure healthcare delivery to address rising costs has been recognised. Value-based health care aims to deliver high and rising value for the patient by addressing unmet needs and controlling costs. Sarcoma is a rare disease and its care is therefore usually not organised as an institutional discipline. It comprises a set of various diagnostic entities and is highly transdisciplinary. A bottom-up approach to establishing sarcoma integrated practice units (IPUs) faces many challenges, but ultimately allows the scaling up of quality and outcomes of patient care, specific knowledge, experience and education. The key for value-based health care – besides defining the shared value of quality – is an integrated information technology platform that allows transparency by sharing values, brings all stakeholders together in real-time, and offers the opportunity to assess quality of care and outcomes, thereby ultimately saving costs. Sarcoma as a rare disease may serve as a model of how to establish IPUs through a supraregional network by increased connectivity, to advance patient care, to improve science and education, and to control costs in the future, thereby restructuring healthcare delivery. This article describes how the value-based health care delivery principles are being adopted and fine-tuned to the care of sarcoma patients, and already partially integrated in seven major referral hospitals in Switzerland.

Starting point

Cost explosion in health care is a global issue. In 2018, many western countries spent roughly 10% – the USA even 17.7% – of their gross domestic product (GDP) on health care [1]. There is global consensus that the value per spent dollar needs to be optimised [2, 3]. Value-based health care (VBHC) aims to deliver high and rising value for the patient, addressing *unmet needs* and controlling costs. Sarcoma care deals with a rare disease and is therefore usually not organised as an institutional discipline; it comprises a set of various diagnostic entities and is highly transdisciplinary.

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Value-based healthcare delivery model

Porter et al. described a healthcare legacy structure, which emerged over decades [4–8]. Such a *siloed system* is organised within disciplines and institutions, provides fee-for-service and measures process compliance, without extramural exchange (fig. 1).

Such systems allow various stakeholders to succeed, but not necessarily the patient. Many support the concept of regionalisation of care based only on patient volume as a key strategy for quality and outcome improvement, specifically for surgical disciplines. However, high volume by itself does not guarantee good outcomes, especially when bad processes are being reinforced by high-volume repetition, without assessing quality indicators [9, 10]. Simply advancing structural changes without process improvements is like pushing on a string [11]. The fundamental purpose and goal of health care is to deliver high and rising value for patients, with value being defined as the *outcomes and quality of care* over the total costs of *delivering these outcomes throughout the entire health cycle* [3, 12]. The key for VBHC – besides defining the shared value of quality – is an integrated information technology platform that allows transparency by sharing values, brings all stakeholders together in real-time, establishes transparency and offers the opportunity to assess quality of care and outcomes, and thereby ultimately saving costs.

Integrated practice units

For the implementation of a VBHCD-based system, the following key steps are required:

(1.) Structuring of an integrated practice unit (IPU) organised around a medical condition by delivering care in a transdisciplinary team whose members devote a significant amount of time to the condition (fig. 2) [13]. An IPU works in dedicated multidisciplinary facilities including all dis-

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ciplines under one roof, and takes responsibility for the full cycle of care. Within the IPU, outcomes, costs, care processes and patient experience are routinely measured and shared on a common platform. The team accepts joint accountability for outcomes and costs, and meets regularly, formally and informally, to discuss and improve care plans, results and processes.

(2.) Outcome measurement with value: Outcomes are measured by condition, not for specialties or procedures, and measurement covers the full cycle of care. They are multidimensional and include what matters most to patients, not just to physicians. Initial conditions and risk factors are standardised for each condition and are measured in the line of care.

Figure 1: The legacy system evolved over decades and is based on individual silo solutions of single institutions without exchange. The value-based system builds on shared commitment to defining and assessing quality and outcome using a shared information technology platform. Such an integrated system will prepare our health system to meet the opportunities of the fourth industrial revolution.

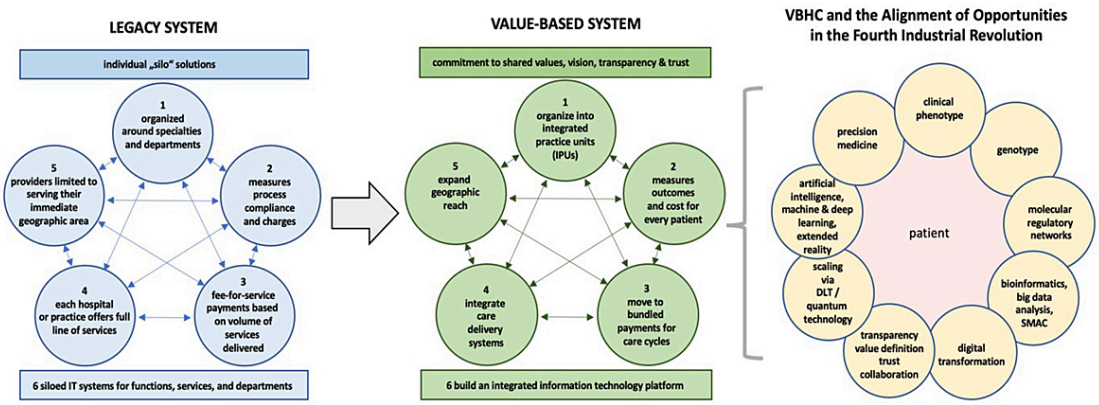
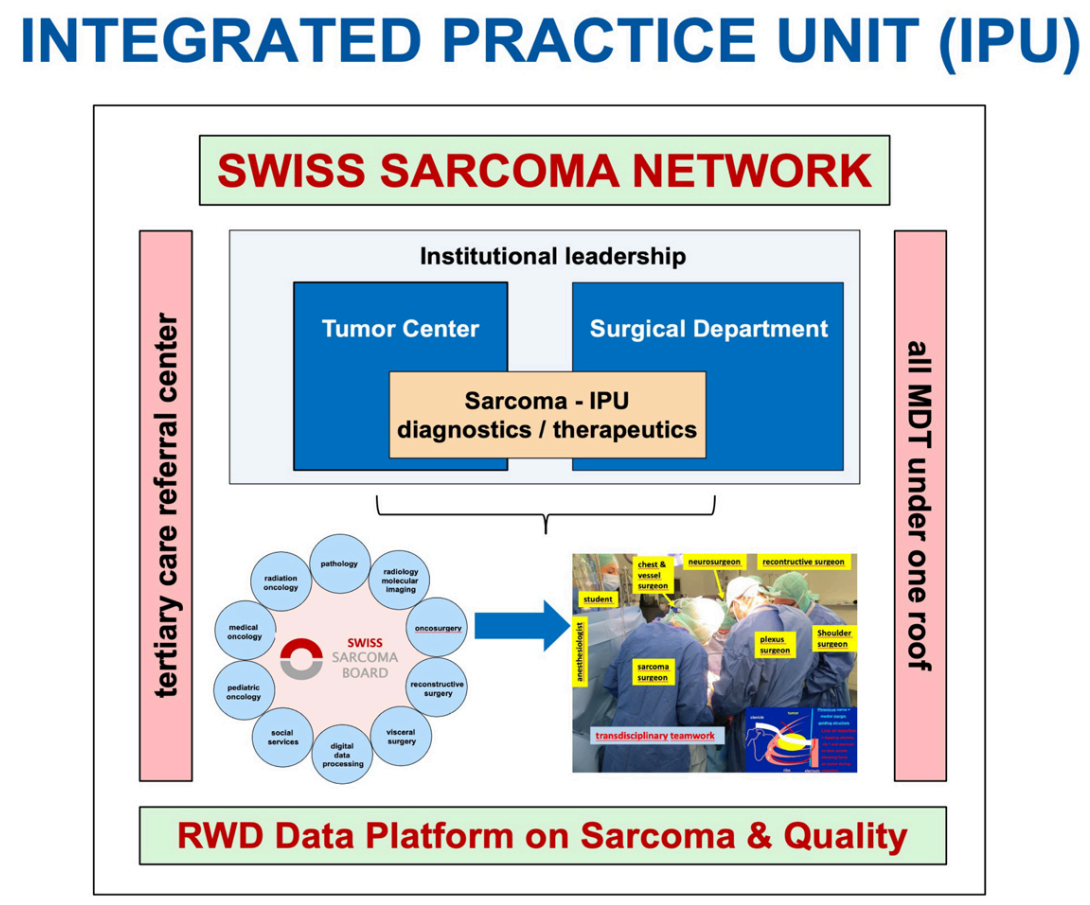


Figure 2: Sarcoma not being a discipline, the sarcoma IPU is built from the surgical transdisciplinary teams and the tumour centre with its associated disciplines. Sharing a common information technology real-world data platform, the sarcoma IPUs can be scaled up across the country.



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(3.) Alignment of reimbursement with value:

– *Cost aggregation* must include the total costs of providing the care for the patient's medical condition that matters for value, not the cost of any individual service or intervention.
– *Cost allocation* includes the allocation of shared costs to individual patients on the basis of each patient's actual use of the resources involved, not the average use.

(4.) Systems integration aims to shift the current confederation of stand-alone units/facilities to clinically integrated care-delivery systems.

(5.) Geographic expansion: The strategic principles for the geographic and value model organise care by condition in IPU hubs, where services are allocated across the care cycle to sites based on capabilities, care complexity, patient risk, cost and patient convenience, while incorporating telemedicine, home services and affiliated provider sites [14]. The IPU develops a formal system to direct patients to the most appropriate site.

(6.) Integrated technology platform: Attributes of a value-based information technology platform include all types of data for the full care cycle using standardised definitions and terminology, allowing storage and extraction from a common warehouse, with the capability to aggregate, extract, run analytics and display data in real-time by condition and over time. The warehouse enables the capture and aggregation of outcomes, costing parameters, and billing capacities for bundled payments.

Opportunities

Traditional sarcoma centres function in institutional silos at best, without a common language for exchange between centres or in the referral network, and therefore not specifically referring to a definition of patient value in terms of outcome and quality over the full cycle of care. They also do not provide the opportunity for patient-centred cost alignment. Conversely, the sarcoma IPU importantly highlights the need to focus on the patient as the centre around whom the entire care cycle needs to be organised in order to explicitly define and assess quality and outcome, entailing adoption of the proposed system change.

What does the future of patient care look like? Medicine's most fundamental element remains the relationship between the patient and the physician, which must therefore be at the heart of health care and which has been a constant across cultures and centuries [15]. Team work with a coordinating physician leader is the bedrock principle for success, and is strengthened through the introduction of a sarcoma IPU.

Challenges

Current structures aim to geographically centralise patient volumes independent of quality indicators, and there is continued debate regarding an organisational shift towards networks [16]. Whereas it is undoubtedly correct to centralise care of complex patients, territorial centralisation has the downside of separating the centre from the periphery. The DKG (Deutsche Krebsgesellschaft), for example, has established process-based criteria for the definition of sarcoma centres which ultimately allow at best only two thirds of all sarcoma patients to be treated at such a centre (www.krebsgesellschaft.de). The largest existing dataset from the National Cancer database shows that only 3310 patients were treated in high-volume centers (defined as centres treating >20 soft tissue sarcoma patients only per year!), whereas 22,000 patients were treated in low-volume centres [10]. Various demographic and socio-cultural reasons obviously prevent patients from travelling, and as long as there are no networks – in which surgical complexity allows centralisation – covering the entire country, these numbers will remain unchanged. The inclusion of all sarcoma patients must be the goal, and therefore collaboration in a network is indispensable [17].

Digital opportunities enable unprecedented connectivity and transparency, which above all will advance the knowledge and experience of all network experts without geographic exclusion. Digital connectivity also allows the spread of a common language with aligned definitions on every aspect of disease and therapy. Such a system allows the definition of quality and complexity care indicators based on which centralisation to units with the most experience (and not for territorial reasons) for the patient's needs will become possible, which is the base of personalised medicine.

Today, 21st century medical technology is often delivered with 19th century organisational structures, management practices and pricing models. The consumer cannot fix the dysfunctional structure of the current system. Healthcare workers are caught within the system, and various incentives prevent current structures from changing and improving. A reset is required, and value-based delivery provides the horizon. The driver to alignment of all unmet needs is the digital real-world data platform, providing a common language for all quality indicators and value definitions to enable transparency, operational efficiency and effectiveness, with instant real-time access for all involved stakeholders.

Outlook

Healthcare transformation is well underway. Value-based thinking is restructuring the organisation of care, outcome measurement, personalised payment models and health system strategy. Standardised outcome measure sets and new costing practices ultimately accelerate value improvement. Government and legal bodies will have a critical role in this process. They can require universal measurement and reporting of provider health outcomes, help shift the reimbursement systems to bundled payments for cycles of care instead of payments for discrete treatments or services, remove obstacles to the restructuring of healthcare delivery around the integrated care of medical conditions, open up competition among providers and across the country, and set policies to encourage greater responsibility of individuals for their health and their health care. Physicians have to define quality indicators and start measuring outcome indices for all medical conditions, thereby providing the base for a value-based healthcare system.

Where are we in Switzerland?

The members of the SwissSarcomaNetwork (SSN; www.swiss-sarcoma.net) comprise all institutions that are

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willing to consecutively assess and share their transdisciplinary sarcoma data within a prospective real-world data platform (prospective RWD Sarcoma Registry of Quality). Within this national network, transdisciplinary sarcoma care is being organised in IPUs across the country. On the international level, SSN is an official member of SELNET, a Sarcoma European and Latin American network which is supported by a Horizon 2020 framework programme of the European Union, and is thereby embedded in the largest existing sarcoma network of multidisciplinary clinical and translational sarcoma experts aiming to improve diagnosis and clinical care in sarcomas.

Together with an international advisory board of world-renowned sarcoma experts from the world sarcoma network, sarcoma quality indicators of work-up, of the weekly Sarcomaboard/MDT tumour conference, of the complexity of treatment, of the outcome as well as of PROMS/PREMS are being defined, totalling more than 70 parameters. These quality metrics and results of their descriptive analysis are automatically generated from the registry and visualised in real-time on an interactive website for all SSN members, thereby enabling the quality management system which has been required by law in Switzerland since April 2021. With such a set-up, predictive outcome analysis becomes ultimately possible. As a next step in the future, a cost tag will be attributed to each structured data parameter in the registry to assess the costs over the entire healthcare cycle, thereby letting VBHC become a reality. To further extend the quality efforts internationally, the Sarcoma Academy (www.sarcoma.academy) was founded to facilitate exchange between international sarcoma experts through sarcoma webinars and forums.

Conflict of interest

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

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Article

Definition of the Surgical Case Complexity in the Treatment of Soft Tissue Tumors of the Extremities and Trunk

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Simple Summary: Soft tissue tumors are heterogeneous tumor entities that often require surgical intervention for treatment. While some tumors are easy to resect, others require extremely complex, interdisciplinary surgery depending on the tumor type, localization and biological behavior. Up to now, there has not been an instrument able to objectify the complexity of such a surgery; therefore, we attempted to establish a complexity score for the description of soft tissue tumor surgeries. Furthermore, we aimed to categorize surgeries in such a way that patients can be assigned the best treatment such that a cost-effective approach can be taken.

Abstract: Background: We intend to establish a complexity score for soft tissue tumor surgeries to compare the complexities of different soft tissue tumor surgeries and to ultimately assign affected patients to appropriate treatments. Methods: We developed a soft tissue tumor complexity score (STS-SCS) based on three pillars: in addition to patient-related factors, tumor biology and surgery-associated parameters were taken into account. The STS-SCS was applied to our sampling group of 711 patients. Results: The minimum STS-SCS was 4, the maximum score was 34 and the average score 11.4 ± 5.9. The scores of patients with malignant diagnoses were notably higher and more widely scattered than those of patients with benign or intermediate malignant tumors. To better categorize the complexities of individual surgeries, we established four categories using the collected data as a reference dataset. Each of the categories contained approximately one-quarter of the registered patients. Discussion: The STS-SCS allows soft tissue tumor surgeries to be retrospectively evaluated for their complexity and forms the basis for the creation of a prospective concept to provide patients with the right intervention in the right geographic location, which can lead to better results and provision of the most cost-effective overall treatment.

Keywords: soft tissue tumors; complexity score; sarcoma

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1. Introduction

Soft tissue tumors are rare, and affected patients often initially present to general practitioners or orthopedic surgeons [1]. The clinical differentiation between benign and malignant lesions is often very difficult, and even highly malignant soft tissue tumors are often misdiagnosed as benign tumors [2]. A reliable diagnosis can often only be made by biopsy, which is the only way to determine the histological subtype and grade according to the FNCLCC system [2]. Unfortunately, soft tissue sarcomas are often not primarily

recognized as such, so the term "whoops procedure" describes the situation where a lump is incompletely removed by a surgeon who is not aware of the malignancy of the soft tissue tumor. In this case, extensive subsequent re-excisions are often required as residual tumor tissue is a risk factor for local recurrence [3].

Surgery is the mainstay of therapy for both benign and malignant soft tissue tumors. Sarcomas originate from the entire skeleton and surrounding soft tissues and display various biological behaviors that are dependent on the biologic entity. The goal of surgery is complete en bloc resection with avoidance of positive margins, whenever possible, to reduce the risk of local recurrences, distant metastases and mortality [4]. Surgical techniques of resection are various and often depend on the anatomic site of the lesion. Furthermore, while some resections are followed by complex reconstructions, others require no further surgical interventions. In addition, chemotherapy and radiotherapy are considered important pillars of multimodal and transdisciplinary sarcoma treatment, either preoperatively, postoperatively or in combination. All of these aspects are evidence that surgery for soft tissue sarcomas is a highly complex transdisciplinary action that needs to be personalized for each patient's specific situation.

There is much debate regarding centralization of complex surgery to reduce costs; however, there are no robust data to define surgical complexity, which is obviously a critical determinant because there is a wide spectrum for a given disease. Defining the complexity of surgical resection in terms of center-based medicine is important for several reasons. As early as 1979, Luft et al. postulated a correlation between the surgical volume and mortality. They showed that for various complex interventions, mortality seemed to be inversely proportional to the volume of operations [5], which was also confirmed by others [6]. Despite a wealth of data, recent studies have highlighted various challenges facing centralization efforts [7]. Volume-based morbidity improvements do not seem to be transferrable to all surgeries, with some studies concluding the opposite [8]. A high surgical volume does not guarantee a good outcome for all types of surgeries, and poor processes may become naturalized in centers due to frequent repetition [7].

Modern healthcare concepts, therefore, include integrating the complexity of a procedure and the complexity of a patient (with associated comorbidities) to determine the optimal location for care [9]. With the advent of value-based healthcare delivery, the definitions of quality and outcomes are pivotal to defining the value for the patient, in addition to the cost package over the full care cycle. In most hospitals, costs are still defined by diagnosis/volume-based accounting systems, which by no means reflect the complexity of soft tissue sarcoma surgery. For all these reasons, we aimed to establish a score for the complexity of soft tissue tumor surgery to enable comparison within a diverse surgical spectrum. As sarcomas are rare, occur in all anatomic locations of the body and their treatment is highly multidisciplinary, surgical treatment involves a wide spectrum of complexity, includes both resections and reconstructions and may, therefore, ideally be suited to such an analysis of surgical complexity.

2. Materials and Methods

2.1. Study Population

All surgeries on soft tissue tumors over a 15-year period performed by a single surgeon were registered in the AdjumedCollect "Sarcoma Surgeon's Registry" (Adjumed Services AG, Zurich, Switzerland; www.adjumed.ch (accessed on 22 October 2021)). The AdjumedAnalyze tool (Adjumed Services AG, Zurich, Switzerland) can be used for basic statistics, such as combinations of parameters, and allows the extraction of data. The individual scores were subsequently calculated in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

2.2. Soft Tissue Tumor Surgery Complexity Score (STS-SCS)

Based on the literature and expertise of experienced sarcoma surgeons, we compiled and defined relevant parameters for an STS-SCS. The score is essentially based on three pillars: the patient, tumor biology and surgery-based parameters (Figure 1).

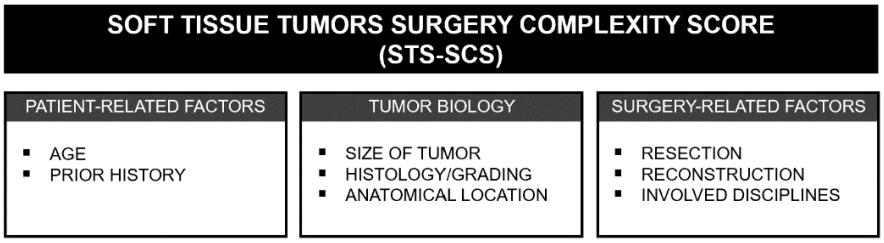


Figure 1. Overview of the three pillars and the individual factors on which the STS-SCS is based.

In the first pillar, patient-related factors such as age and prior history—in particular, previous radio- or chemotherapy—were summarized. It was shown that elderly patients with soft tissue sarcomas of the extremities have lower overall survival compared with younger patients [10]. Neoadjuvant therapies such as radio- or chemotherapy play an increasing role in the treatment of soft tissue tumors and must be included in perioperative management. The number of available neoadjuvant modalities is constantly increasing, and the use of possible therapies must be individually assessed due to the heterogeneity of tumors. Patients with advanced disease, in particular, can often benefit from neoadjuvant therapy modalities, but there are also associated risks. For example, neoadjuvant radiotherapies may lead to wound-healing disorders, while chemotherapies can lead to a delay in surgical treatment or even tumor progression during chemotherapy. In addition, complications during neoadjuvant CHT can significantly delay surgery and prolong the overall treatment time [11]. Previous whoops operations for misjudged soft tissue tumors also complicate perioperative management and often entail excessive re-excisions to reduce the risk of local recurrence [3].

For patients with soft tissue tumors, it has been shown that the smaller the tumor at diagnosis, the better the prognosis [12]. Histological grading seems to be the most important factor for the prognoses of patients with soft tissue tumors and, thus, has an even higher significance than histological typing [13]. In addition to the histological type, the anatomical location of soft tissue tumors also seems to be decisive. For example, it has been shown that metastases occur more frequently in patients with sarcomas of the lower extremities than the upper extremities, and that these tumors are, by far, more frequently larger and deeper [14]. The centralization of soft tissue tumor surgeries in high-volume hospitals can especially improve the survival of patients with non-low-grade and deep-seated tumors [15].

Due to the mesenchymal origin of sarcomas, these tumors often involve multiple anatomical structures and regions [16]. Depending on the location and proximity to surrounding organs, the removal of several structures may be necessary for sarcoma resection. If only soft tissues were removed, a score of 1 was assigned; if other structures such as muscles, nerves, bones, periosteum, tendons or vessels had to be removed, additional points were given. This challenge may require the expertise of different surgical subspecialties, so a multidisciplinary treatment team will include surgical oncologists from several different specialties such as orthopedics, thoracic surgery, general surgery, vascular surgery, neurosurgery, urology and gynecology as well as reconstructive plastic surgery. In addition to the interdisciplinary challenges, the involvement of vascular structures also seems to have an influence on the recurrence rate. It was shown that when the tumor was radiologically surrounded by large vessels, vascular resection and bypass reconstruction provided improved local control [17]. The involvement of vascular structures in a sarcoma significantly complicates surgery but is not, in itself, a contraindication for sarcoma resection [18].

Following sarcoma resection, reconstruction is often not necessary; however, in selected cases, patients may benefit greatly. Reconstructive procedures can be, at times, extremely elaborate, depending on the type and extent. The heterogeneity in tumor reconstruction was thus taken into account with a procedure-specific evaluation system. However, it is obvious that not all possible types of reconstruction can be adequately represented by a score, especially since the possibilities are very extensive and the indication for each patient is individual.

Finally, the previously identified relevant factors were examined for their individual influences on the complexity of surgery and weighted accordingly. This resulted in a total score (Table 1) based on the listed parameters and their corresponding weighting, which was then individually determined for each patient, using the data extracted from Adjumed, by adding the individual factors together.

Table 1. STS-SCS system indicating the weighting of each parameter.

			Points	**Maximum**
Patient's Age	≤17 years		1	
	18–64 years		0	
	≥65 years		1	1
Histology/Grading	Benign		1	
	Simulator		1	
	Intermediate		2	
	Blood-based solid tumor		3	
	Metastasis		5	
	Malignant	G1	5	
	Malignant	G2	6	
	Malignant	G3	7	7
Prior History *	Preoperative radiotherapy		2	
	Preoperative chemotherapy		2	
	Prior whoops		2	6
Size of Lesion	5 cm or less		1	
	more than 5 cm, but no more than 10 cm		2	
	more than 10 cm, but no more than 15 cm		3	
	More than 15 cm		4	4
Anatomical Location	Superficial		1	
	Deep		2	2
Resected Structures (soft tissue, muscles, nerves, bones, periosteum, tendons, vessels) **	1		1	
	2		2	
	3		3	
	4		4	
	5		5	
	6 or more		6	6
Type of Reconstruction ***	Mesh graft		1	
	Tendon/ligament reconstruction		1	
	Bone cementation		1	
	Open reduction internal fixation (ORIF)		1	
	Bone autograft		2	
	Bone allograft chips		2	
	Other bone reconstruction		2	
	Vessel reconstruction		2	
	Nerve reconstruction		2	

Table 1. *Cont.*

		Points	Maximum
	Lymphovenous reconstruction	2	
	Intra-abdominal reconstruction	2	
	Pedicled tissue transfer	3	
	Chest wall reconstruction	3	
	Free tissue transfer	4	16
Number of Involved Disciplines ****	One discipline	0	
	Two disciplines	1	
	Three disciplines	2	
	Four disciplines	3	
	Five and more disciplines	4	4
Total		max.	46

* The points in the section "prior history" can be added together, resulting in a maximum score of 6 in this field. ** For each resected structure (such as muscle, nerve, vessel, etc.) a point is added. *** The four highest scores in the section "type of reconstruction" are summed up. An intervention (for example, various nerve reconstructions) can be listed numerous times. **** If one single surgeon is sarcoma surgeon but has the credentials also for vascular reconstruction, then 2 disciplines are registered.

3. Results

3.1. Characteristics of Soft Tissue Tumor Patients

In this study, we examined the data of 711 patients. The mean age of the analyzed patients was 51.0 ± 18.2 years. Of the operated patients, 70% were between 18 and 64 years old. Males accounted for 383 of the patients, and 328 were females (Figure 2). The male-to-female ratio was 1.17. Of the patients, 263 had benign tumors (37%), 118 patients had tumors with intermediate malignancy (17%) and 270 patients suffered from malignant (38%) soft tissue tumors. The remainder of the patients (8%) had metastases, hematologic solid tumors or tumor simulators (a tumor that may imply a sarcoma on imaging but turns out to be a benign mesenchymal non-tumorous lesion). The most common benign diagnosis was, by far, lipoma (131 patients; 18%). We found that 51 patients (7%) had atypical lipomatous tumors, which are classified as tumors of intermediate malignancy. The most common malignant diagnosis was undifferentiated/unclassified pleomorphic sarcoma (UPS) (76 patients; 11%), followed by myxoid liposarcoma (42 patients; 6%) and myxofibrosarcoma (33 patients; 5%). Other diagnoses were much rarer.

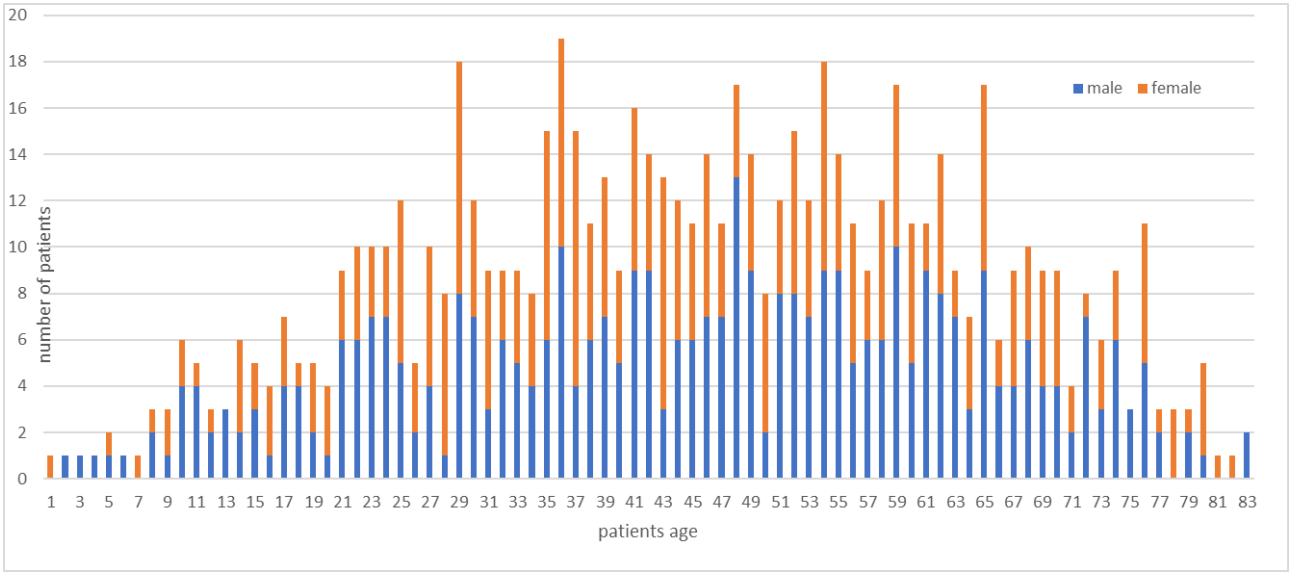


Figure 2. Age and gender distribution in the subject group.

3.2. Application of the STS-SCS

The STS-SCS was applied to our sampling group of 711 patients and the individual scores were calculated for each patient using Microsoft Excel. The minimum score was 4 and the maximum score 34, with an average score of 11.4 ± 5.9. The scores of patients with malignant diagnoses (17.5 ± 4.6) were notably higher and more widely scattered than those of patients with benign (6.8 ± 1.8) or intermediate malignant tumors (10.2 ± 4.1) (Figure 3).

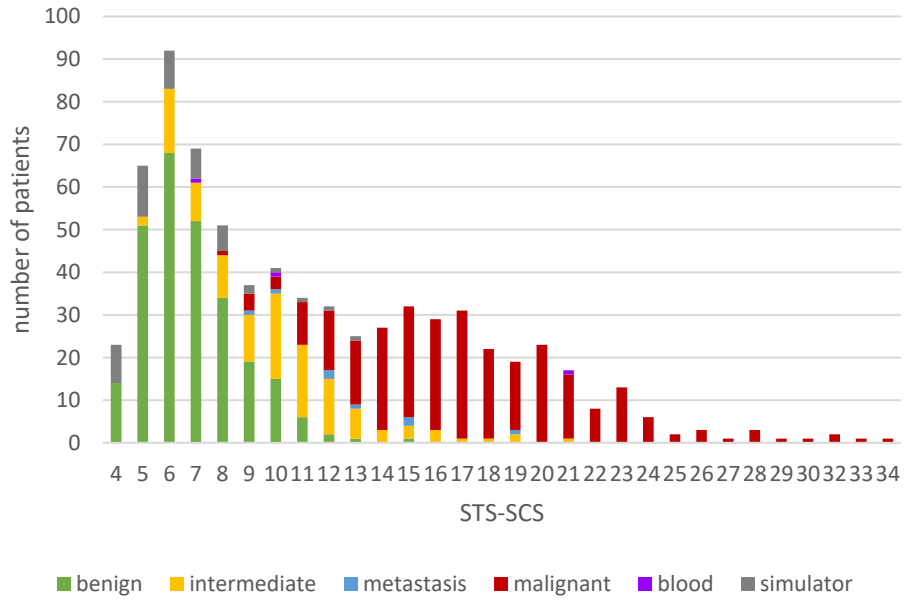


Figure 3. Distribution of the totals of the soft tissue tumor surgery complexity score (STS-SCS) in the sampling group.

3.3. Categorization of Soft Tissue Tumor Surgery Complexity

To better categorize the complexity of individual surgeries, we established four categories using the collected data as a reference dataset. Each of the categories contained approximately one-quarter of the registered patients (Table 2).

Table 2. Division of surgeries into four categories.

Category	Complexity Score	Number of Patients	Percentage (%)
1	≤6	180	25.3
2	7–9	157	22.1
3	10–15	191	26.9
4	≥16	183	25.7

Category 1 included patients with a score lower than 7 points. This covers a relatively wide range of scores and included 180 (25.3%) patients. This category contained patients with benign, intermediate malignant tumors and tumor simulators. Patients with a score of between 7 and 9 points were assigned to category 2, which covered only a very small range of points, but still included 157 patients (22.1%). Most patients in this range had benign or intermediate malignant diagnoses, but there were also a few malignant diagnoses. Category 3 included patients with a score of 10–15 points and comprised 191 patients (26.9%). In the highest category, 4, there were 183 patients (25.7%) with almost exclusively malignant diagnoses, with a few exceptions. The highest category covered the largest range, and the scores were further apart from each other than those in the lower categories (Figure 4).

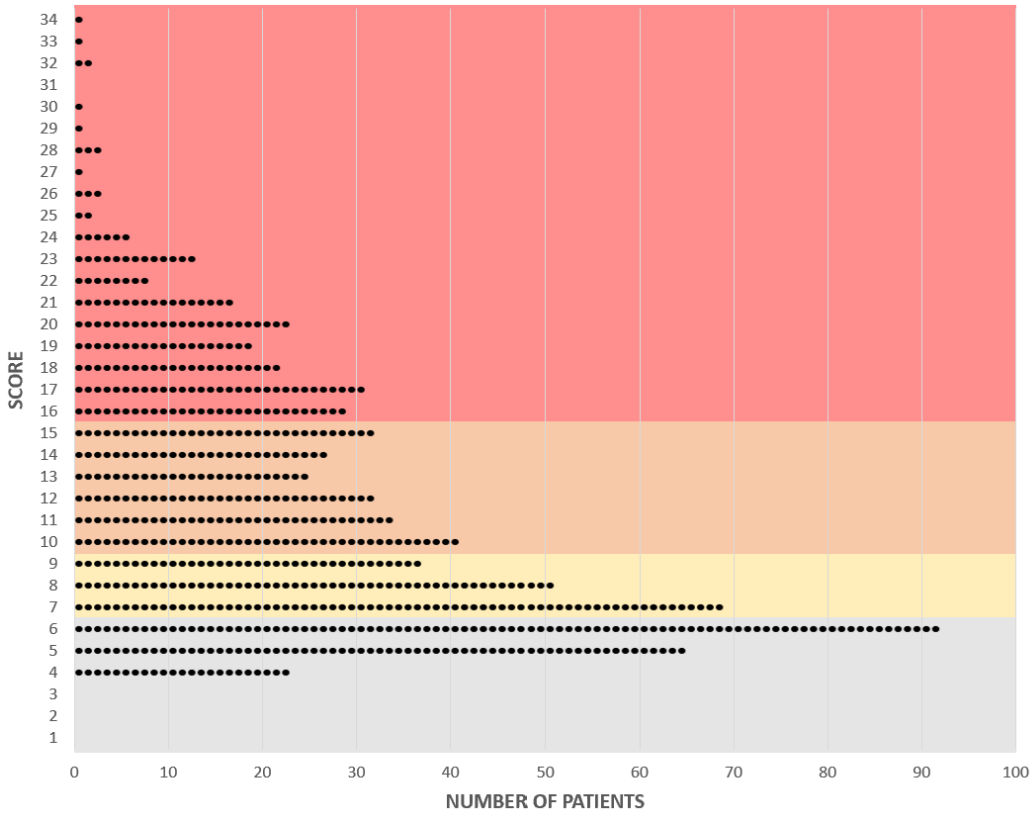


Figure 4. Graphical representation of individual scores and their allocation to the categories of complexity. Each point represents a patient. Category 1: gray, Category 2: yellow, Category 3: orange, Category 4: red.

4. Discussion

In our study, we defined the STS-SCS based on three main pillars: patient-related factors (such as age and prior history), tumor biology (tumor size, histology/grading and anatomical location) and surgery-associated factors, such as the type of resection and reconstruction or the involved disciplines. This score was then applied to a sample group of 711 patients with various soft tissue tumor diagnoses. An individual score was calculated for each of the subjects. Based on these data, four complexity categories were defined that allow the assignment of the individual surgeries to four complexity levels. This strategy allowed the assignment of each soft tissue tumor operation to a complexity level and, thereby, the comparison of the different interventions.

This is the first time such an approach has been attempted; therefore, there were no alternative methods for comparison, which made the selection and weighting of factors challenging. It will never be possible to include all potentially relevant factors to fully describe a patient (e.g., comorbidities), but the current STS-SCS is intended to establish a basis for discussion. Just as particularly complex patients may not be adequately represented, unusually complicated surgeries had to be broken down and, therefore, may not yet be adequately covered by the selected categories.

In the value-based geography of care according to Porter et al. [9], the best possible cost-effective quality care for the patient is defined by the complexities of the procedure and the patient, which in an integrated system, allows the direction of patients requiring complex care to regional or central hubs, while those patients who need less complex care are moved to the most cost-effective local centers (Porter geography model). To realize such a model of geographically-based care, a tool to assess and define the complexity of a surgical procedure is mandatory; we have proposed such a tool, the STS-SCS, which maps the considerations into a complexity score. The integration of patient- and procedure-related factors allows the patient to be matched to the best possible treatment site as well

as the optimal treatment team. Not only does the adequate allocation of patients increase the output, but it also allows the cost of treatment to be reduced for specific diseases or treatments [19]. Assigning the patient to the ideal treatment site seems to be an intuitive matter; however, its implementation, in practice, does not seem to be that easy, and the instruments for decision making are not yet available for sarcoma care. Therefore, the STS-SCS provides a tool to facilitate decisions related to the allocation of soft tissue tumor patients to appropriate treatment sites.

Considering complexity is not only important in terms of the treatment location but also the treatment team. Geography is a powerful tool to optimize value in three dimensions: the right mix of personnel, working together at the right location and with integration across time [9]. Porter et al. defined integrated practice units in which teams over a geographical region communicate and exchange to enhance the quality of care [9]. Patients with benign and malignant soft tissue tumors are often first seen by general practitioners or general and orthopedic surgeons, and making the correct diagnosis is often difficult, which frequently leads to unplanned excisions [20]. In addition, establishing the correct pathological diagnosis of a sarcoma is often difficult, and misdiagnoses often occur due to confusion with benign tumors [20]. Centralized pathological assessment of soft tissue tumors, for example, was shown to save costs while improving the quality of diagnoses [21]. Such an integrated exchange over a geographical region among multidisciplinary and cooperating integrated practice units helps to establish a complex diagnosis and initiate appropriate therapeutic measures [22]. The STS-SCS is an instrument that facilitates and objectifies the allocation of patients to the appropriate care site while considering their comorbidities and possible complications.

The definition of complexity for soft tissue tumor surgery using the STS-SCS also serves as a basis for assessing the quality of soft tissue sarcoma surgery. Up to now, it has been common practice to use the surgical volume as a predictor of the outcome [6], and for some soft tissue tumors, such as large, high-grade and retroperitoneal tumors, it has been shown that a good outcome is associated with a high volume [23,24]; similar results were also obtained for soft tissue tumors of the extremities [25]. Further to this, it has been shown that treatment in a multidisciplinary team improves the surgical margins for deep-seated lesions [26], while the French sarcoma group reported an impact on outcome by the multidisciplinary team approach, but interestingly not by surgical volume [27]. However, the definition of further quality indicators has been lacking until recently, which resulted in our intention to develop an approach to comprehensively assess the quality of sarcoma surgery. Certainly, and foremost, the quality of sarcoma surgery depends on the complexity of the procedure, which must be extensively considered when defining quality. Using the STS-SCS as a basis together with the extended database developed in the framework of this project, we can describe the complexity of a surgery as a common basis and, in a further step, use these tools to make considerations regarding quality.

The outcome for disease control and the quality of surgery not only depends on technical aspects but also on the correct diagnosis and, specifically, on the correct indication to perform the surgery [28]. Indication quality encompasses the appropriateness and necessity of medical interventions but continues to only be given a subordinate role in our current practice [28]. It is, therefore, crucial to establish scientific evidence and guidelines that facilitate the physician's assessment of the appropriateness of an intervention. The STS-SCS greatly facilitates the ability to bundle specific procedures or groups of similar procedures for comparison and analysis and, thereafter, extrapolate to define the indication quality for performing a specific soft tissue tumor resection or reconstruction, thus making the indication quality an entry point for the quality discussion. Once the quality of a surgery is defined, this information can be extrapolated to the choice of the correct indication for the surgery regarding evidence-based principles and standards, which include the results of clinical studies' and guidelines.

5. Conclusions

Currently, we are able to retrospectively assess surgeries according to their complexity using the STS-SCS, which was developed in our study. This score makes it possible, for the first time, to categorize soft tissue tumor surgeries based on their complexity, which allows patients to receive the right intervention or treatment at the right site, which may lead to better outcomes and more cost-effective treatment overall. Based on Porter's principles and the STS-SCS presented in this article, a prospective approach to model soft tissue surgery evaluation was developed to assign patients with soft tissue tumors to the appropriate surgery site based on their individual risk factors and planned surgical intervention.

Author Contributions: Conceptualization, A.F. and B.F.; data curation, A.F. and B.F.; methodology, A.F., P.H. and B.F.; project administration, A.F.; supervision, B.F.; visualization, A.F.; writing—original draft, A.F.; writing—review and editing, A.F., M.F.S., P.G., S.B., P.H. and B.F. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was approved by the ethics committee of the canton of Zurich (Basec no. 2019-01107).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

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Communication

Rethinking the Prognostic Role of Necrosis in Soft-Tissue Sarcoma: Multidisciplinary Insights from the Sarcoma Academy

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Simple Summary: Soft-tissue sarcomas are rare cancers that can arise almost anywhere in the body and come in many different forms. Because they vary so much, doctors have a hard time predicting how each tumor will respond to treatment. One common way to judge success has been to look at how much of the tumor appears dead (called "necrosis") after chemotherapy or radiotherapy. But this can be misleading, because some sarcomas are partly dead even before treatment, while others die off for reasons that have nothing to do with therapy. An international group of pathologists, surgeons, oncologists, and radiologists reviewed the latest evidence and agreed that a better yardstick is how much living (viable) tumor is left rather than how much is dead. They also highlighted new imaging techniques and shared pathology standards and real-world data projects that could make these measurements more precise and useful for patients.

Abstract: Background: Soft-tissue sarcomas (STSs) represent a heterogeneous group of malignancies with widely varying treatment responses and biological behaviors. While spontaneous necrosis (present at diagnosis) is recognized in established sarcoma grading

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systems, the prognostic significance of therapy-induced necrosis remains uncertain. Inconsistent definitions, methodological variability, and clinical confounders further complicate the interpretation of necrosis as an independent prognostic marker. **Methods:** This communication synthesizes findings from an international, multidisciplinary webinar hosted by the Sarcoma Academy, critically assessing the utility of therapy-induced necrosis in STS management. Discussions encompassed surgical, pathological, oncological, and radiological perspectives, emphasizing how necrosis is defined, measured, and contextualized in patient care. **Results:** Heterogeneity in STS subtypes, varied treatment protocols, and sampling inconsistencies challenge the prognostic value of post-treatment necrosis. While substantial necrosis may sometimes signal effective therapy, it can also reflect the tumor's aggressive nature. The panel underscored the utility of measuring the percentage of viable tumor cells, rather than necrosis alone, to obtain a more standardized and reproducible measure of therapy response. Emerging approaches—such as radiomics, molecular profiling, immune-based analyses, and real-world evidence (RWE) protocols—offer promising avenues for refining prognostication and guiding personalized therapy in STS. **Conclusions:** A focus solely on therapy-induced necrosis is insufficient to predict outcomes in STS. Instead, a multidisciplinary framework—combining standardized pathology protocols, quantification of viable tumor cells, advanced imaging, and innovative clinical trial designs—can better capture both treatment effects and underlying tumor biology. Future collaborative studies and hybrid trial methodologies are needed to determine which STS subgroups gain the most from intensified treatments aimed at maximizing necrosis, and how to balance such interventions with surgical considerations, toxicity, and overall patient well-being.

Keywords: soft-tissue sarcoma; tumor necrosis; prognostic marker; neoadjuvant therapy; radiomics; real-world evidence; hybrid trial design; personalized medicine

1. Introduction

Soft-tissue sarcomas (STSs) are a heterogeneous group of malignancies arising from mesenchymal tissues, encompassing more than 50 distinct histological subtypes [1]. Despite their rarity, STSs collectively pose significant clinical challenges due to variable responses to treatment, a broad range of biological behaviors, and limited consensus on optimal management strategies. One key histopathological feature that has garnered attention in both research and clinical practice is tumor necrosis. Traditionally, the presence and extent of necrosis have been recognized as important parameters within established sarcoma grading systems, such as the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system, which considers spontaneous necrosis (at diagnosis) alongside tumor differentiation and mitotic count to determine tumor grade and thereby stratify patient prognosis [2,3].

In high-grade osteosarcoma (and similarly in Ewing sarcoma), therapy-induced necrosis after neoadjuvant chemotherapy frequently correlates with improved overall and event-free survival, making it a statistically reliable—but not infallible—predictor [4–6]. Even in these bone sarcomas, some patients with high post-chemotherapy necrosis still experience relapses, emphasizing that necrosis alone does not capture the full complexity of tumor genetics, host factors, and microenvironment. Attempts to translate this necrosis-based concept to STS have proven more challenging. Unlike osteosarcoma—where relatively uniform histology and standardized chemotherapy protocols prevail—STSs include numerous subtypes with diverse biology and varied treatment regimens [7]. As a result, a simple link between extensive therapy-associated necrosis and better outcomes is not consistently

observed in STSs. Several additional factors, such as distinguishing spontaneous from treatment-related necrosis, contribute to the difficulty of establishing necrosis as a universal prognostic marker [8–10].

Consequently, many centers now quantify the percentage of residual viable tumor cells (%VTC) as a more reproducible indicator of treatment effect [11,12].

In this paper, the term "necrosis" will be used in two principal contexts. Spontaneous necrosis refers to tumor cell death arising from inherent tumor biology (for example, outgrowing its blood supply), whereas preoperative therapy-induced necrosis indicates cell death attributable to neoadjuvant interventions—whether chemotherapy, radiotherapy, or combined modalities. Where relevant, "response" follows the concept outlined by Wang and Palm, highlighting the proportion of viable tumor cells remaining as a standardized index of therapeutic effect [11]. This approach aligns with a growing consensus that STS research and clinical practice require more reproducible, refined outcome measures.

Against this backdrop, the Sarcoma Academy (www.sarcoma.academy) (accessed on 24 May 2025) organized a webinar (https://www.youtube.com/watch?v=hJgkeReNpEQ accessed on 24 May 2025) on 12 December 2024 to examine the evolving role of post-treatment necrosis in STS. The panel comprised pathologists, surgeons, radiation oncologists, medical oncologists, and researchers, all exploring necrosis from multiple angles: pathological assessment; correlations with treatment outcomes; integration into established grading systems; and the application of novel diagnostic tools, such as molecular profiling, advanced imaging, and immunologic characterization. Panelists were deliberately drawn from leading institutions across North America, Europe, South America, and Asia, selected on the basis of recent peer-reviewed work on therapy-induced necrosis, to ensure a balanced, globally representative perspective. Special focus was placed on the role of % viable tumor cells and other comprehensive measures of response, aiming to bolster prognostic accuracy and standardize assessments across institutions. Through these multidisciplinary presentations and discussions, participants pinpointed key knowledge gaps, debated contradictory findings, and charted potential paths for collaborative research. In this paper, we synthesize those insights, critically review the current evidence on necrosis in STSs, and propose strategies to improve both clinical decision-making and future investigative directions.

2. Pathology Overview

2.1. Defining Necrosis in STS

Necrosis in soft-tissue sarcomas can manifest through various microscopic patterns, each reflecting different underlying processes within the tumor. Coagulative necrosis is the most common type, featuring preservation of cellular outlines but loss of nuclear staining. Over time, these regions may display fibrosis of varying extent, hemorrhage residues, "ghost cells", or pseudocystic change, complicating the task of determining whether the cell death is therapy-induced or spontaneous. For instance, in myxoid liposarcoma, a notable reduction in tumor cell density (often replaced by fibrous tissue) may follow radiotherapy, whereas in other subtypes, partially destroyed cellular components may represent a transitional stage rather than definitive necrosis. Importantly, spontaneous necrosis (arising from intrinsic tumor aggressiveness or poor vascularization) must be distinguished from therapy-induced necrosis, which can reflect neoadjuvant treatment efficacy [2,3,13]. For research protocols, ultrasound-guided core-needle biopsy—targeted with color-Doppler or intravenous contrast—can precisely sample macroscopic necrotic zones and provide quantitative tissue confirmation of imaging findings.

Given these complexities, many investigators have proposed quantifying the percentage of viable tumor cells (% viable cells) rather than necrosis alone [11,12,14]. Unlike

necrosis, which can be challenging to measure consistently, "% viable cells" encompasses all non-viable tissue changes (necrosis, fibrosis, hemorrhage, inflammation, hyalinosis, or tissue maturation), providing a more holistic view of therapy impact. One caveat is that this snapshot fails to incorporate *baseline* necrosis—tumors already harboring extensive necrotic regions before therapy might still appear largely non-viable afterward, even without a strong cytotoxic effect. As a result, imaging-based or so-called "delta" approaches that compare pre- and post-treatment necrosis may capture treatment effectiveness more accurately. Nevertheless, "% viable cells" remains a more reproducible and standardized metric than conventional estimates of necrosis, aligning with emerging evidence on its prognostic value in STS [11,12].

Despite these advances, the FNCLCC grading system is designed exclusively for untreated tumors, thus focusing on spontaneous necrosis at initial diagnosis and excluding post-treatment changes. Moreover, pathology protocols for STSs—unlike standardized frameworks used in bone sarcomas—can vary in regard to how tissue blocks are selected, embedded, and interpreted [2,3,14–16]. Consensus-based guidelines for % viable-cell assessment are outlined in Section 4.3.

2.2. Heterogeneity of Necrosis

Multiple interrelated factors contribute to the broad variability in STS necrosis. Intrinsic tumor biology (growth kinetics, vascularization patterns, and molecular drivers) influences the degree of spontaneous necrosis and how the tumor responds to treatment. Treatment protocols also vary widely: standard fractionation radiotherapy may induce more gradual cell death than (ultra-)hypofractionated or dose-escalated regimens [17], and the addition of systemic chemotherapy can accelerate necrosis while simultaneously producing complex microscopic findings (e.g., inflammatory infiltrates or fibrotic transformation) [18].

The timing of surgery after neoadjuvant therapy further complicates interpretation. Tumors resected soon after high-dose radiotherapy or chemotherapy may not show the full extent of delayed cell death or tissue reorganization [19]. By contrast, an extended interval between therapy completion and resection can permit necrosis to evolve into fibrous or cystic areas that pathologists might interpret differently. In osteosarcoma or Ewing sarcoma, standardized grading systems (e.g., Huvos and Salzer-Kuntschik) explicitly quantify chemotherapy-induced necrosis, but no widely accepted equivalent exists for STSs beyond the EORTC-STBSG guidelines [14]. Developing or adapting such assessment schemas must account for STS heterogeneity to ensure that the measurement of necrosis is clinically meaningful.

This temporal dimension is therefore especially relevant to preoperative therapy-induced necrosis: the interval between completing neoadjuvant treatment and surgical resection can either mask or exaggerate the true amount of cell death related to preoperative treatment. Consequently, the adoption of "% viable cells" as a primary endpoint, alongside robust imaging assessments, remains key to harmonizing how STS therapy-induced response is measured across different institutions and timelines [11,12]. To facilitate inter-institutional consistency, we outline a template protocol—minimum one tissue block per cm of tumor, EORTC-STBSG-based viable-cell scoring, and concordant MRI/PET correlation—that will be circulated for multicenter validation and refinement.

3. Critical Analysis of Existing Evidence

3.1. Summaries of the Four Presented Studies

Dr. Dürr opened the webinar by sharing results from a large retrospective cohort of ~800 patients with both soft-tissue and bone sarcomas. This analysis compared spontaneous

(pre-therapy) necrosis in resected, untreated tumors with post-neoadjuvant necrosis (from chemotherapy and/or radiotherapy) across multiple STS subtypes. Although necrosis levels were higher after neoadjuvant therapy, no clear improvement in overall survival was observed—contrasting with high-grade osteosarcoma, in which therapy-induced necrosis often predicts favorable outcomes. Notably, spontaneous necrosis at diagnosis often correlated with more aggressive tumor biology and poorer prognosis, underscoring its established role in the FNCLCC grading system. Dr. Dürr concluded that necrosis, whether spontaneous or therapy-induced, should be interpreted within a broader clinical context that includes tumor subtype, surgical margins, and timing of resection [20]. This viewpoint challenges the assumption—extrapolated from bone sarcomas—that a higher percentage of necrosis alone translates to improved survival in STS patients. He proposed % viable tumor cells as a potentially more informative metric [11,12].

3.1.1. Bridging Perspective

Whereas Dr. Dürr's large-cohort data cast doubt on the universal prognostic value of therapy-induced necrosis in heterogeneous STS, Dr. Wang's work (presented next) offered a complementary perspective drawn from multicenter clinical trials [11,12]. The juxtaposition of these findings highlights the complexity of interpreting necrosis across different study designs, patient subsets, and therapeutic protocols.

3.1.2. Dian Wang, Rush University—RTOG 9415 and 0630 Trials [11,21]

Dr. Wang presented findings from two Radiation Therapy Oncology Group (RTOG) trials evaluating neoadjuvant therapy in STS: RTOG 9415, which combined chemotherapy and radiation, and RTOG 0630, which used preoperative radiation alone (50 Gy in 25 fractions) [11,21]. Both trials defined a complete response as no viable tumor cells in the resected specimen, encompassing all forms of non-viable tissue (necrosis, fibrosis, and hemorrhage). Although such profound responses were uncommon, patients who achieved them had notably improved disease-free, metastasis-free, and overall survival. Dr. Wang attributed these outcomes to the intensity and consistency of neoadjuvant regimens and emphasized that near-complete or complete tumor obliteration—if attainable—may have substantial prognostic implications in STS. At the same time, he acknowledged practical limitations, such as subtype variability and real-world adherence issues.

3.1.3. Arash Naghavi, Moffitt Cancer Center, HEAT Trial, and Precision Radiation

Dr. Naghavi discussed patients treated with radiation therapy alone, aiming for a "favorable pathologic response", defined as $\geq$95% necrosis—again, consistent with minimal residual viable tumor cells [11,12,22]. Achieving such a high response fraction correlated with an increased likelihood of R0 resection and prolonged progression-free survival, suggesting that radiation treatment alone can independently induce meaningful therapy-related necrosis. He also introduced the HEAT trial's "habitat-based" dose-escalation protocol, wherein hypoxic or resistant tumor regions ("radiomic habitats") receive higher doses. Preliminary data indicate that this approach can increase the extent of non-viable tumor tissue, potentially enhancing local control. Complete (100%) response remains challenging, but even partial improvements in non-viable tissue can confer prognostic benefits.

3.1.4. Julien Montreuil, University of Miami—Diverse Cohort Analysis

Dr. Montreuil presented an STS cohort treated with varied neoadjuvant regimens (including adjuvant brachytherapy) or none at all. Nearly half of the patients who received no neoadjuvant therapy exhibited $\geq$90% necrosis in their tumors, suggesting that spontaneous necrosis alone can be substantial. This finding challenges the notion that extensive necrosis automatically reflects effective treatment. Instead, Montreuil emphasized the role of surgi-

cal factors—particularly achieving clear margins and avoiding unplanned excisions—in predicting local control and overall survival, as confirmed later in the discussion. His group concluded that while therapy-induced necrosis remains an important observation, quantifying its actual contribution to the prediction of oncologic outcomes requires novel methodologies such as liquid biopsy or radiomics to isolate the specific "delta" necrosis attributable to treatment.

3.2. Challenges in Prognostication

Accurately interpreting necrosis in STSs is hampered by inconsistent thresholds—some protocols consider ≥90% necrosis as a good response, whereas others require ≥95% or even complete necrosis to define a robust response. This variability impedes direct comparisons across studies and can yield conflicting clinical recommendations. Furthermore, pathology sampling methods differ significantly: some centers embed the entire specimen, while others sample only selected tumor blocks, risking under- or overestimation of necrosis. Multiple confounders also obscure straightforward survival correlations. Treatment approaches (single-agent vs. multi-agent chemotherapy, and standard- vs. (ultra-)hypo-fractionated radiotherapy), tumor grade, histological subtype, and margin status each exert strong influences on outcomes, potentially overshadowing necrosis as a prognostic indicator. High-risk STSs, for instance, which are usually also high-grade tumors, may already harbor extensive spontaneous necrosis, complicating efforts to distinguish additional therapy-induced necrosis. This is analogous to the RECIST response, which is neither consistently predictive nor sufficient on its own [23]. Looking forward, radiomics could potentially help to address this by quantifying changes between baseline and post-therapy imaging, thereby enabling a more precise evaluation of the impact of neoadjuvant treatment on tumor viability [24,25].

3.3. Insights and Integrations

Despite these complexities, robust evidence shows that intensive neoadjuvant regimens can induce notable necrosis in STSs. However, local tumor cell death does not always translate into better systemic control: high-grade subtypes can appear sensitive initially but still relapse or harbor undetected micrometastases. Conversely, data from large cooperative trials (e.g., RTOG 9415, 0630), as well as retrospective analyses, reveal that near-complete or complete pathologic response correlates with improved disease-free and metastasis-free survival in certain patient cohorts [26].

Such heterogeneous results underline the need to integrate necrosis measurements with other markers—molecular or immunologic profiles, surgical margin quality, and advanced imaging—to assemble a more personalized prognostic framework. In this scenario, therapy-induced necrosis becomes one key piece among many, rather than a standalone predictor of patient outcomes. By situating necrosis within a multifactorial matrix, clinicians and researchers can better account for unique tumor features, local therapy variables, and the risk of occult metastatic spread, ultimately guiding more tailored treatment strategies.

4. Consensus Statements

4.1. Therapy-Induced Necrosis as a Standalone Marker

Although chemotherapy-induced necrosis is well established and clinically relevant for bone sarcomas, it remains a controversial predictor in STSs treated with preoperative radio- or chemotherapy when viewed in isolation. This ambiguity supports transitioning toward more precise metrics, such as % viable tumor cells, which can standardize and reproducibly assess therapy response. Moreover, rather than focusing solely on necrosis, a broader concept of tissue changes, including necrosis, fibrosis, edema, and structural remodeling, may be captured via MRI and potentially correlate with outcomes in localized STSs.

4.2. Incorporating Other Factors

A more reliable approach embeds necrosis data into a multifactorial framework that also takes into account surgical margins, histological subtype, immunologic features, and advanced imaging. Such an integrated strategy acknowledges that surgical margins often dominate the evaluation of local control and survival outcomes, regardless of necrosis levels. Additionally, using % viable cells as a primary endpoint can unify the quantification of treatment effects across diverse STS subtypes.

4.3. Standardization and Protocols

A unifying theme from the webinar was the urgent need for standardized pathological assessment and consensus-based guidelines for measuring and reporting necrosis. Because the FNCLCC system covers only spontaneous necrosis, recent work by Wardelmann et al. [14] highlights the urgent need for a consensus protocol that combines pathological and imaging criteria for therapy-induced necrosis. Harmonizing criteria for differentiating viable tumor tissue from necrotic regions—whether therapy-induced or spontaneous—would enhance data comparability among institutions. This standardization is vital for enabling rigorous meta-analyses and promoting robust, collaborative research.

4.4. Future Research Directions (Innovative Methodologies)

Because of STS complexity, innovative methodologies can surpass basic necrosis thresholds in prognostication. Approaches such as radiomics-based MRI, digital pathology, molecular biomarkers, and immune profiling may deepen our understanding of tumor behavior. Meanwhile, real-world evidence (RWE) and pragmatic trials will allow for the inclusion of larger, more diverse populations, capturing real-life clinical environments and generating more applicable insights. Embedding patient-reported outcomes (PROs) and systematic toxicity monitoring will ensure that therapy intensification is balanced with patient well-being. In addition to MRI-based radiomic analyses, FDG-PET can quantify metabolic response in soft-tissue sarcomas, aiding in the distinction between viable tumor tissue and necrotic or fibrotic areas [27,28].

4.5. Target Trial Emulation and Hybrid Designs

Because of STS rarity and diversity, target trial emulation and other hybrid designs offer the chance to generate high-level evidence without the constraints of conventional randomized controlled trials (RCTs) [29,30]. These alternative methodologies enable researchers to leverage observational data and advanced statistical techniques, thereby creating RCT-like conditions in real-world settings. Hybrid RCTs combine elements of traditional randomized trials with real-world data collection or adaptive methods—such as broad inclusion criteria, embedded observational cohorts, or continuous data analysis—to reflect routine practice more closely. This blended model can yield nuanced assessments of necrosis as a prognostic or predictive factor in STS, while also capturing the complexities of everyday clinical management.

5. Discussion

5.1. Expert Opinions and Points of Agreement

A central takeaway from the Sarcoma Academy webinar was the intrinsic complexity of therapy-induced necrosis in the prognostic landscape of STS. While some participants observed strong correlations between extensive necrosis and favorable outcomes, others cautioned that high necrosis can also reflect an inherently aggressive tumor phenotype rather than a purely robust treatment response.

Standardized pathology protocols for evaluating necrosis and viable tumor cells emerged as a clear need. Studies linking necrosis to outcome [11,12] often include all non-viable components (e.g., necrosis, fibrosis, hemorrhage, and inflammation), leading many experts to suggest that percent viable tumor cells might serve as a more uniform method for quantifying response across different institutions.

Furthermore, surgical margins—rather than necrosis alone—remained a consistent determinant of local control and overall survival. Even a seemingly necrotic tumor may recur if resection is incomplete. Meanwhile, the presence of residual viable cells after intensive therapy underscores the resilience of certain STS subtypes. This observation reinforces the importance of high-quality surgery and underscores the value of novel biomarkers or imaging strategies that go beyond necrosis alone to predict treatment impact accurately.

It is also crucial to distinguish quality of clinical management (e.g., suboptimal staging and unplanned excisions) from the tumor's intrinsic response to therapy. While poor management can negatively affect outcomes, it does not necessarily reflect the tumor's innate sensitivity or resistance. Rather, these factors highlight the importance of specialized, multidisciplinary centers that can integrate accurate diagnostics with the most effective treatment strategies.

5.2. Clinical and Research Implications

5.2.1. Clinical Context

Attempts to escalate therapy solely to increase necrosis (e.g., adding more chemotherapy agents, higher radiation doses, or hyperthermia) remain controversial unless supported by robust data linking high necrosis to demonstrable survival benefits. Near-complete necrosis can be achieved in certain high-intensity or multimodal regimens, but results vary substantially across STS subtypes and clinical settings. As a result, individualized decision-making is essential—patient comorbidities, tumor subtype biology, sequencing of therapy, and the likelihood of achieving negative margins must all be weighed when considering treatment intensification. Because necrosis-response relationships differ by histotype, developing subtype-specific guidelines for interpreting viable-cell percentages is a recognized priority for forthcoming multicenter collaborations.

5.2.2. Research Perspectives

From a research standpoint, real-world evidence (RWE) and pragmatic trials provide broader patient populations and more authentic practice patterns than conventional randomized trials. Capturing diverse therapeutic regimens, including standard or hypofractionated radiotherapy; combination chemotherapy; and specialized interventions, like hyperthermia, can elucidate how best to induce meaningful necrosis while minimizing toxicity. Embedding patient-reported outcomes (PROs) in these frameworks ensures that quality of life remains central to any strategy aimed at maximizing necrosis.

Adaptive and hybrid trial designs can further refine therapy intensification. Such methodologies enable investigators to adjust interventions based on interim analyses, thereby identifying the subset of patients most likely to benefit from enhanced necrosis. In the context of rare tumors like STSs, where classical RCTs are often impractical, these adaptive designs may uncover more nuanced correlations between therapy-induced necrosis and survival endpoints. Emerging analyses of long-term trial data also suggest that continuous, nuanced metrics (e.g., dimensional variation) outperform binary or categorical response criteria in predicting survival, although their clinical utility remains uncertain [23]. These consensus views are further underpinned by aggregated retrospective cohort data from multiple high-volume sarcoma centers and national registries, providing a real-world evidential base for our recommendations. In parallel, international consensus initiatives—

linking groups such as EORTC-STBSG, NRG Oncology, and EURACAN—are drafting a unified pathology-plus-imaging response score, which forthcoming pragmatic trials will prospectively validate across diverse STS subtypes. Practically, we recommend that clinicians (i) report the percentage of viable tumor cells using a harmonized scoring sheet; (ii) correlate this with post-therapy MRI/PET findings obtained at the same time-point; and (iii) document margin status in the same report, forming a concise three-item checklist for treatment decisions.

5.2.3. Radiologist's Point of View in Necrosis Assessment

In assessing therapy-induced necrosis in soft-tissue sarcomas (STS), imaging plays a critical role in providing non-invasive insights into tumor response. Contrast-enhanced MRI is the primary imaging tool used, with necrosis typically defined as low signal intensity on T1-weighted imaging, high signal intensity on T2-weighted imaging, and absence of contrast enhancement, best evaluated with regard to the pre-treatment baseline examination. Quantitative imaging, such as diffusion-weighted imaging can be used for the evaluation of therapy response [31]. This imaging technique is well-established as a prognostic factor, as demonstrated by Crombé et al. (2019), who showed that MRI features correlate with histological grade and patient outcomes in STSs [7]. Additionally, PET/CT and PET/MRI have proven complementary to MRI by offering functional imaging that provides further insight into tumor metabolism and necrotic areas, as is crucial for monitoring therapeutic response. Beyond visual assessment, radiomics-based extraction of high-dimensional imaging features from serial MRI or PET datasets enables quantitative tracking of necrotic and viable tumor compartments over time, thereby providing an objective and reproducible biomarker of treatment response during follow-up [24,25]. Recent studies have also highlighted the utility of these imaging techniques in rare histotypes. For instance, Di Masi et al. demonstrated that MRI findings, including necrosis and tumor size, were associated with metastatic outcomes in Clear Cell Sarcoma, a rare STS subtype, reinforcing the relevance of imaging in therapeutic monitoring [32]. However, in certain high-grade and aggressive STS subtypes, such as Alveolar Soft Part Sarcoma (ASPS) and Malignant Solitary Fibrous Tumor (SFT), imaging may show limited or no visible necrosis, even in cases where the tumors are biologically aggressive. This poses a challenge for imaging-based necrosis assessment and highlights the need for careful consideration of imaging findings in these histotypes. As such, a comprehensive evaluation, combining imaging with other diagnostic modalities, is crucial for accurately assessing the therapeutic response in these tumors.

5.3. Considering the Consequences of Escalating Preoperative Therapy to Increase Necrosis

A pivotal question raised during the webinar concerned whether clinicians should intensify or prolong neoadjuvant therapy (e.g., additional chemotherapy, hyperthermia, and higher radiotherapy doses) specifically to push necrosis beyond certain thresholds. One major concern is that longer or more aggressive regimens may inadvertently promote resistant clones, potentially offsetting local gains by heightening the risk of micrometastatic spread. Such regimens can also delay surgery, allowing new tumor cells more time to disseminate.

Because STS subtypes vary greatly in their biology and therapy sensitivities, universal escalation of preoperative therapy may be a strategy that does not benefit every patient. Indeed, surgical margin status, inherent tumor aggressiveness (e.g., grade), and the host's immunologic milieu can overshadow raw necrosis percentages in shaping outcomes. Consequently, while near-complete necrosis sometimes correlates with better local and/or disease-free survival, its value as an independent prognostic marker must be balanced against the risk of selecting resistant clones and postponing definitive surgical resection.

Moving forward, research should clarify which STS subtypes or clinical scenarios stand to gain the most from extended neoadjuvant regimens, and which tumors may be better addressed by earlier surgery followed by adjuvant therapy. Until these data emerge, a measured, individualized approach remains prudent—assessing whether increased local tumor-cell kill outweighs the potential for systemic compromise and surgical delays.

Figure 1 and Table 1, together, provide an integrated overview of necrosis in STSs. The flowchart on the left outlines the logical pathway from recognizing necrosis (whether spontaneous or preoperative therapy-induced) to understanding how various confounders—such as sampling bias, threshold inconsistencies, and margin status—may influence its interpretation. Each node in the flowchart is labeled (A–E) to match the corresponding entries in Table 1. The table expands on these labels with concise bullet points, comparing spontaneous necrosis to therapy-induced necrosis, detailing key factors (e.g., timing of surgery, tumor biology, dose fractionation, and immune context), and highlighting clinical implications. By consulting both visuals side by side, readers can quickly grasp the broader conceptual sequence shown in the flowchart while referencing the table for more granular or comparative details relevant to clinical decision-making and future research directions.

Table 1. Table Summarizing Necrosis in Soft Tissue Sarcomas: From Etiologies to Clinical Decision-Making

Label	Topic or Factor	Detail/Key Points	Connection to Flow Chart
A	Spontaneous Necrosis	- usually indicates inherent tumor aggressiveness, poor vascularization. - not necessarily reflective of treatment efficacy. - correlates with worse outcomes in all STS subtypes.	Referenced at node (2) for difference in etiologies.
B	Preoperative Therapy induced Necrosis	- driven by chemo, radiation (or combination). - percent necrosis often used as a proxy for treatment response. - high necrosis (˜90–95%) can correlate with better DFS/MFS in specific subgroups.	Node (2) to compare with spontaneous necrosis.
C	Confounders & Variability	- sampling bias, threshold inconsistency (10%, 90%, etc.). - timing of surgery vs. therapy (risk of resistant clones). - overlapping effect of surgical margins.	Node (3) describes multiple confounders that Influence necrosis interpretation.
D	Integration with other markers/Modalities	- radiomics, molecular profiling, immunologic infiltration data. - real-world evidence (RWE), pragmatic trials, & patient reported outcomes (PROs). - guides personalizing therapy beyond necrosis alone.	Node (4) where necrosis merges with advanced diagnostics ad trial designs.
E	Clinical Decisions/Future Directions	- balancing therapy escalation vs. risk of overtreatment/toxicity. - importance of early resection, negative margins. - standardized protocols for measuring necrosis in prospective studies.	Node (5) final step in the flowchart: linking necrosis to actual treatment outcomes.

Table 1 Provide an integrated overview of necrosis in STS. The table expands on these labels with concise bullet points, comparing spontaneous necrosis to therapy-induced necrosis, detailing key factors (e.g., timing of surgery, tumor biology, dose fractionation, and immune context), and highlighting clinical implications. By consulting both visuals side by side, readers can quickly grasp the broader conceptual sequence shown in the flow chart while referencing the table for more granular or comparative details relevant to clinical decision-making and future research directions.

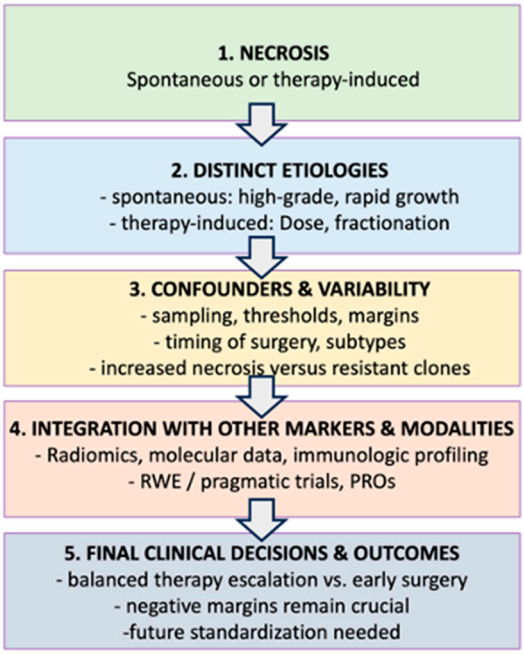


Figure 1. Flow Chart Summarizing Necrosis in Soft Tissue Sarcomas: From Etiologies to Clinical Decision-Making.

6. Conclusions

Soft-tissue sarcomas (STSs) represent a diverse spectrum of malignancies whose management often requires nuanced, multidisciplinary approaches. Although tumor necrosis is an established histopathological feature in bone sarcomas, its role as a definitive and independent prognostic indicator in STS remains far less certain. Presentations at the Sarcoma Academy webinar highlighted how necrosis may be shaped by both intrinsic tumor biology and therapeutic interventions—chemotherapy, radiotherapy, or combined modalities—leading to inconclusive or confounded associations with long-term outcomes.

1. **Therapy-induced necrosis alone is not a definitive prognostic indicator in STS.**
   High levels of necrosis may reflect either inherent tumor aggressiveness or effective therapy, complicating interpretation—especially when differentiating spontaneous necrosis (as used in the FNCLCC system) from treatment-related cell death. A uniform pathologic protocol that measures % viable tumor cells may provide an alternative or complimentary approach, but consistency is critical. However like necrosis, the potential prognostic value of % viable tumor cells is also likely to depend on factors such as tumor subtype, timing of resection, and surgical margins.
2. **Percent of viable tumor cells (rather than necrosis alone) offers a more reliable measure of therapeutic effect.**
   Reporting the percentage of viable tumor cells (%VTC) provides a uniform endpoint—the amount of living tissue that remains post-therapy. All other treatment-related changes (necrosis, fibrosis, hemorrhage, and inflammation) are classified as non-viable, a simplification that reduces inter-observer variation and enables more reliable cross-study comparison.
3. **Complete pathologic response is rare but may correlate with better outcomes in selected settings.**
   In certain prospective trials (e.g., RTOG 9514, 0630), 19–27% of patients achieved complete absence of viable tumor cells, often linked to improved survival (and retrospective series [26]). However, due to STS heterogeneity, potential toxicities, and the possibility of selecting resistant clones by delaying surgery, universal es-

calation of therapy to maximize necrosis remains neither routinely advisable nor consistently beneficial.

4. **Surgical resection margins trump necrosis and subtype for local control.**
   Securing negative surgical margins remains the cornerstone of local control in STS and outweighs both necrosis extent and histological subtype. Although tumor biology and other factors contribute, margin status consistently exerts the strongest influence on recurrence risk.
5. **Pathologic and radiologic measures of response are complementary but distinct.**
   Pathologists assess histological changes, including necrosis, viable cells, and fibrosis, whereas radiologists evaluate imaging-based criteria (e.g., tumor shrinkage and metabolic shifts). Integrating both perspectives provides a more comprehensive picture of therapeutic impact.
6. **Jointly agreed pathology-plus-imaging protocols are essential for comparability across centers.**
   Inconsistent thresholds and variable pathological sampling underscore the need for universally accepted protocols (for example, [13]). Harmonizing radiological response criteria (e.g., RECIST or PERCIST) with standardized pathology procedures is similarly essential.
7. **Integrating imaging-based biomarkers, molecular data, and immunologic profiling may enhance prognostic accuracy.**
   Techniques such as radiomics, genomic analysis, and immune microenvironment characterization can provide deeper insights into tumor behavior, enabling more precise risk stratification.
8. **Real-world evidence and pragmatic trials can circumvent some limitations of traditional RCTs, improving clinical relevance.**
   Broader, more inclusive study designs in RWE frameworks capture a wider range of patient and treatment variations, refining our understanding of necrosis, % viable cells, and response in everyday STS care.
9. **Patient-reported outcomes and toxicity data should be standard secondary endpoints, ensuring treatments remain patient-focused.**
   Balancing efficacy with side-effect profiles is imperative, ensuring any push to increase necrosis remains aligned with patient well-being and quality of life.
10. **Target trial emulation and hybrid study designs can yield better causal insights in rare, heterogeneous STSs.**
    These methodologies enable more nuanced exploration of necrosis and % viable cells in smaller or diverse patient populations, approximating randomized conditions while reflecting real-world clinical practice.

Overall, therapy-induced necrosis is but one facet of STS prognostication. Although near-complete response appears promising—particularly in combined chemo-radiation regimens—cohesive research efforts and uniform assessment protocols remain vital to unlocking necrosis's true clinical significance. By embedding necrosis evaluation into a broader, patient-centered care model—one that considers margins, molecular profiles, and overall functional outcomes—treatment strategies can be more precisely tailored to maximize benefit while minimizing risk.

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Development and Validation of the Bone Tumor Surgery Complexity Score

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Abstract: Bone tumors often manifest with non-specific symptoms such as pain and swelling, often posing diagnostic challenges. Optimal treatment requires centralized care in specialized centers, emphasizing the need for complete tumor removal and interdisciplinary collaboration. We developed the Bone Tumor Surgery Complexity Score (BT-SCS) based on a retrospective study of 501 patients. The BT-SCS, structured around patient demographics, tumor biology, and surgical parameters, categorizes surgical cases into four groups to comprehensively assess complexity. Application of the BT-SCS resulted in scores ranging from 3 to 33, with an average score of 14 ± 7.2. Patients with malignant tumors had higher scores (19.6 ± 5.2) compared to those with benign (10.0 ± 3.8) or intermediate malignant tumors (14.6 ± 7.1). Patients with pelvic tumors registered the highest scores (16.0), followed by extremities/trunk (14.3) and spinal tumors (13.6). The BT-SCS was validated against the Case Mix Index (CMI), using an independent cohort of bone and soft tissue cases. This validation process, utilizing Loess smoothing, illustrated the BT-SCS's granular differentiation of surgical complexity, particularly in the lower-to-mid-range of case severities. The BT-SCS represents a significant shift from volume-based to complexity-based assessments in surgical care, aligning with evolving healthcare paradigms. It serves as a tool for strategic patient allocation to treatment centers, aiming to improve outcomes and benchmarking in sarcoma care. The score's development and application in clinical practice align with the focus on patient-centered and value-based healthcare. Future enhancements, including machine learning integration and outcome data, will refine its categorization process, enhancing clinical utility.

Keywords: bone tumors; complexity score; bone sarcoma; benchmarking; value-based healthcare; quality indicator; surgical planning; validation

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1. Introduction

Bone tumors represent a challenging aspect of oncology, characterized by their rarity and the subtlety of their clinical presentation [1]. Patients often exhibit non-specific symptoms such as pain, swelling, or fractures, if any symptoms at all, making early detection and diagnosis challenging [2]. The differentiation between benign and malignant bone tumors is further complicated by the overlap of symptoms with other conditions, necessitating advanced radiological and histological examination methods for accurate diagnosis.

Surgical intervention is pivotal in the management of bone tumors, aiming for complete resection with tumor-free margins to ensure optimal patient outcomes. Given the primary occurrence of bone sarcomas in the extremities, alongside their potential to originate

from any bone or soft tissue, a multidisciplinary approach is crucial [3]. It is widely recognized that patients benefit significantly from treatment at specialized sarcoma networks, where comprehensive care and expertise are available to address the unique challenges posed by these tumors [4].

Historically, the relationship between surgical volume and patient outcomes has been a topic of considerable research, with higher-volume centers often achieving better results [5]. This correlation suggests a benefit to centralizing care; however, it also underscores the complexity of attributing outcomes solely to volume, as it may not adequately reflect the expertise of individual surgeons or account for the multifaceted nature of surgical procedures [6–8]. Recent studies have begun to explore beyond volume, suggesting that a detailed understanding of surgical complexity and patient-specific factors is essential for optimizing care [9–11].

In this context, we previously developed the "Soft Tissue Sarcoma Surgery Complexity Score (STS-SCS)" to quantify surgical interventions' complexity in soft tissue tumors [12]. Building on this work, the current study introduces the "Bone Tumor Surgery Complexity Score (BT-SCS)", aiming to extend the same rigorous evaluation to surgeries involving bone tumors. This novel scoring system is designed to provide a standardized method for assessing surgical complexity, incorporating factors such as tumor location, size, and the necessary surgical skills for successful intervention.

The BT-SCS is rooted in the principle that a comprehensive evaluation of both procedural complexity and the patient's overall health status is crucial for determining the most appropriate care setting. This approach aligns with the shift towards value-based healthcare, which prioritizes outcomes and quality over volume [13,14]. By accurately assessing and benchmarking surgical complexity, we can better allocate resources, minimize patient wait times, and enhance the efficiency and effectiveness of care [15–17].

Furthermore, the BT-SCS facilitates a more nuanced understanding of the challenges inherent in bone tumor surgery. It underscores the importance of interdisciplinary collaboration, particularly in complex cases requiring advanced surgical techniques and postoperative care. Through this standardized complexity assessment, we aim to support surgeons in planning and executing procedures, ultimately improving patient outcomes and contributing to the broader goals of healthcare quality and cost efficiency.

2. Materials and Methods

2.1. Study Population

A fellowship-trained surgeon performed a total of 501 surgeries on bone tumors over a 15-year period. These surgical procedures were recorded in the "Sarcoma Surgeon's Registry", managed by Adjumed Services AG in Zurich, Switzerland (website: www.adjumed.ch, accessed on 30 May 2023). To conduct basic statistical analyses and extract data, the AdjumedAnalyze tool, provided by Adjumed Services AG, was used. Subsequently, individual scores were calculated using Microsoft Excel, a product of Microsoft Corporation that is based in Redmond, WA, USA. All patients included in this study were discussed at an interdisciplinary board, provided by the SwissSarcomaNetwork (website: https://www.swiss-sarcoma.net/, accessed on 13 September 2023).

2.2. Development of the Bone Tumor Surgery Complexity Score (BT-SCS)

Drawing from the literature and insights from seasoned sarcoma surgeons, we formulated the Bone Tumor Surgery Complexity Score (BT-SCS). This score was developed in a manner analogous to that of the Soft Tissue Sarcoma Surgery Complexity Score, which we previously delineated [12]. The BT-SCS is based on insights from the literature and experienced surgeons. It is fundamentally structured around three core domains—patient characteristics, tumor biology, and surgical parameters (Figure 1). The considerations that led to the content of the score are outlined below.

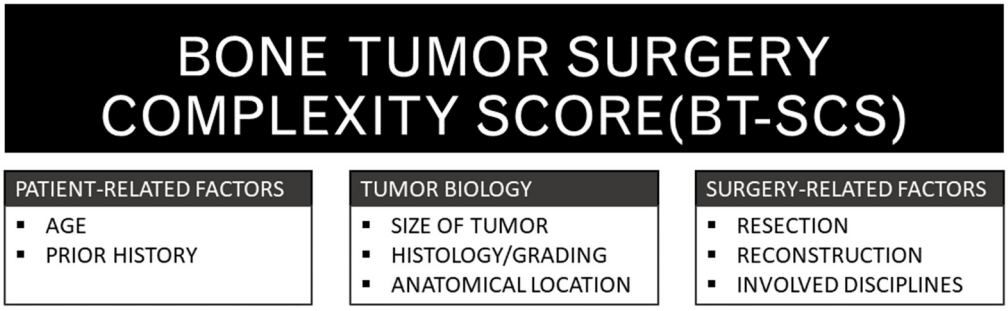


Figure 1. A schematic representation of the three foundational domains and their respective factors underpinning the BT-SCS.

After establishing the foundational domains of the BT-SCS, we further refined the concept of surgical case complexity specifically for this study. This refinement involved operationalizing complexity in a measurable and replicable manner, ensuring that it encompasses the full scope of surgical challenges, from patient preparation and surgical planning to the execution of the procedure and postoperative management. This comprehensive approach allowed us to systematically evaluate and score the complexity of each surgical case individually, contributing to the robustness and applicability of the BT-SCS in clinical practice.

2.2.1. Patient Characteristics

Factors pertinent to the patient, such as age and medical history, especially prior radiotherapy or chemotherapy, were incorporated, mirroring the approach in the STS-SCS. Notably, older osteosarcoma patients exhibit a poorer prognosis than their younger counterparts [18,19]. Studies indicate that osteosarcoma in individuals over 18 years is linked with a notably higher recurrence rate and worse outcomes [20]. However, surgical interventions in pediatric patients present unique challenges, due to their rarity and the specific requirements necessitated by the patient's age, impacting both surgeons and anesthesiologists.

Historically, osteosarcoma patients faced grim prognoses, with many succumbing in a short span of time. However, advancements in surgical techniques and the advent of chemotherapy have revolutionized outcomes. A multidisciplinary approach has bolstered the rate of conservative procedures to 85% and enhanced the prognosis, with up to 70% 5-year disease-free survival (DFS) for nonmetastatic patients [21]. Neoadjuvant therapies, while beneficial, come with associated risks. For instance, neoadjuvant radiotherapy might impede wound healing, and chemotherapy could delay surgical intervention. Furthermore, improperly positioned biopsy channels outside the intended surgical zone can complicate bone tumor surgeries. Hence, a collaborative approach between radiologists and surgeons is paramount for optimal biopsy planning.

2.2.2. Tumor Biology

Tumor size plays a pivotal role in surgical complexity, with larger tumors posing greater challenges [22]. Benign bone tumors, which seldom recur locally, are typically managed with complete excision or curettage [1]. Intermediate malignant bone tumors, characterized by aggressive local growth, necessitate wide excision. In contrast to benign tumors, they occasionally metastasize, predominantly to the lungs. Malignant tumors, while infrequent, have the propensity for distant metastasis in addition to local growth and recurrence. Bone sarcomas, contingent on histological type and grade, present a metastasis risk ranging from 20 to 100% [1]. Their local invasive growth makes malignant bone tumors particularly challenging to excise, in comparison to benign tumors. Certain bone tumors, especially those located in the spine or pelvis, are inherently challenging due to their deep anatomical positioning.

2.2.3. Surgical Parameters

Surgical strategies vary based on tumor histology, location, and size. Meticulous planning is essential, especially when considering pelvic anatomy, with the objective of optimizing functional outcomes, while minimizing morbidity [23]. Such surgeries demand profound expertise from the entire medical team, particularly radiologists and surgeons. An interdisciplinary team, comprising orthopedic oncologists, medical oncologists, and radiation oncologists, is recommended for bone tumor management [24]. The intricate nature of bone tumor surgeries often necessitates collaboration across multiple surgical disciplines, including orthopedics, plastic surgery, and neurosurgery [25]. Post-excision, patients frequently undergo complex reconstructions. We have encapsulated this diverse range of surgical interventions within the BT-SCS, using a point-based system.

2.2.4. Methodology and Rationalization of BT-SCS Scoring Criteria

In the development of the BT-SCS, each surgical parameter was evaluated and quantified based on a multifaceted approach, considering the effort, level of technical difficulty, time consumption, frequency, and skill requirement. This evaluation was substantially informed by a structured modified Delphi process, which involved extensive and iterative discussions over four rounds, among a diverse panel of expert sarcoma surgeons. These experts span the spectrum of orthopedic oncology, as well as reconstructive surgery, providing a broad and inclusive range of perspectives. The Delphi process was meticulously designed to foster open, critical dialogue and consensus-building, ensuring that the scoring criteria developed are deeply rooted in the practical and varied experiences of expert sarcoma surgeons.

It is important to note that while the BT-SCS offers a structured framework for assessing surgical case complexity, it inherently contains subjective elements and should be seen as a starting point for ongoing refinement. Throughout this process, the expert panel was tasked with identifying and defining the most impactful parameters that influence surgical complexity, leading to the prioritization of factors such as anatomical location and associated surgical risks. The score is designed to assess surgical case complexity in its purest form, independent of patient outcomes. As such, it aims to provide a baseline for surgical planning and resource allocation, with the understanding that future iterations will continue to evolve, based on clinical feedback and emerging surgical insights.

Additionally, while developing the BT-SCS, we recognized the inherent heterogeneity of bone tumors. Rather than focusing extensively on the histological diversity of these tumors, our scoring system is designed to emphasize the surgical challenges presented by their anatomical locations. This approach ensures that the BT-SCS remains broadly applicable and relevant across all types of bone tumors. It prioritizes the practical aspects of surgical intervention—such as accessibility, proximity of critical structures, and potential for surgical complications—which are crucial for assessing and planning complex surgical procedures. By concentrating on these surgical variables, the BT-SCS provides a standardized tool that assists in anticipating the complexities involved, irrespective of the tumor's histological type.

2.2.5. Conclusion

The BT-SCS amalgamates the multifaceted factors associated with bone tumor surgical resections into a comprehensive score (Table 1). Each factor is weighted based on its significance. We subsequently applied this score to a cohort of 501 patients, with data sourced from Adjumed.

Table 1. BT-SCS system, indicating the weighting of each parameter.

			Points	Maximum
Patient's Age	≤17 years		1	
	18–64 years		0	
	≥65 years		1	1
Histology/Grading	Benign		1	
	Simulator		1	
	Intermediate		2	
	hematologic tumors of bone (incl. myeloma and lymphoma)		3	
	Metastasis		5	
	Malignant	G1	5	
	Malignant	G2	6	
	Malignant	G3	7	7
Prior History *	Preoperative radiotherapy		2	
	Preoperative chemotherapy		2	
	Prior unplanned Excision (UE)		2	6
Anatomical Location	Extremities	Upper extremity	1	
	Extremities	Lower extremity	1	
	Trunk		1	
	Spine/pelvis		3	3
Size of Lesion	Appendicular skeleton, trunk, skull, and facial bone lesions			
	No evidence of primary tumor		0	
	≤8 cm		1	
	>8 cm		2	
	Discontinuous tumors in primary bone site		3	
	Pelvis			
	Tumor confined to one pelvic segment with no extraosseous extension			
		Tumor ≤ 8 cm in greatest dimension	1	
		Tumor > 8 cm in greatest dimension	2	
	Tumor confined to one pelvic segment with extraosseous extension or two segments without extraosseous extension			
		Tumor ≤ 8 cm in greatest dimension	2	
		Tumor > 8 cm in greatest dimension	3	
	Tumor spanning two pelvic segments with extraosseous extension			
		Tumor ≤ 8 cm in greatest dimension	3	
		Tumor > 8 cm in greatest dimension	4	
	Tumor spanning three pelvic segments or crossing the sacroiliac joint			
		Involves sacroiliac joint and extends medial to the sacral neuroforamen	4	
		Encasement of external iliac vessels or presence of gross tumor thrombus in major pelvic vessels	5	
	Spine			
	One vertebral segment or two adjacent vertebral segments		1	
	Confined to three adjacent vertebral segments		2	
	Four or more adjacent segments or any nonadjacent vertebral segments		3	
	Extension into spinal canal		3	
	Evidence of gross vascular invasion or tumor thrombus in the great vessels		3	5

Table 1. *Cont.*

				Points	Maximum
Type of Bone Resection	Biopsy, radiofrequency ablation, HIFU, cryotherapy, curettage/intralesional/piece-meal/decompression surgery			1	
	Resection of muscles			1	
	Resection of vessels			2	
	Resection of nerves			1	
	Resection of tendons			1	
	Hemicortex resection			2	
	Transarticular bone resection			4	
	Joint-sparing (intercalary segmental) resection			2	
	Extra-articular resection			5	
	En bloc vertebrectomy			5	
	Rotationplasty			6	
	Epiphysiolysis			2	
	Resection–replantation			6	
	Tikhoff–Linberg resection			6	
	Internal hemipelvectomy	Type I		6	
	Internal hemipelvectomy	Type II		8	
	Internal hemipelvectomy	Type III		6	
	Internal hemipelvectomy	Type IV		7	
	Amputations	Forequarter		6	
	Amputations	External hemipelvectomy	Transacetabular	6	
	Amputations	External hemipelvectomy	Transiliac	6	
	Amputations	External hemipelvectomy	Transhemisacral without spinopelvic dissociation	6	
	Amputations	External hemipelvectomy	Transhemisacral with spinopelvic dissociation	8	
	Amputations	External hemipelvectomy	Hemicorporectomy	10	
	Amputations	Upper extremity	Transarticular shoulder/elbow—humerus	4	
	Amputations	Upper extremity	Forearm/wrist	3	
	Amputations	Upper extremity	Hand/finger	2	
	Amputations	Lower extremity	Hip disarticulation	5	
	Amputations	Lower extremity	Thigh/knee disarticulation	5	
	Amputations	Lower extremity	Leg	3	
	Amputations	Lower extremity	Foot/digits	2	26 **
Type of Reconstruction	Cementation/ORIF			2	
	Artificial bone substitute/autograft/allograft chips			2	
	Bulk allograft			3	
	Pasteurized autograft			3	
	Nonvascularized fibula			4	
	Vascularized fibula based on fibular artery			6	
	Vascularized fibula based on tibialis anterior			6	
	Pedicled-tissue transfer			3	
	Free-tissue transfer			4	
	Skin/mesh graft			1	
	Nerve, vessel, and lymphovenous reconstruction			4	

Table 1. *Cont.*

		Points	Maximum
Type of Reconstruction	Tendon reconstruction	2	
	Conventional prosthesis	2	
	Modular tumor prosthesis	4	
	Custom-made prosthesis	6	
	Growing prosthesis	6	
	Spinal instrumentation with pedicle screws/rods	3	
	Arthrodesis	3	
	Pseudarthrosis/flail joint/cement spacer	2	
	Cañadell distraction epiphysiolysis	4	
	Distraction osteogenesis	5	
	Goretex, Trevira, etc.	2	
	Stump after amputation	2	18 ***
Number of Involved Disciplines ****	One discipline	0	
	Two disciplines	1	
	Three disciplines	2	
	Four disciplines	3	
	Five or more disciplines	4	4
Total		max.	70

* The points in the section "prior history" can be added together, resulting in a maximum score of 6 in this field. ** Max. 3 different types of resections can be added together. *** Max. 3 different types of reconstructions can be added together. **** If one single surgeon is a sarcoma surgeon, but also has the credentials for vascular reconstruction, then 2 disciplines are registered.

2.3. Categorization of Complexity Scores

The categorization of surgical cases into four groups based on the BT-SCS was guided by a desire to create a practical and functional classification system for clinical use. Each category represents a distinct level of complexity, with approximately 25% of patients allocated to each group. This division was determined based on the score distribution in our study population and aimed to facilitate an easier interpretation and application of the BT-SCS in clinical settings. It is important to note that this categorization is a preliminary step, serving as a basis for potential clinical integration and future refinement. The division into quartiles is not intended to correlate directly with patient outcomes, but to provide a structured approach to understand and manage varying degrees of surgical case complexity in bone tumor treatment.

2.4. Statistics

Descriptive statistics were employed to analyze the data. Continuous variables, such as age and the Bone Tumor Surgery Complexity Score (BT-SCS), were summarized using measures of central tendency (mean) and dispersion (standard deviation). Categorical variables, like gender and tumor type, were presented as frequencies and percentages. The distribution of the BT-SCS across different tumor types and locations was visualized using appropriate graphical representations. Comparisons of BT-SCS scores across different tumor types were made using the mean and standard deviation values. All statistical analyses were conducted using Microsoft Excel (Version 16.78.3).

2.5. Validation of the Surgical Complexity Score against the Case Mix Index (CMI)

In our endeavor to establish a robust Surgical Complexity Score for soft tissue [12], and now extended to bone tumors, we recognize the necessity of validation against a well-established standard. The Case Mix Index (CMI), widely and internationally acknowledged for its significance in reflecting the complexity and resource requirements of hospital patient

populations, offers an ideal benchmark. The CMI's widespread utilization, especially in billing and reimbursement processes (based on case complexity) across various healthcare systems globally, underscores its relevance and robustness as a comparative standard. By aligning our newly developed complexity score with the CMI, we aim to affirm its validity and applicability in the clinical setting, thereby enhancing its potential for broader acceptance and implementation.

For the validation of our newly established Bone and Soft Tissue Tumor Surgery Complexity Scores (BS-/STT-SCS), we selected an (temporally) independent cohort of patients from our dedicated sarcoma treatment, Sarconnector® warehouse (Table 2). This cohort, distinguished from the initial development set, encompasses a diverse array of bone and soft tissue sarcoma cases, meticulously documented and analyzed within our RWTD/E data warehouse [13]. By conducting a comparative analysis against the established CMI values within this independent patient set, we seek to rigorously assess the congruency and predictive accuracy of our complexity scores, using Locally Estimated Scatterplot Smoothing (LOESS). This step is crucial for establishing the reliability and clinical utility of the BT/STS-SCS, setting the stage for its integration into surgical planning and healthcare resource optimization for sarcoma care.

Table 2. This table characterizes the independent patient cohort for validation purposes of the BS- and STS-SCS.

Parameter	Number of Patients
Patients (m/f)	363 (205/158)
Age/range	51 (7–88)
Soft tissue tumors	284
Bone tumors	79
Benign	117
Intermediate	83
Malignant	163
SST Cat 1 [1]	18
SST Cat 2	55
SST Cat 3	88
SST Cat 4	106
BS Cat 1 [2]	7
BS Cat 2	23
BS Cat 3	26
BS Cat 4	14
CMI [3]	
- mean (SD)	1.5 (SD)
- range	0.38, 13.98
- median (IQR)	0.86 (0.71, 1.38)

[1] SST = soft tissue tumors; [2] BS = bone tumors; [3] CMI = Case Mix Index.

3. Results

3.1. Characteristics of Bone Tumor Patients

In this study, we investigated the surgeries of 501 patients with both benign and malignant diagnoses. In this patient population, the average age was 36.0 ± 20.1 years; the youngest patient was 5 years old and the oldest patient was 89. The expected first frequency peak of bone tumor diagnoses in adolescence and young adulthood is evident. The second peak found in the literature, which is supposed to occur in older adulthood, is not explicitly reflected in our data (Figure 2). Of the patients studied, 285 were male, representing a proportion of 57%, and 216 were female (43%). The male-to-female ratio was 1.32. Most patients operated on during this study had malignant tumors (180 patients, 36%), 148 had benign tumors (30%), and 107 had tumors with intermediate malignancy (21%). In total, 43 patients (9%) had metastases from other primary tumors. A minority suffered from tumor simulators (tumors which may imply a sarcoma on imaging, but are later revealed to be a benign lesion) and hematologic tumors of bone (incl. myeloma and lymphoma).

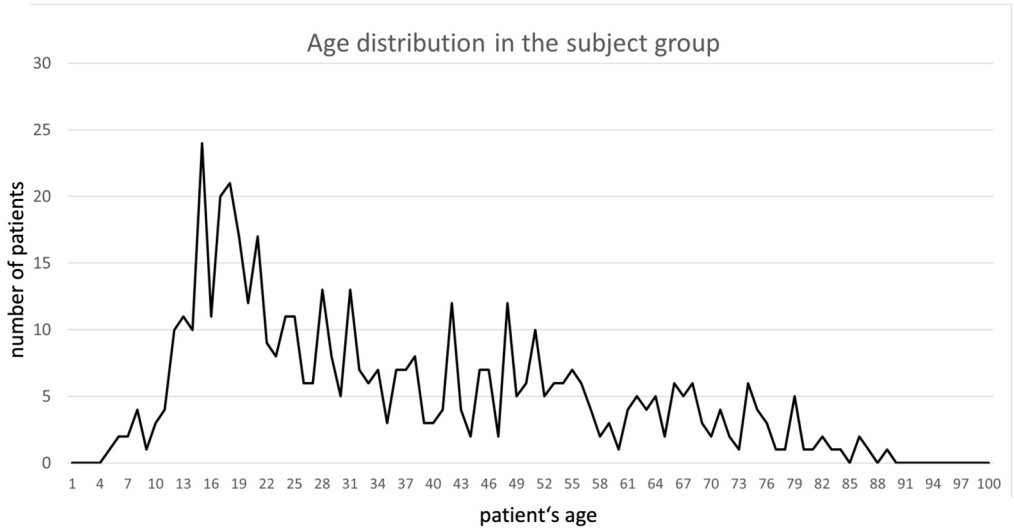


Figure 2. Age distribution in the subject group.

3.2. Application of the BS-SCS

The BT-SCS was applied to our sampling group of 501 patients and the individual scores were calculated for each patient using Microsoft Excel. The minimum score was 3 and the maximum score was 33 (out of 70), with an average score of 14 ± 7.2. The scores of patients with malignant diagnoses (19.6 ± 5.2) were notably higher than those of patients with benign (10.0± 3.8) or intermediate malignant tumors (14.6 ± 7.1) (Figure 3). Patients with tumors of the pelvis had the highest scores (16.0), followed by patients with tumors of the extremities and trunk (14.3) and patients with tumors of the spine (13.6) (Figure 4). The following examples illustrate these scores. The patient with a total score of 3 was a 42-year-old patient with no relevant prior history. He presented with a painful limitation of motion of the right knee. After an uneventful surgery, using curettage, by a single surgeon, single fragments of a benign finding, namely, synovial chondromatosis, could be detected histologically. The highest score of 33 was received by a 29-year-old patient who presented with an approx. 6 cm large, highly malignant, undifferentiated, high-grade pleomorphic sarcoma of the pelvic bone. After 3D planning, a type I internal hemipelvectomy was performed through the sacral ala, followed by complex reconstruction with instrumentation with rods and screws and a vascularized fibular autograft (based on fibular artery). Specialists from the fields of sarcoma surgery, reconstructive surgery, orthopedics, traumatology, and neurosurgery were involved in this complex operation. The patient was treated with both neoadjuvant and adjuvant chemotherapy.

3.3. Categorization of Bone Tumor Surgery Complexity

To better categorize the complexity of individual surgeries, we established four categories, using the collected data as a reference dataset. Each of the categories contained approximately one-quarter of the registered patients (Table 3).

As previously elucidated in the methodology, the present proposition delineates a framework for categorizing patients intended for implementation in routine clinical settings. For instance, careful consideration is warranted as to whether individuals assigned to category 4 should consistently undergo treatment within specialized clinical facilities.

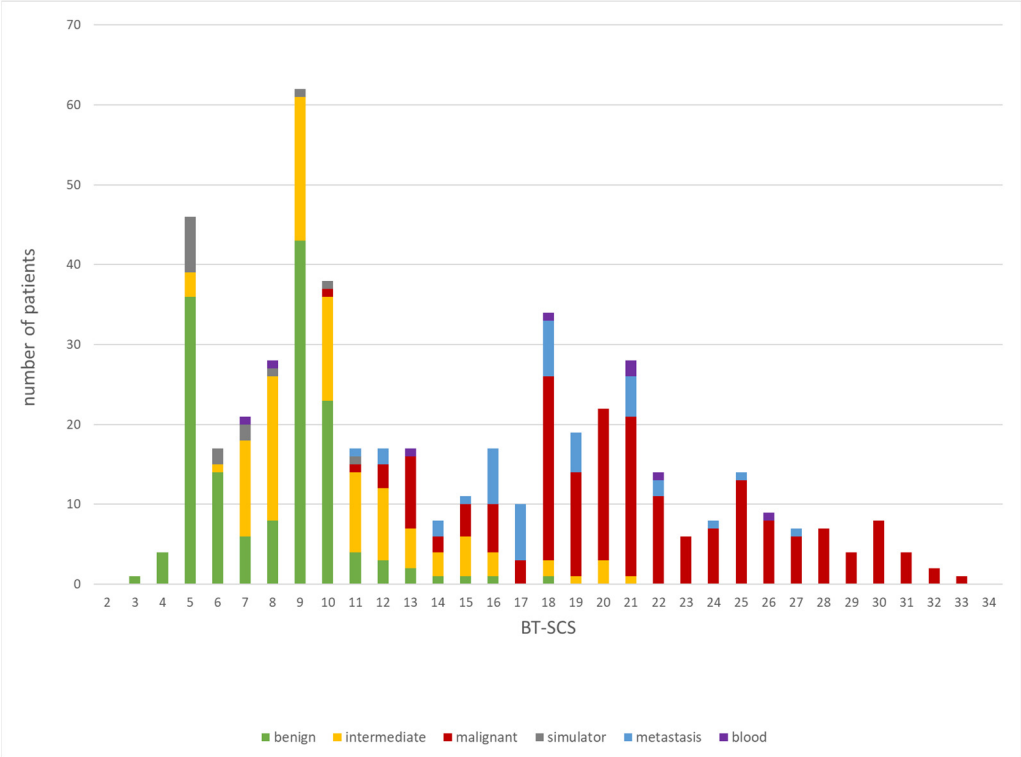


Figure 3. Distribution of the totals of the Bone Tumor Surgery Complexity Score (BT-SCS) in the sampling group.

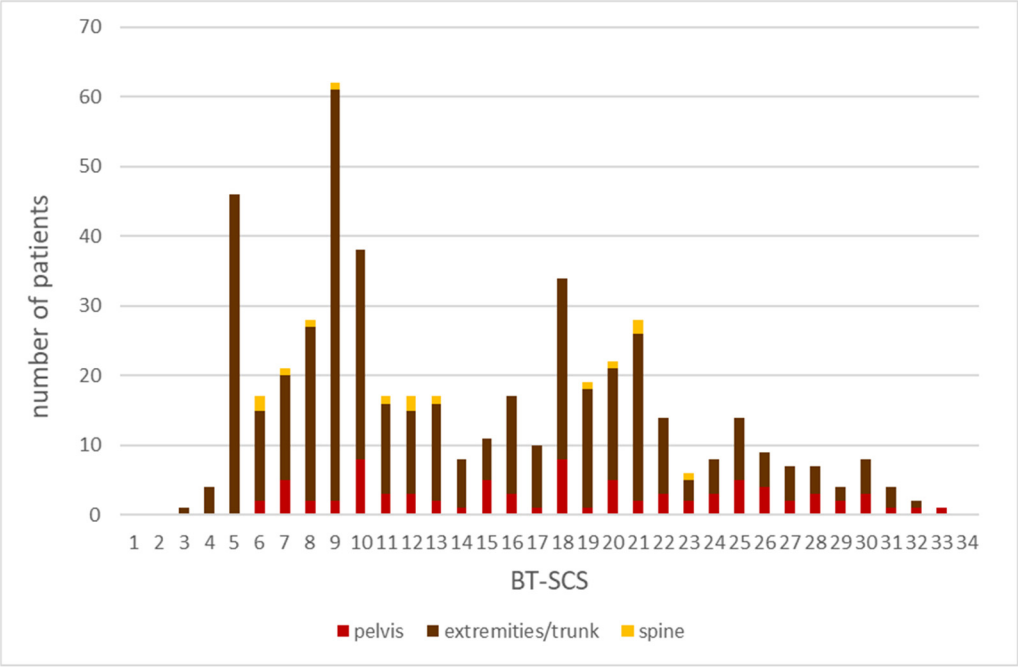


Figure 4. Distribution of the totals of the Bone Tumor Surgery Complexity Score (BT-SCS) in the sampling group, with respect to tumor localization.

Table 3. Division of surgeries into four categories.

Category	Complexity Score	Number of Patients	Percentage (%)
1	≤8	117	23.4%
2	9–11	117	23.4%
3	12–19	133	26.5%
4	≥20	134	26.7%

Category 1 consisted of patients scoring below 9 points, representing a wide range of scores and comprising 117 patients (23.4% of the total). Within this category, patients had diverse diagnoses, including benign and intermediate tumors, as well as tumor simulators. Category 2 encompassed patients with scores ranging from 9 to 11 points, which was a relatively narrow range, but still accounted for 117 patients (23.4%). The majority of patients falling in this range had benign or intermediate diagnoses, but a few had malignant diagnoses. Patients with scores between 12 and 19 points were placed in Category 3, which included 133 patients (26.5%). Finally, Category 4, the highest category, included 134 patients (26.7%), exclusively including patients with malignant diagnoses (refer to Figure 5).

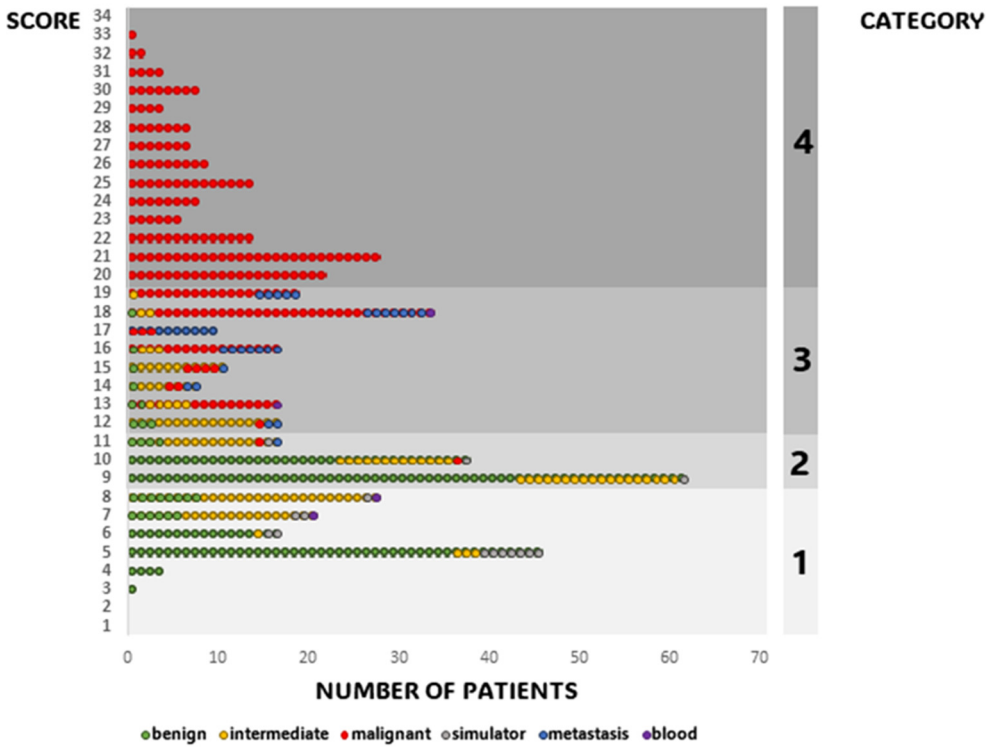


Figure 5. Graphical representation of individual scores and their allocation to the categories of complexity. Each point represents a patient. The malignancy of the tumors is shown in colors, as described.

3.4. Validation of Complexity Scores with Case Mix Index

In examining the association between our newly established Surgical Complexity Score and the traditional Case Mix Index (CMI) through Loess smoothing analysis, we observed a nuanced relationship, indicative of the complexity score's granularity (Figure 6). The analysis revealed a steep initial ascension in the complexity score corresponding to lower CMI values, which implies that our complexity score is capable of discerning surgical case variances with a high degree of sensitivity, especially at lower and medium levels of case mix severity. As CMI values increased, the complexity score demonstrated a plateau,

suggesting that our score may provide a more detailed stratification of surgical cases than what is reflected by CMI alone. This plateau also points to a potential ceiling effect in the CMI's ability to differentiate complex cases at higher severity levels. Importantly, the wide confidence intervals at the extremities of the CMI range caution against overinterpreting the complexity score's behavior at these points, due to sparser data. Overall, these findings emphasize the added value of the Surgical Complexity Score in capturing the intricacies of case complexity, thereby offering a refined tool that surpasses the granularity of CMI, particularly in the lower-to-mid-range of case severities, where clinical decision-making and resource allocation could be most impacted.

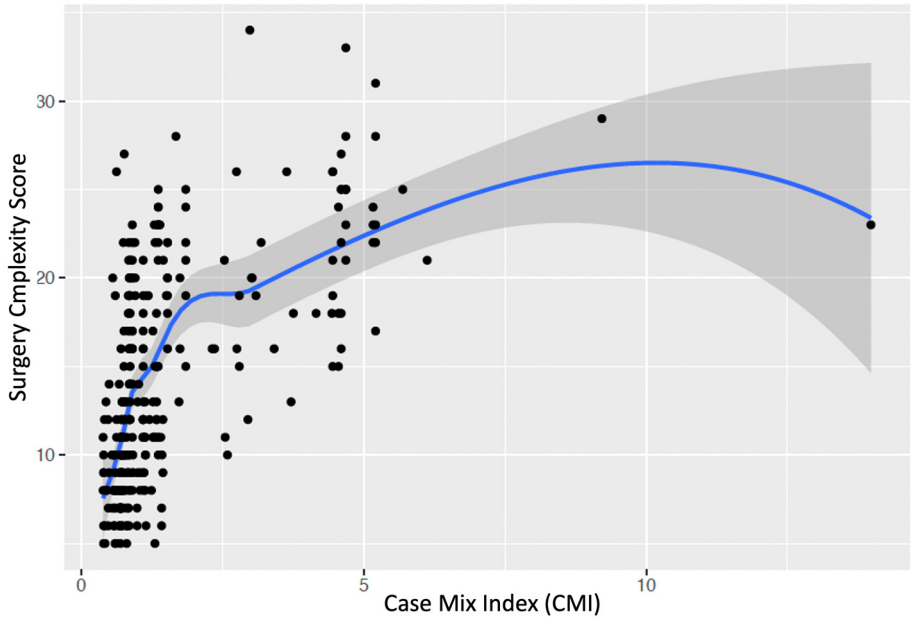


Figure 6. Comparison between Case Mix Index (CMI) and surgical complexity scores using Loess smoothing.

4. Discussion

This study primarily aimed to develop and validate the Bone Tumor Surgery Complexity Score (BT-SCS), a comprehensive tool designed for assessing the complexity of bone tumor surgeries. Our findings indicate that the BT-SCS, encompassing patient characteristics, tumor biology, and surgical parameters, offers a nuanced and multi-dimensional approach to understanding surgical case complexity. By systematically analyzing 501 cases, we demonstrated the practicality and relevance of the BT-SCS in categorizing surgical complexity, which is crucial for optimized surgical planning and resource allocation in bone tumor treatments, as supported by current research in the field [11,26].

The practical application of the Bone Tumor Surgery Complexity Score (BT-SCS) within clinical settings is multifaceted. Its incorporation into surgical planning processes allows for a more stratified approach to case management, supporting clinical decision-making by quantifying the anticipated complexities of each surgical intervention. Consequently, it provides a framework for the judicious allocation of healthcare resources, potentially mitigating risk and optimizing patient flow. Importantly, ongoing discussions within the surgical and oncological communities suggest that the BT-SCS can refine existing benchmarks for surgical complexity, such as the CMI, by providing a more granular assessment of surgical needs. In terms of patient care, the BT-SCS can guide the referral process, ensuring that patients with complex bone tumor surgeries are directed to specialized networks equipped with the necessary expertise and resources to effectively handle such cases. Moreover, the BT-SCS stands as a benchmarking tool, enabling the comparison of surgical outcomes across different institutions and fostering an environment of continuous improvement in

patient care. This tool's potential for impacting patient outcomes emphasizes the necessity for its integration into routine clinical protocols and training programs for surgical teams.

The definition of surgical case complexity in our study comprehensively incorporates a range of factors, including preoperative considerations, intraoperative challenges, and postoperative outcomes. This holistic approach acknowledges the multifaceted nature of surgical procedures, particularly in the treatment of bone tumors [1]. By encompassing these diverse aspects, the Bone Tumor Surgery Complexity Score (BT-SCS) provides a more accurate and thorough assessment, crucial for preoperative planning, intraoperative decision-making, and postoperative care. Our work highlights the importance of a broad perspective on surgical complexity, which is essential in guiding both clinical decision-making and resource allocation, thereby enhancing patient care in orthopedic oncology, which aligns with the evolving paradigms in surgical assessment and patient care [27].

The BT-SCS scoring system was meticulously developed to provide a quantitative measure of surgical complexity in bone tumor cases. We are continually refining the system based on feedback from its practical applications, highlighting areas where additional data could enhance its precision and reliability. This methodology not only ensures clarity and consistency in scoring but also aligns with the real-world complexity encountered in clinical practice, thereby enhancing the score's applicability and validity, as emphasized in recent studies [28,29].

The development of the BT-SCS epitomizes the shifting paradigm in surgical evaluation, moving from volume-based to complexity-based assessments. As we further validate the BT-SCS against additional clinical outcomes, it becomes clear that this tool is crucial for advancing precision medicine in orthopedic oncology, facilitating surgical decisions tailored to individual needs.

The categorization of surgical cases into four distinct groups in our study was based on the BT-SCS, which was structured to reflect varying levels of complexity in bone tumor surgeries. This grouping, independent of direct patient outcomes, was strategically chosen to facilitate clearer understanding and communication within clinical settings. It enables healthcare professionals to quickly assess and allocate resources according to the anticipated complexity of each case. These operational insights are critical as we continue to enhance the scoring system's design and utility in clinical practice.

The Bone Tumor Surgery Complexity Score (BT-SCS) offers significant utility in surgical planning and resource allocation, facilitating a structured approach to assessing and managing bone tumor surgeries. Recognizing its limitations, such as potential biases from its retrospective design and the inherent subjectivity in any scoring system, is vital. Future research should focus on expanding the applicability of the BT-SCS in diverse settings, increasing sample diversity, and incorporating outcome metrics to enhance the score's comprehensiveness and predictive accuracy. Continuous refinement, based on emerging research and medical community feedback is essential for maintaining the score's relevance and utility in evolving clinical scenarios.

Future enhancements of the BT-SCS should include integrating machine learning techniques and patient outcome data to refine the categorization process. These technological advancements will enable more adaptive and responsive updates to the scoring system, accommodating changes in surgical techniques and patient demographics.

5. Conclusions

The development and validation of the Bone Tumor Surgery Complexity Score (BT-SCS) underscore its utility as a pivotal tool in the paradigm shift from volume-based to complexity-based assessments in bone tumor treatments. By providing a quantifiable, multi-dimensional approach to surgical case complexity, the BT-SCS enhances surgical planning, facilitates optimized resource allocation, and could potentially lead to improved patient care by enabling precise, tailored surgical interventions. Its development, through a meticulous consensus process among experienced sarcoma surgeons and a rigorous validation against the established Case Mix Index, illustrates the BT-SCS's robustness and

applicability in clinical practice. The prospective use of this tool in diverse clinical settings promises to support decision-making, improve benchmarking processes, and contribute to a value-based healthcare model. Future research endeavors should aim to further integrate patient outcomes into the BT-SCS framework, enhancing its predictive accuracy and clinical utility. As precision medicine continues to evolve, the BT-SCS is poised to become an essential component of patient-centered care, embodying the principles of modern, value-based healthcare systems.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy.

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Impact of Institutional Practices and Surgical Complexity on Sarcoma Surgery Costs: Driving Efficiency in Value-Based Healthcare

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Simple Summary: Sarcomas are rare cancers that are complex to treat and can be expensive to manage, especially when considering surgery costs. This research investigates how much sarcoma surgeries cost across three different hospitals in Switzerland and examines what factors might cause these costs to vary. By consistently using the same surgeon for all procedures, the study ensures that differences in surgical expertise do not affect the results, allowing a clear focus on hospital practices and the complexity of tumor impact costs. The findings aim to help hospitals better plan and manage resources, potentially leading to more cost-effective treatments. This study could influence how healthcare systems approach the financial aspects of treating complex cancers, encouraging a shift towards more standardized and economically sustainable practices.

Abstract: Background: Sarcomas present a unique challenge within healthcare systems due to their rarity and complex treatment requirements. This study explores the economic impact of sarcoma surgeries across three Swiss tertiary healthcare institutions, utilizing a consistent surgical approach by a single surgeon to eliminate variability in surgical expertise as a confounding factor. Methods: By analyzing data from 356 surgeries recorded in a real-world-time data warehouse, this study assesses surgical and hospital costs relative to institutional characteristics and surgical complexity. Results: Our findings reveal significant cost variations driven more by institutional resource management and pricing strategies than by surgical techniques. Surgical and total hospitalization costs were analyzed in relation to tumor dignity and complexity scores, showing that higher complexity and malignancy significantly increase costs. Interestingly, it was found that surgical costs accounted for only one-third of the total hospitalization costs, highlighting the substantial impact of non-surgical factors on the overall cost of care. Conclusions: The study underscores the need for standardized cost assessment practices and highlights the potential of predictive models in enhancing resource allocation and surgical planning. By advocating for value-based healthcare models and standardized treatment guidelines, this research contributes to more equitable and sustainable healthcare delivery for sarcoma patients. These insights affirm the necessity of including a full spectrum of care costs in value-based models to truly optimize healthcare delivery. These insights prompt a reevaluation of current policies and encourage further research across diverse geographical settings to refine cost management strategies in sarcoma treatment.

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Keywords: sarcoma surgery; healthcare economics; healthcare cost management; institutional resource utilization; surgical complexity; value-based healthcare; quality indicators; tumor complexity scores; predictive cost modelling; benchmarking

1. Introduction

Sarcomas, due to their rarity and the complexity of their treatment, present challenges within healthcare systems [1–3]. While advancements in oncological therapies have been made, understanding the economic impact of sarcoma treatments across different hospital settings remains limited [4–9]. This gap hinders the effective management and optimization of healthcare resources. Our study addresses this gap by elucidating the variations in surgical and hospital costs of sarcoma treatments within tertiary healthcare environments, supporting the shift towards value-based healthcare models.

Despite clinical advancements, the economic aspects of these treatments, particularly cost variability across different healthcare settings, are underexplored [5,6,10]. Most studies focus on clinical efficacy, often neglecting the substantial economic burdens these treatments impose [11,12]. Our study fills this gap by providing a detailed comparison of surgical and hospital costs and analyzing how institutional characteristics and surgical complexities impact healthcare economics.

Utilizing the Swiss Sarcoma Network (SSN) and the Sarconnector® data warehouse, this study assesses the impact of surgical complexity and institutional characteristics on treatment costs [13]. Leveraging advanced real-world-time data analytics, this research offers insights for more effective resource allocation and enhanced cost-efficiency in managing complex sarcoma surgeries.

The primary objective of this study is to analyze cost disparities across three distinct hospital settings, examining how institutional resources and surgical complexity influence economic outcomes. Importantly, all surgeries were performed by the same surgeon, eliminating variability in surgical expertise and isolating the institutional effects on costs. This study also explores the durations of hospital stays and surgeries to further understand factors contributing to healthcare efficiency and cost management.

2. Materials and Methods

This study utilized data from the Swiss Sarcoma Network (SSN), housed in the Adjumed.ch database, and transitioned to the Sarconnector® data warehouse (BF & PH, Zurich, Switzerland) [13,14]. We analyzed a cohort of 356 consecutive patients undergoing surgery for soft tissue or bone tumors across three large Swiss tertiary hospitals. The surgeries, all performed by the same surgeon, aimed to compare surgical and hospital costs, with secondary endpoints including durations of hospital stays and surgical procedures.

Tumor type and dignity were assessed per the 2020 WHO Classification.

Surgical complexity was evaluated using the published Soft-Tissue Tumor Complexity Score (STS-SCS) for soft tissue tumors and a preliminary Bone Tumor Complexity Score (BT-SCS) for bone tumors, capturing the intricacy of each case.

Cost data were meticulously standardized to focus on medically related expenses and extracted from detailed billing records to ensure consistency across the data. These include hospitalization and surgery costs, crucial for evaluating the economic aspects of sarcoma treatment across different institutional settings (Table 1).

Table 1. Definition of costs.

Category	Subcategory	Description
Hospitalization Costs	**Individual Costs**	
	Total Individual Costs	Direct individual costs specifically attributed to the patient's hospital stay.
	Medication Costs	Costs specifically incurred for medications uniquely used in this case during hospitalization.
	Material and Implant Costs	Costs for materials and implants specifically used for this patient during hospitalization.
	Common Costs	
	Total Common Costs	General overhead costs that are shared among various patients but are part of the hospitalization expenses.
	Operating Room costs	Costs associated with the use of operating rooms include infrastructure, personnel, and minor materials shared among surgical specialists.
	Anesthesia and Recovery Room Costs	Costs related to anesthesia services and the recovery room are applicable to multiple patients during hospitalization.
	Intensive Care Costs	Costs for intensive care are shared across patients needing such services during hospitalization.
	Medical (Fraternity) Staff Costs	Costs for surgical and general medical staff involvement spread over multiple cases during hospitalization.
	Nursing Costs	Nursing costs at the ward level, shared among patients during hospitalization.
Surgical Costs	**Direct Costs**	
	Operating Room Usage Costs	Costs associated with operating room time (patients arrival until leaving), including all aspects of OR management and nursing costs as well as apportionment of indirect costs.
	Surgical Staff Costs	Direct costs for medical fraternity present in the operating room, calculated based on surgical service time.
	Anesthesia Costs	Anesthesia costs during surgery and for the (anesthesia-led) recovery room. During surgery, the cost is calculated in one of four categories, depending on the type of anesthesia. In the recovery room, a minute-based cost is calculated.
	Indirect Costs	
	Anesthesia Costs	Apportionment of indirect costs.

Table 1 summarizes hospitalization and surgery costs from sarcoma surgeries at three Swiss healthcare institutions, detailing: ***Individual costs:*** Costs are directly and uniquely attributable to a specific patient's treatment. These are the expenses incurred that can be exclusively associated with a single case. ***Common costs:*** Costs incurred by the healthcare facility that are shared among multiple patients. These costs are not exclusive to any single patient's care and are distributed across various treatments and services. ***Direct (surgical) costs:*** These are costs in a surgical setting that are directly associated with the patient's surgery, such as operating room usage and staffing. ***Indirect (surgical) costs:*** These costs are not directly tied to the actual performance of the surgery but are necessary to support the surgical process.

This methodological approach ensures comprehensive coverage of cost and care complexities, facilitating an in-depth comparative analysis across the three institutions. Detailed demographic and complexity data, along with raw numbers of tumor entities and categories, are systematically presented in the appendices to support further granular analyses.

Categorical variables were described as numbers (percentage), while numerical variables were described as medians (1st quartile, 3rd quartile). Differences between categorical variables were tested using the Chi-square or Fisher's exact test. Differences between numerical variables were tested using the Kruskal–Wallis test (for comparisons between

>2 groups), Student's t-test, or the Mann–Whitney test. Pearson correlation coefficients were calculated.

Costs, strictly representing direct medical expenses, were analyzed using multivariable linear regression to adjust for complexity score, tumor dignity, institution, and procedural durations, identifying cost drivers and institutional variations. The beta coefficient and corresponding 95% Confidence Interval (CIs) were reported. The analyses differentiated between impacts derived from numerical and categorical complexity scores to provide a more comprehensive understanding of how each type of scoring influences cost distribution and resource utilization. $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using R statistical software (Version 4.3.1.).

3. Results

We have included 356 consecutive patients in our analysis. Of those, 132 were treated in institution A, 121 were treated in institution B, and 103 were treated in institution C. Patient characteristics are presented in Table 2. The median age and the gender distribution of patients across all institutions showed no significant variations between institutions. Tumor dignity varied across the institutions ($p = 0.03$), with Institution C treating a higher proportion of malignant cases. The complexity scores, which reflect the surgical challenge, showed significant differences among the institutions ($p = 0.002$), particularly with Institution C handling more complex cases. The Case Mix Index (CMI), indicative of patient case complexity and resource utilization, also differed significantly, with Institution C having a higher median CMI of 1.09 compared to 0.85 in the others ($p = 0.001$).

Table 2. Patient characteristics stratified by institution.

	Overall n = 356	**Institution A n = 132**	**Institution B n = 121**	**Institution C n = 103**	***p*-Value**
Age	51.0 (34.0, 65.0)	52.5 (37.0, 67.0)	51.0 (34.0, 62.0)	48.0 (33.0, 63.0)	0.33
Female	157 (44.1%)	56 (42.4%)	45 (46.3%)	45 (43.7%)	0.82
Dignity					0.03
Benign	115 (32.3%)	42 (31.8%)	50 (41.3%)	23 (22.3%)	
Intermediate	80 (22.5%)	31 (23.5%)	26 (21.5%)	23 (22.3%)	
Malignant	161 (45.2%)	59 (44.7%)	45 (37.2%)	57 (55.4%)	
Complexity score					0.002
1	25 (7.0%)	8 (6.0%)	14 (11.6%)	3 (2.9%)	
2	77 (21.6%)	34 (25.8%)	31 (25.6%)	12 (11.7%)	
3	110 (30.9%)	33 (25.0%)	40 (33.1%)	37 (35.9%)	
4	118 (33.1%)	46 (34.8%)	29 (24.0%)	43 (41.7%)	
Case mix index (CMI)	0.86 (0.71, 1.37)	0.85 (0.70, 1.38)	0.85 (0.70, 1.30)	1.09 (0.77, 1.63)	0.001

Numerical variables presented as Median (1st quartile, 3rd quartile).

3.1. Duration of Hospital Stay

In our analysis of 356 patients, we observed significant differences in the median duration of hospital stays across three institutions (Table 3). Institution A reported a median stay of 4 days (interquantile range 2.0 to 8.0), Institution B had a shorter median stay of 3 days (interquantile range 2.0 to 7.0), and Institution C experienced a longer median stay of 5 days (interquantile range 3.0 to 11.5), with these variations reaching statistical significance ($p < 0.001$). Additionally, the duration of hospital stays varied significantly with tumor dignity; patients with benign tumors had a median stay of 2 days (interquantile range 2.0 to 3.5), those with intermediate tumors stayed for 4 days (interquantile range 2.0 to 7.0), and patients with malignant tumors stayed for 8 days (interquantile range 5.0 to 13.0). A clear trend of increasing hospital stay duration with higher complexity scores was also observed; the median stay was 2 days for scores 1 and 2, 4 days for score 3, and

9 days for score 4 ($p < 0.001$ for all). These findings underscore the impact of institutional characteristics, tumor dignity, and complexity on the length of hospitalization.

Table 3. Duration of stay, tumor dignity, and complexity score. Results are reported as Median (1st quartile, 3rd quartile).

Characteristic	Overall	Institution A	Institution B	Institution C	*p*-Value
Duration of Stay	4.0 (2.0–8.0)	4.0 (2.0–8.0)	3.0 (2.0–7.0)	5.0 (3.0–11.5)	<0.001
By Tumor Dignity					<0.001
-benign	2.0 (2.0–3.5)	2.0 (2.0, 3.0)	2.0 (1.0, 3.0)	3.0 (2.0, 4.0)	
-intermediate	4.0 (2.0–7.0)	4.0 (3.0, 7.0)	3.0 (2.0, 6.0)	4.0 (2.5, 7.5)	
-malignant	8.0 (5.0–13.0)	8.0 (4.5, 13.0)	7.0 (5.0, 9.0)	9.0 (5.0, 15.0)	
By Complexity Score					<0.001
-Score 1	2.0 (1.0–3.0)	1.5 (1.0, 2.25)	2.0 (2.0, 3.0)	2.0 (2.0, 2.0)	
-Score 2	2.0 (2.0–3.0)	2.0 (2.0, 3.0)	2.0 (1.0, 2.5)	3.0 (2.0, 4.0)	
-Score 3	4.0 (2.25–7.0)	4.0 (3.0, 7.0)	4.0 (2.0, 7.0)	3.0 (2.0, 6.0)	
-Score 4	9.0 (5.0–13.0)	9.0 (5.25, 13.0)	7.0 (5.0, 9.0)	10.0 (5.5, 14.5)	

Numerical variables are presented as Median (1st quartile, 3rd quartile).

The relationship between complexity score and hospital stay duration is depicted in Figure 1, showing a substantial, statistically significant correlation coefficient of 0.70 ($p < 0.001$). The trend line demonstrates an increase in stay duration as complexity scores rise, with the confidence interval indicating the estimate's precision.

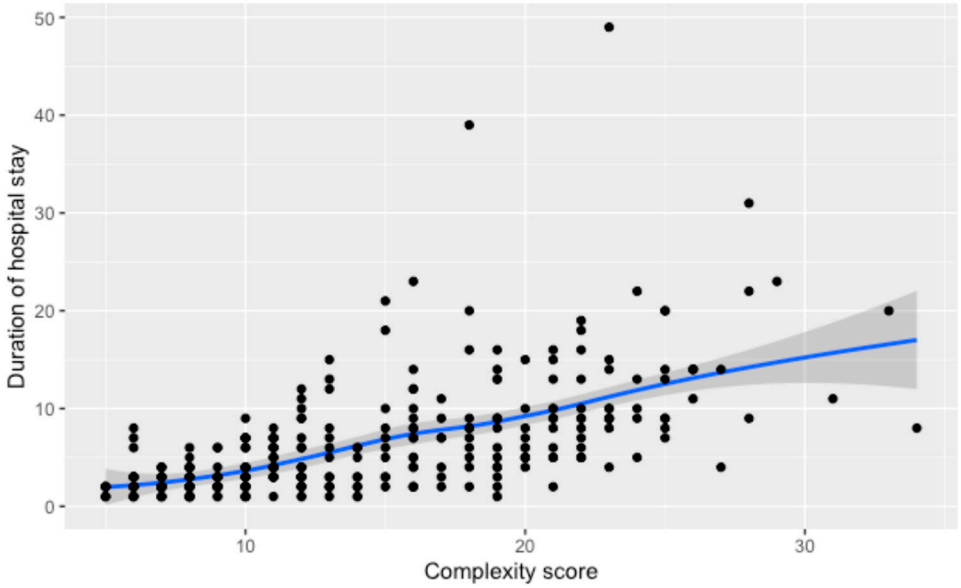


Figure 1. Relationship between the numerical complexity score and duration of hospital stay. Loess smoothing was applied to allow for a potential non-linear relationship.

3.2. Duration of Surgery

The median duration of surgery across the study cohort was 89.5 min, with an interquartile range of 56 to 165 min, and no significant differences were observed between institutions ($p = 0.76$). A detailed analysis by tumor dignity revealed significant variability, with benign tumors requiring the least time at a median of 60 min, intermediate tumors at 86 min, and malignant tumors demanding the most time at a median of 150.5 min ($p < 0.001$). Surgery duration also increased with tumor complexity, rising from a median of 44 min for the least complex cases (score 1) to 163 min for the most complex

cases (score 4), substantiating the strong influence of tumor complexity on surgical time ($p < 0.001$) (Table 4).

Table 4. Overall duration of surgery, tumor dignity, and complexity score. Results are reported as Median (1st quartile, 3rd quartile).

Characteristics	Overall	Institution A	Institution B	Institution C	*p*-Value
Duration of surgery	89.5 (56.0–165.0)	83.5 (61.0, 176.0)	89.0 (56.0, 147.0)	90.0 (53.0, 199.5)	0.76
Tumor Dignity					<0.001
-benign	60.0 (43.0–82.3)	62.5 (40.0–75.8)	57.5 (47.3, 94.8)	60.0 (41.5, 89.3)	
-intermediate	86.0 (58.0–123.5)	82.0 (61.5–120.0)	87.5 (58.8, 108.8)	90.0 (40.0, 167.0)	
-malignant	150.5 (80.3–277.5)	185.0 (87.0–374.0)	144.0 (93.0, 237.0)	147.0 (60.5, 255.5)	
Complexity Score					<0.001
-Score 1	44.0 (33.0–59.0)	46.5 (38.0–78.8)	48.5 (38.0, 58.8)	32.0 (31.0, 36.0)	
-Score 2	57.5 (43.3–75.8)	62.0 (41.0–75.8)	55.0 (46.5, 73.0)	52.0 (42.0, 81.0)	
-Score 3	90.0 (58.0–136.0)	77.0 (62.0–106.0)	106.0 (74.0, 152.5)	77.5 (41.3, 161.8)	
-Score 4	163.0 (103.8–336.0)	198.5 (112.0–383.5)	144.0 (93.0, 246.0)	158.0 (113.0, 281.0)	

Comparing the numerical complexity score and the duration of surgery, we found a non-linear relationship. Initial increases in complexity correlate with a linear rise in surgical time, but for scores beyond 20, the duration sharply ascends, as demonstrated by the steepening curve. A regression analysis shows that surgeries for patients with a complexity score higher than 20 take, on average, 255 additional minutes compared to those with lower scores (95% CI; 223,287), $p < 0.001$, underscoring the substantial impact of high complexity on surgery duration (Figure 2).

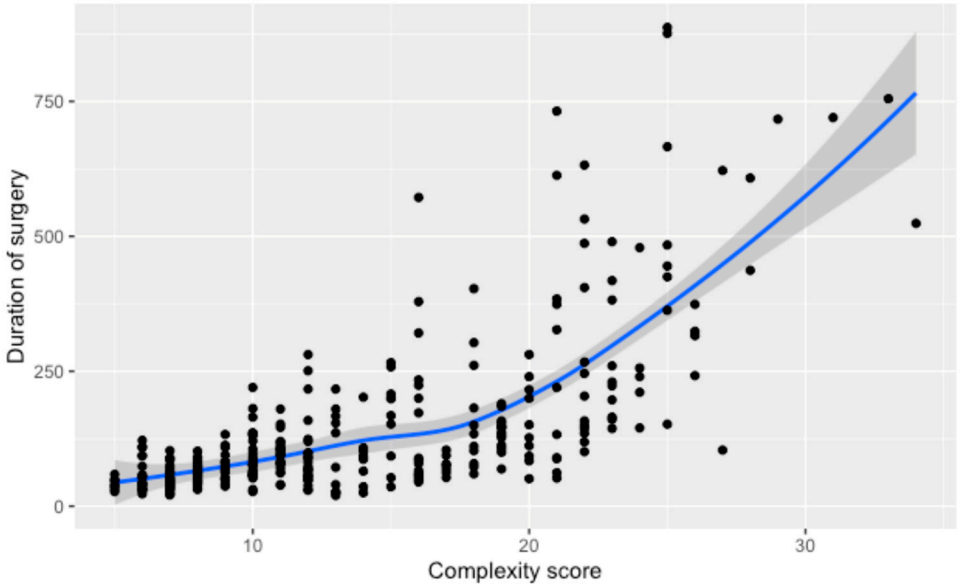


Figure 2. Relationship between the numerical complexity score and the duration of surgery. Loess smoothing was applied to allow for a potential non-linear relationship.

3.3. Costs of Surgery

The median cost of tumor surgery within the patient cohort was CHF 3519, with an interquartile range from CHF 2502 to CHF 5945. Institution-specific analysis revealed significant cost differences: CHF 3118 for Institution A, CHF 3408 for Institution B, and CHF 4611 for Institution C, with statistically significant variations among them ($p = 0.001$). When examining costs by tumor dignity, benign surgeries were least expensive at a median of CHF 2570, while malignant surgeries were most costly at CHF 5502, showing significant

cost differences ($p < 0.001$). Furthermore, costs rose with increasing complexity scores, from CHF 2207 for the simplest surgeries to CHF 5964 for the most complex, reflecting the substantial impact of complexity on surgical costs ($p < 0.001$) (Table 5).

Table 5. Overall costs for surgery, tumor dignity, and complexity score. Results are reported as Median (1st quartile, 3rd quartile).

Factor	Overall [CHF]	Institution A [CHF]	Institution B [CHF]	Institution C [CHF]	*p*-Value
Costs Surgery					0.001
	3519 (2502–5945)	3118 (2228–6142)	3408 (2464–5050)	4611 (2957–7885)	
Total Cost by Dignity					<0.001
-benign	2570 (1998–3321)	2259 (1868–2743)	2612 (2016–3578)	3087 (2532–3841)	
-intermediate	3545 (2571–5062)	3317 (2385–4325)	3262 (2332–4001)	4693 (3388–7044)	
-malignant	5502.7 (3270–10,281)	6137 (3076–10694)	4616 (3709–7871)	5349 (3074–12,762)	
Total Cost by Complexity Score					<0.001
-Score 1	2207 (1584–2760)	2247 (1455–2709)	2041 (1689–2511)	3087 (2074–3278)	
-Score 2	2431 (1969–3035)	2259 (1889–2915)	2473 (2064–2987)	2990 (2342–3631)	
-Score 3	3531 (2627–5250)	3010 (2366–3796)	3846 (2918–5375)	3767 (2924–5559)	
-Score 4	5964 (3948–11,747)	6300 (4108–11,491)	4616 (3709–8039)	6291 (4811–13,715)	

A non-linear rise in surgery costs with increasing complexity scores is depicted in Figure 3, showcasing a moderate climb until reaching a score of 20. Beyond this point, there's a marked and notable upsurge in expenses. Cases that exceed a complexity score of 20 exhibit an average cost increase of CHF 7627, signaling a substantial elevation in the financial burden for surgeries of greater complexity.

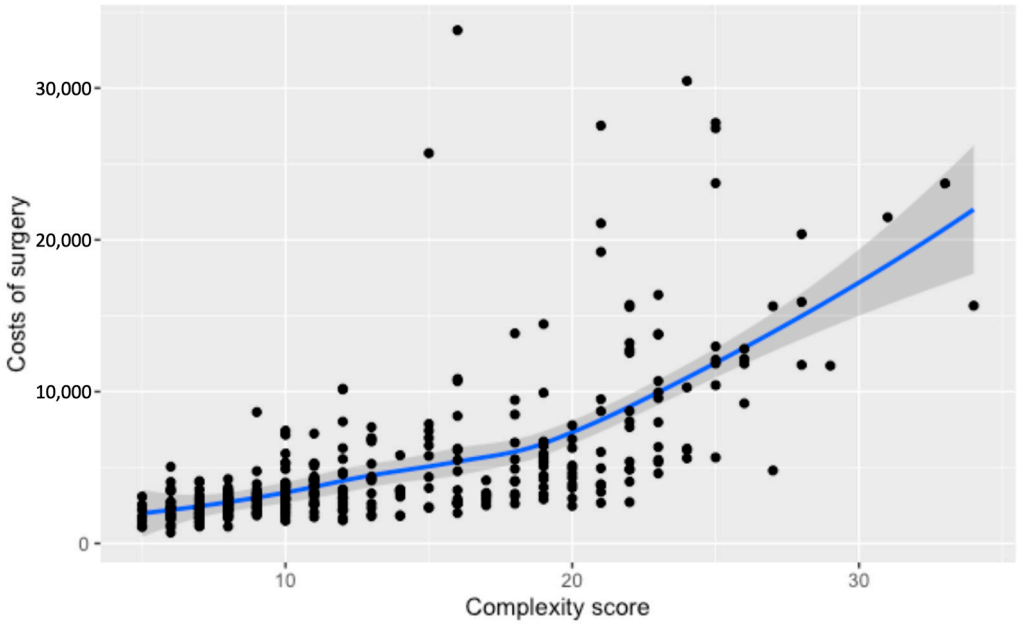


Figure 3. Relationship between the numerical complexity score and the costs of surgery (c). Loess smoothing was applied to allow for a potential non-linear relationship.

The comparison across institutions depicts a divergence in surgery costs in relation to complexity scores (Figure 4). Institution C's curve is positioned above the rest, indicating consistently higher costs throughout the complexity spectrum. The separation between the institutional curves becomes pronounced at higher complexity levels, particularly after surpassing a score of 20. These cost discrepancies among institutions have been statistically substantiated, with Institution C incurring significantly higher expenses than A and B

($p < 0.001$). The visualization underscores the pronounced impact that both the complexity of surgical procedures and institutional factors have on the cost of care.

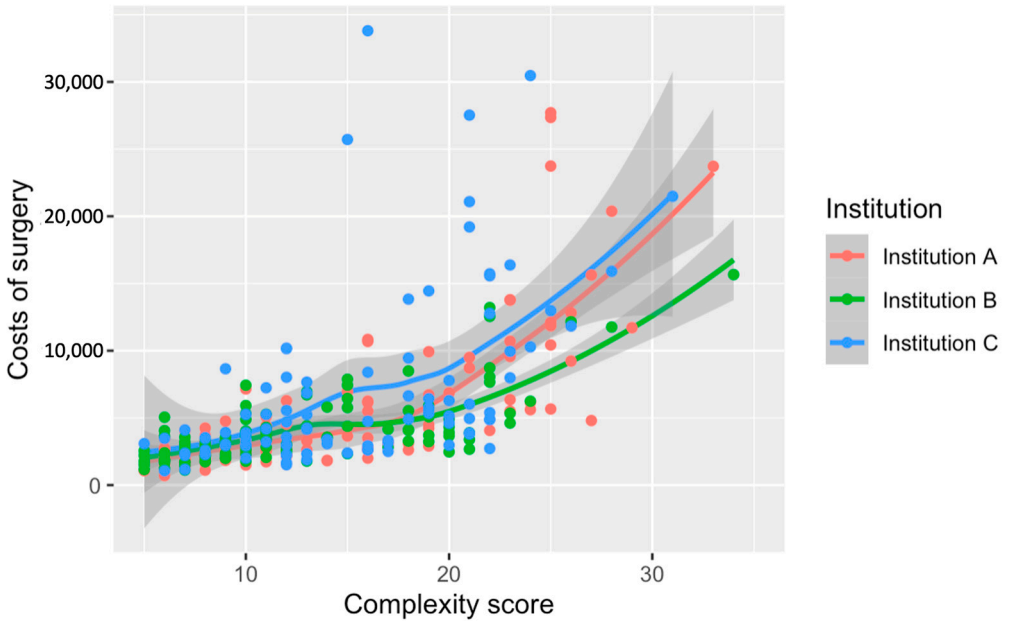


Figure 4. Relationship between the numerical complexity score and costs of surgery stratified by institution. Loess smoothing was applied to allow for a potential non-linear relationship.

3.4. Total Costs for Hospitalization

The median total cost for all patients involved in the study was CHF 10,378, with an interquartile range from CHF 6865 to CHF 18,806. Institutionally, median total costs varied, with Institution A at CHF 8827, Institution B at CHF 10,564, and Institution Cat at CHF 11,990, indicating a marginal statistical difference ($p = 0.05$). Total costs demonstrated a significant disparity with tumor dignity, with benign tumors costing CHF 6828, intermediate CHF 10,062, and malignant CHF 18,374 ($p < 0.001$). A statistically significant gradient was also seen with complexity scores, showing CHF 5650 for score 1, escalating to CHF 22,779 for score 4 ($p < 0.001$). Adjusted for variables such as complexity score, tumor dignity, and durations of surgery and hospital stay, Institution B's total costs were on average CHF 1737 higher than A, and costs in Institution C were CHF 1426 lower compared to B (Table 6).

Table 6. Total costs for hospitalization, tumor dignity, and complexity score.

Factor	Overall Median Cost [CHF]	Institution A [CHF]	Institution B [CHF]	Institution C [CHF]	*p*-Value
Total Costs	10,378 (6865–18,806)	8827 (6116–16,719)	10,564 (6852–17,310)	11,990 (8121–26,390)	0.005
Cost by Tumor Dignity					<0.0001
–Benign	6828 (5419–8739)	5825 (4939–7291)	7189 (5569–10,875)	7363 (6161–8816)	
–Intermediate	10,062 (7119–13,004)	8745 (6567–12,226)	9616 (6954–12,449)	12,221 (9467–16,404)	
–malignant	18,374 (10,160–37,228)	20,123 (8878–38,691)	18,079 (12,877–31,054)	18,627 (10,292–40,374)	
Cost by Complexity Score					<0.001
–Score 1	5650 (5217–8007)	5535 (4988–5708)	5882 (5235–9202)	6525 (5609–7568)	
–Score 2	6568 (5431–7814)	5942 (4939–7761)	6852 (5604–7775)	7312 (6120–8001)	
–Score 3	10,367 (7118–15,369)	8705 (6619–12,186)	13,817 (8459–17,281)	10,876 (7019–14,072)	
–Score 4	22,779 (11,752–39,198)	23,526 (10,692–41,764)	18,079 (12,368–26,846)	25,677 (12,579–43,020)	

Total costs demonstrate a progressive increase in association with higher complexity scores. A steady incline in costs becomes more pronounced at higher complexity levels, reflecting the growing financial impact of more intricate surgical cases. When Loess smoothing is applied, the data reveal a generally upward, albeit less pronounced, trend

in total costs with rising complexity, contrasting with the more marked effects on surgery duration and direct surgery costs (Figures 5 and 6).

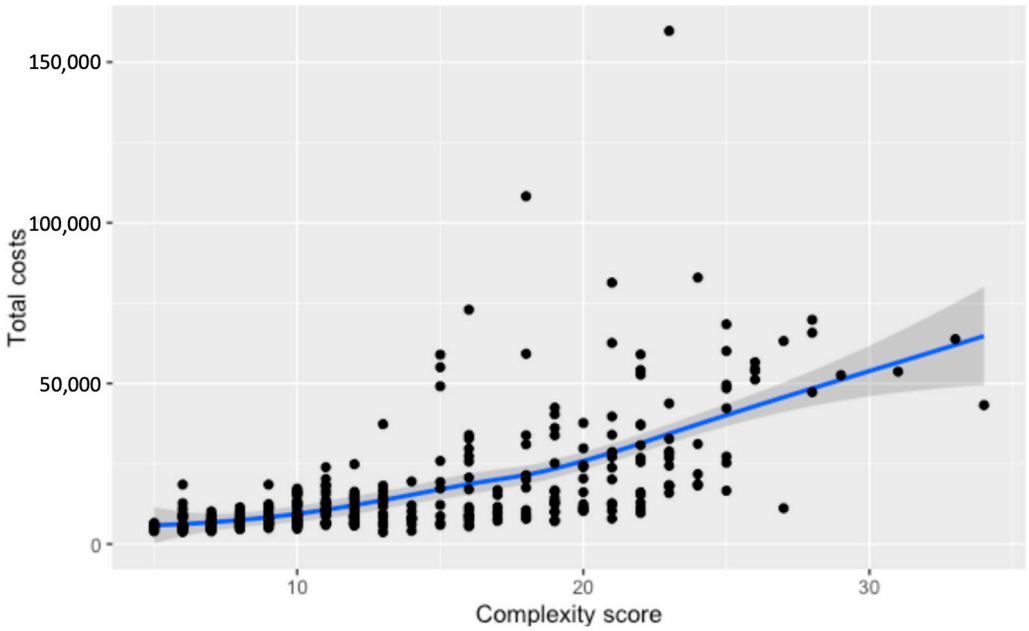


Figure 5. Relationship between the numerical complexity score and total costs for hospitalization. Loess smoothing was applied to allow for a potential non-linear relationship.

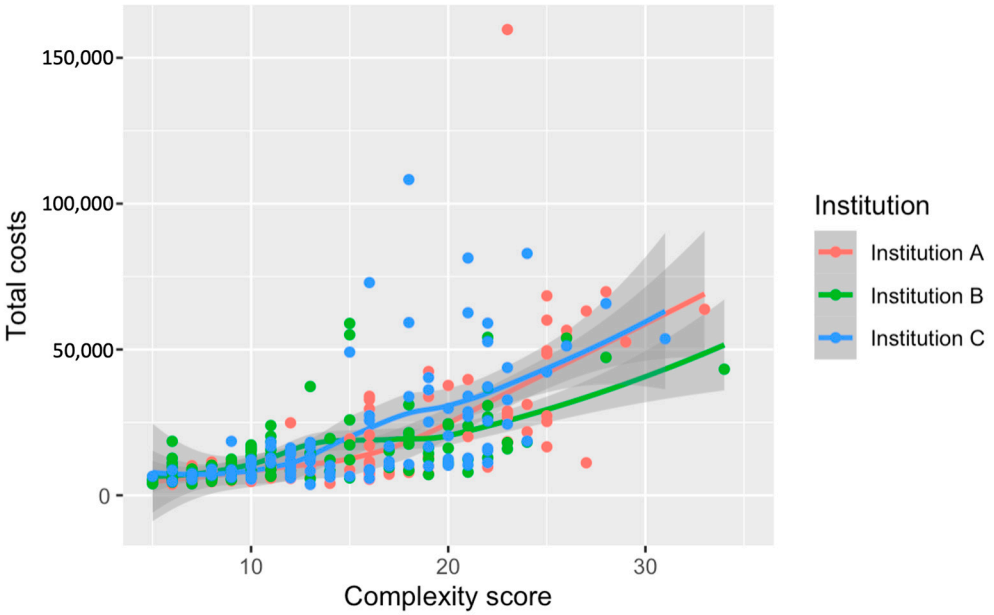


Figure 6. Relationship between the numerical complexity score and total costs for hospitalization stratified by institution. Loess smoothing was applied to allow for a potential non-linear relationship.

4. Discussion

Our investigation revealed significant variations in financial and operational metrics across three healthcare institutions in one country, particularly emphasizing the role of surgical complexity and tumor characteristics in influencing cost metrics. All surgeries were performed by the same surgeon, thus eliminating variations in surgical expertise and technique as potential confounders. While this approach helps isolate institutional factors such as resource utilization, efficiency, and possible institutional policies on pricing

strategies, it is also crucial to recognize that variations in surgical expertise among different surgeons can significantly impact economic policies and overall healthcare costs. Future research should consider the influence of surgeon expertise on cost variability to provide a more comprehensive understanding of economic factors in healthcare.

The median total costs for all patients were CHF 10,378, with Institution C exhibiting notably higher expenses at CHF 11,990, suggesting variations in institutional resource allocation and management efficiency. While surgical costs averaged CHF 3519, they constituted only about one-third of the total hospitalization costs, underscoring the significant role of postoperative care and extended hospital stays. Furthermore, our analysis demonstrated substantial disparities in costs based on tumor dignity, with malignant tumors resulting in the highest expenditures at a median of CHF 18,374, directly correlating tumor severity and treatment complexity with increased healthcare expenditures. Complexity scores strongly correlated with both surgical and hospitalization costs, showing a non-linear increase in expenses as complexity scores exceeded 20, emphasizing the critical need for precise surgical and resource planning.

Our study's insights into the economic impact of institutional policies and resource management on sarcoma surgery costs align with and expand upon existing literature. Kuek et al. discuss how surgical costs influence the quality of care across economic environments, underscoring the role of cost in treatment accessibility and quality [5]. Similarly, Morattel et al. illustrate how unplanned surgeries escalate costs, supporting our emphasis on the economic benefits of strategic preoperative planning [15]. Alamanda et al. quantify the financial impact of reexcising incompletely excised sarcomas, highlighting the economic advantages of precise surgical interventions [16]. These studies collectively advocate for standardized practices to mitigate cost disparities, resonating with our observations of non-linear cost increases with higher complexity scores. Additionally, our research underscores the potential of predictive modeling and value-based healthcare frameworks to optimize resource allocation [10].

Our examination of cost variations across three institutions revealed significant disparities that are more reflective of institutional policies and system-level efficiencies than differences in surgical expertise. Differences in the use of surgical supplies, the adoption of new technologies, and the extent of ancillary services provided might account for the observed variations in expenditures. While our approach helps isolate these factors, it is important to note that variations in surgical expertise among different surgeons can significantly impact economic policies and overall healthcare costs. Future research should consider the influence of surgeon expertise on cost variability to provide a more comprehensive understanding of economic factors in healthcare.

The management of high-complexity cases provides further insights into how institutional protocols and the availability of specialized support services influence costs. Despite uniform surgical expertise, variation in expenses could be attributed to differing approaches in preoperative care, postoperative management, and the use of intensive care facilities. This underscores the necessity for standardized guidelines that can streamline care pathways across institutions, potentially reducing unnecessary variations in patient care and associated costs.

Moreover, this study reinforces the importance of establishing clear and consistent definitions of what constitutes surgical and hospital costs across different settings. A standardized approach to cost categorization and accounting would enhance the ability to compare and benchmark costs meaningfully across institutions. This is particularly relevant in settings where surgical interventions are performed by the same healthcare professionals, highlighting that differences in costs are largely driven by institutional practices and policies rather than individual surgeon performance.

The disparities in surgical costs across institutional settings and varying complexity scores highlight the necessity for refined surgical planning and patient care, underscoring the urgent need for targeted resource allocation strategies. Given the unique and diverse nature of sarcoma surgeries, our study advocates for harmonized accounting practices that

accommodate the exceptional nature of each surgical case, promoting cost management that reflects the true complexity and needs of each procedure.

Our findings strongly support the advancement of value-based healthcare initiatives, suggesting that integrating predictive models based on complexity scores could significantly enhance preoperative planning and patient outcomes. Such models could serve as a cornerstone for developing more streamlined care pathways, particularly for managing complex and severe cases. Moreover, the clear trends in cost relative to complexity and tumor severity provide a robust framework for predictive budgeting and resource planning.

Furthermore, the potential for policy adjustments based on our findings is substantial. Policymakers are encouraged to consider the benefits of shifting towards a value-based healthcare model that prioritizes efficiency and cost-effectiveness, especially in the treatment of high-complexity surgical cases [17–21]. By adopting policies that foster the implementation of such models, healthcare systems can better manage expenditures while improving clinical outcomes.

Our study, while offering insightful contributions to understanding surgical cost variations in sarcoma treatment, has inherent limitations that must be acknowledged. One significant challenge is the lack of uniformity in cost assessment across the different institutions. The definitions of surgical and hospital costs varied, which might have influenced the comparability of our findings. Although efforts were made to standardize these definitions, the subtleties in cost allocation and accounting practices could lead to different interpretations, potentially affecting the study's outcomes. Future research should aim to refine these definitions and develop a more standardized approach to cost assessment in healthcare settings to enhance comparability [22].

Additionally, the geographical and cultural homogeneity of the institutions involved—all located within a small country with minimal cultural and demographic differences—may limit the extrapolation of our results to the international community. While our study is based on data from Swiss hospitals, the findings highlight important factors that could be relevant to other healthcare systems with the necessary adaptations. The similar patient profiles across these institutions might obscure broader variations that could become apparent in a more diverse sample. Despite this, the evident cost disparities found within such a homogenous group underscore the intrinsic differences in institutional cost management and highlight the need for further investigation into the underlying causes of these variations.

These limitations underscore the complexity of healthcare cost analysis and point to the necessity for ongoing research that includes a broader range of institutions and more diverse geographical settings. This would help to validate the findings and potentially reveal additional insights that could inform policy changes and lead to more equitable and efficient healthcare delivery.

5. Conclusions

This study demonstrates significant cost variations in sarcoma surgery, primarily driven by institutional practices rather than surgical expertise. By using a consistent surgeon across all cases, we isolated institutional influences, such as resource utilization, management efficiency, and pricing strategies, which significantly affect healthcare expenditures. Notably, surgical costs constituted only a third of total hospitalization costs, emphasizing the need for comprehensive cost assessments that encompass the full spectrum of care.

We advocate for the adoption of standardized treatment guidelines and value-based healthcare models that integrate full-spectrum cost considerations, enhancing cost-effectiveness and sustainability in managing complex medical conditions. Further research should account for variations in surgical expertise and include geographical settings to validate and refine these strategies, ensuring equitable and efficient healthcare delivery for conditions like sarcoma.

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Exploring Risk Factors for Predicting 30-Day Postoperative Morbidity in Musculoskeletal Tumor Surgery

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Abstract: Background: This study investigates the risk factors associated with postoperative complications in musculoskeletal tumor surgeries and evaluates the impact of benchmarking in enhancing surgical outcomes. **Methods**: Conducted at a tertiary referral center, this retrospective analysis included 196 patients who underwent surgeries for various musculoskeletal tumors, ranging from soft tissue to bone sarcomas. Patient and tumor characteristics, along with surgical interventions and outcomes, were comprehensively assessed using the Charlson Comorbidity Index and the Clavien-Dindo classification. **Results**: Key findings indicate that surgical reconstruction, ASA 3 status, bone tumor presence, and the need for multiple erythrocyte transfusions significantly increase postoperative morbidity. Notably, no significant correlation was found between the Charlson Comorbidity Index scores and the occurrence or severity of complications, challenging the utility of this index in predicting short-term surgical outcomes. **Conclusions**: This study highlights the importance of tailored surgical approaches and emphasizes rigorous preoperative assessments to mitigate risks and enhance patient care. Despite its insights, limitations include its retrospective nature and single-center scope, suggesting a need for broader, multicenter studies to generalize findings. Overall, our results underscore the necessity of integrating clinical assessments with benchmarking data to optimize outcomes in the complex field of musculoskeletal tumor surgery.

Keywords: musculoskeletal sarcoma surgery; benchmarking; real-world-time data assessment; risk factors; 30-day morbidity; Clavien-Dindo complications; Charlson Comorbidity index

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1. Introduction

Musculoskeletal tumor surgeries present unique challenges due to their complexity and the substantial risk of postoperative complications [1]. Identifying and understanding the risk factors associated with these complications is crucial for optimizing patient outcomes and enhancing healthcare efficiency [2]. This study focuses on exploring these risk factors, aiming to contribute to better surgical planning and risk management.

Benchmarking has emerged as a vital practice in healthcare to evaluate and improve patient outcomes [3–5]. By comparing practices and outcomes across institutions or between disciplines, benchmarking helps establish best practices and set standards of care, particularly in high-stakes fields like sarcoma surgery [6,7]. In this context, our study aims to establish the standardized use of benchmarking in sarcoma care to understand how different risk factors influence postoperative morbidity.

Furthermore, the complexities of musculoskeletal tumor surgery, encompassing a broad spectrum of tumor types and surgical interventions, necessitate a detailed examination of postoperative risks. Therefore, this study aims to fill gaps in current knowledge by systematically assessing these risks in relation to patient-specific factors such as the Charlson Comorbidity Index and the nature of the tumor (bone vs. soft tissue). Additionally, we employ the Clavien-Dindo classification of complications to provide a standardized framework for evaluating and reporting surgical outcomes, which is crucial for developing effective risk stratification tools [8–11].

2. Materials and Methods

2.1. Study Design

This was a retrospective observational study that used real-world-time data from a tertiary referral center (Cantonal Hospital of Lucerne).

This study was designed to encompass the broad spectrum of musculoskeletal tumor surgeries, ranging from minor excisions to major resections across various anatomical locations, including both benign and malignant lesions. This comprehensive approach reflects the clinical reality surgeons face in orthopedic oncology, thereby enhancing the relevance and applicability of our findings to diverse healthcare settings [3].

2.2. Tumor Classification and Surgical Interventions

Malignant, benign, and intermediate (locally aggressive or rarely metastasizing) musculoskeletal tumors were included based on pathological assessments and clinical behavior. Each tumor was classified not only by its nature but also by its location and the type of surgical intervention used, according to the WHO 2020 classification [12]. This detailed categorization allows for a precise analysis of outcomes and complications associated with specific surgical treatments [13].

2.3. Study Population and Data Collection

This study included a consecutive cohort of patients from a real-world-time data warehouse who underwent surgical procedures for all musculoskeletal tumors presented at a tertiary referral institution over a four-year period (9 January 2018 to 11 April 2022) [3]. The cohort included patients with both soft tissue and bone tumors, encompassing the entire spectrum from benign and intermediate to malignant tumors and sarcomas. All surgeries were performed by an experienced fellowship-trained sarcoma surgeon (BF) with more than 20 years of experience. Comprehensive data were collected from medical records, including patient demographics, tumor characteristics, surgical details, and postoperative outcomes.

2.4. Assessment of Comorbidities

To systematically assess the impact of comorbidities on surgical outcomes, the Charlson Comorbidity Index (CCI) was calculated [8]. The CCI quantifies the severity of comorbid conditions that might alter the risk of mortality, with each condition assigned a specific weight based on its potential influence on mortality risk. This scoring system encompasses a range of conditions, including but not limited to, heart disease, diabetes, and hypertension, thus providing a comprehensive measure of patient health status. Details of the conditions included in the CCI and their respective weights are presented in Table 1 [9–11].

Table 1. Charlson Comorbidity Index scoring system [8].

Condition	Weight
Myocardial infection	1
Congestive Heart Failure	1
Peripheral Vascular Disease	1
Cerebrovascular Disease	1

Table 1. *Cont.*

Condition	Weight
Dementia	1
Chronic Pulmonary Disease	1
Rheumatic Disease	1
Peptic Ulcer Disease	1
Mild Liver Disease	1
Diabetes without Complications	1
Diabetes with Complications	2
Hemiplegia or Paraplegia	2
Renal Disease	2
Any Malignancy	2
Moderate or Severe Liver Disease	3
Metastatic Solid Tumor	6
AIDS/HIV	6

Overview of the Charlson Comorbidity Index (CCI) showing each condition considered in the index and the associated weights used to assess overall comorbidity and predict mortality risk in patients.

2.5. Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics, with categorical variables (e.g., gender, tumor location) presented as frequencies and percentages and continuous variables (e.g., age, tumor size) as means (± standard deviation) or medians (1st quartile [Q1], 3rd quartile [Q3]), based on distribution. Key associations, such as between the Charlson Comorbidity Index and 30-day postoperative morbidity, were visualized using a density plot and analyzed using chi-square or Fisher's exact tests for categorical variables and Student's t-test or Mann–Whitney U tests for continuous ones. Complications were classified according to the Clavien-Dindo classification, which stratifies surgical complications by their severity (Table 2). This categorization helps in the standardized reporting of adverse outcomes and facilitates comparison across studies. Multivariable logistic regression was applied to identify independent predictors of complications, adjusting for potential confounders. Statistical significance was set at a p-value of less than 0.05, with all analyses conducted in R (version 4.3.1).

Table 2. Clavien-Dindo classification [9,10].

I	Any deviation from the normal postoperative course without the need for pharmacological treatment re surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. Also included is wound infection opened at the bedside.
II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Also included are blood transfusions and total parenteral nutrition.
IIIa	Requiring surgical, endoscopic, or radiological intervention.
IIIb	Intervention under general anesthesia.
IVa	Life-threatening complication (including CNS complications) requiring ICU management; single organ dysfunction.
IVb	Multiorgan dysfunction.
V	Death of patient

3. Results

3.1. Patient and Tumor Characteristics

This study analyzed 187 patients undergoing 196 musculoskeletal tumor surgeries, encompassing an array of soft tissue and bone lesions. Specifically, 146 patients presented

with soft tissue lesions and 41 with bone lesions, classified into 100 malignant, 42 intermediate, and 45 benign types. Noteworthy, a significant subset of soft tissue lesions were lipomatous, with a variety of other types including undifferentiated sarcomas and myo-/fibroblastic tumors. Bone lesions varied from chondrogenic to osteoblastic and included rare types such as Ewing sarcomas and notochordal tumors. Detailed categorizations of these lesions are provided in Table 3.

Table 3. Patient and tumor characteristics.

Category	Total Number	Malignant	Intermediate *	Benign	Specific Types (Number)
Total Patients	187	100	42	45	
Soft Tissue Lesions	146	76	34	36	Lipomatous (64), Undifferentiated Sarcomas (18), Myo-/Fibroblastic (27), Uncertain Origin (14), Smooth Muscle (9), Nerve Sheath (4), Fibrohistiocytic (3)
Bone Lesions	41	24	8	9	Chondrogenic (14), Osteoblastic (12), Ewing Sarcomas (3), Giant-cell rich (2), giant cell tumor (2)

This table Overview of patient demographics and tumor characteristics, detailing the distribution and classification of lesions among the 187 patients studied. The table breaks down the total number of patients presenting with soft tissue and bone lesions, their categorization into malignant, intermediate, and benign types, and details specific tumor types within each category. (* locally aggressive or rarely metastasizing according to WHO 2020).

3.2. Demographic Overview

The demographic and clinical characteristics of the analyzed patients, including age, gender, racial composition, and health status, highlight significant variations in patient profiles and medical complexities. Detailed demographic data, stratified by tumor type and presented with associated complication rates, are outlined in Tables 4 and 5.

Table 4. Demographic and tumor characteristics stratified by dignity.

Category	Total (n = 187)	Sarcoma (n = 129)	Benign Tumor (n = 58)
Age [years] median (Q1, Q3)	57 (42, 67)	58 (46, 70)	50 (37, 63)
Female	86 (46%)	58 (45%)	28 (48%)
Caucasian	185 (99%)	127 (98%)	58 (100%)
Functional Status			
Independent	137 (92%)	86 (91%)	51 (94%)
Partially Independent	10 (6.7%)	9 (9.5%)	1 (1.9%)
Dependent	2 (1.3%)	0 (0.0%)	2 (3.7%)
Unknown	36 (19.3%)	34 (26.4%)	4 (6.9%)
ASA Status			
1	41 (22%)	20 (16%)	21 (36%)
2	115 (61%)	82 (64%)	33 (57%)
3	31 (17%)	27 (21%)	4 (6.9%)
Current Smoker	24 (13%)	13 (10%)	11 (20%)
Disseminated Cancer	7 (3.7%)	5 (3.9%)	0 (0.0%)
Tumor Location			
Appendicular	148 (79%)	102 (79%)	46 (79%)
Axial	39 (21%)	27 (21%)	12 (21%)

Table 4. *Cont.*

Category	Total (*n* = 187)	Sarcoma (*n* = 129)	Benign Tumor (*n* = 58)
Tumor Type			
Bone	41 (22%)	26 (20%)	15 (26%)
Soft Tissue	146 (78%)	103 (80%)	43 (74%)
Charlson Comorbidity score > 5	24 (13%)	22 (17%)	2 (3.4%)

This table summarizes demographic and clinical characteristics of the study population, stratified by tumor classification. Age is presented as a median with first (Q1) and third quartiles (Q3). Categorical variables are presented as n (%). Complications were captured using the Clavien-Dindo classification.

Table 5. Complications stratified by dignity.

Category	Total (*n* = 196)	Sarcoma (*n* = 134)	Benign Tumor (*n* = 62)
Complications according to Clavien-Dindo			
No complications	148 (75.5%)	94 (70.1%)	54 (87.1%)
Grade 1	25 (12.8%)	20 (14.9%)	5 (8.1%)
Grade 2	13 (6.6%)	13 (9.7%)	0 (0%)
Grade 3	10 (5.1%)	7 (5.2%)	3 (4.8%)
Presence of complication	48 (24.5%)	40 (29.8%)	8 (12.9%)

This table summarizes the complications according to Clavien-Dindo stratified by dignity. Categorical variables are presented as n (%).

3.3. Comorbidities and Medication

The study cohort exhibited a range of comorbid conditions, with hematologic diseases, central nervous system disorders, and gastrointestinal issues being the most prevalent. Additional comorbidities included respiratory, cardiovascular, and neuromuscular disorders, along with specific cases of previous childhood malignancies and bleeding disorders (Table 6). This diversity in health conditions highlights the medical complexity of the patient population and underscores the importance of comprehensive preoperative assessment.

Table 6. Overview of comorbidities details the prevalence rates of these conditions, providing a clear picture of the health challenges faced by the patient cohort.

Comorbidity	Number of Patients (%)
Hematologic Disease	21 (11.2%)
Central Nervous System Disorder	20 (10.7%)
Gastrointestinal Disease	17 (9.1%)
Chronic Obstructive Pulmonary Disease	1 (0.5%)
History of Other Pulmonary Disease	7 (3.7%)
Congestive Heart Failure	1 (0.5%)
Neuromuscular Disorder	1 (0.5%)
Previous Childhood Malignancy	2 (1.1%)
Bleeding Disorder	2 (1.1%)
Diabetes mellitus	6 (3.2%)

Overview of the prevalence of various comorbidities among the 187 patients studied. Data are presented as the number (%) of included patients.

3.4. Therapy

The treatment modalities for the 187 patients encompassed a combination of radiotherapy, chemotherapy, and surgical interventions. A significant portion of the cohort

underwent neoadjuvant treatments, reflecting the complex therapeutic strategies employed in managing musculoskeletal tumors (Table 7). Surgical approaches varied significantly, with the majority of surgeries being elective, highlighting the planned and non-urgent nature of most interventions.

Table 7. Treatment modalities and surgery type for study population.

Treatment Type	Number of Sarcoma Patients	Percentage (%)
Neoadjuvant Radiotherapy	64	32.7
Adjuvant Radiotherapy	7	3.6
Neoadjuvant Chemotherapy	18	9.2
Neoadjuvant and Adjuvant Chemotherapy	3	1.5

This table Summary of treatment modalities and types of surgery. The table details the number and percentage of sarcoma patients that received various types of radiotherapy and chemotherapy.

3.5. Association between Reconstruction and 30-Day Postoperative Morbidity

This study assessed the impact of surgical reconstruction on postoperative complications. Analysis indicated a notably higher complication rate in patients undergoing reconstruction compared to those without. Specifically, reconstruction surgeries exhibited a 33.7% complication rate versus 16.8% in non-reconstruction cases, demonstrating a statistically significant difference ($p = 0.008$). Notably, the type of tumor and tissue significantly influenced complication rates, with sarcoma and bone tumor patients showing the highest rates post-reconstruction (Table 8).

Table 8. Association between reconstruction and 30-day postoperative morbidity.

Patient Group	Surgeries with Reconstruction $n = 89$	p-Value	Surgeries without Reconstruction $n = 107$
Overall Complication Rate	30/89 (33.7%)	**0.008** *	18/107 (16.3%)
Complication Rate by Tumor			
Sarcoma	27/79 (34.2%)	0.98 **	13/55 (23.6%)
Benign Tumor	3/10 (30%)		5/52 (9.6%)
Complication Rate by Tissue Type			
Bone Tumor	13/27 (48.2%)	**0.09** **	4/17 (23.5%)
Soft Tissue Tumor	17/62 (27.4%)		14/90 (15.6%)

This table details the association between surgical reconstruction and 30-day postoperative morbidity, comparing complication rates among patients undergoing reconstruction versus those who did not, further stratified by tumor and tissue type. Statistical significance is noted where applicable. * comparing patients with reconstruction versus patients without; ** comparing benign with sarcoma or bone tumor with soft tissue tumors.

3.6. Complications

The occurrence and nature of complications among the 185 patients and 196 surgeries were analyzed. Complications were observed after 48 (24.5%) surgeries, with a higher incidence in sarcoma patients (29.8%) compared to those with benign tumors (12.9%, $p = 0.007$). Complication rates varied significantly based on the type of treatment and tumor characteristics. Notably, adjuvant therapy—both radiotherapy (57.1%) and chemotherapy (66.6%)—was associated with higher complication rates compared to other treatment modalities.

Complications were more prevalent in patients with bone tumors (38.6%) than in those with soft tissue tumors (20.4%). Additionally, axial tumor location, functional status, and the presence of metastasis influenced complication rates, underscoring the impact of patient and tumor specifics on surgical outcomes. The most common complications included infections, wound dehiscence, and the requirement for blood transfusions or reoperations (Tables 9 and 10).

Table 9. Summary of postoperative complications and associated parameters.

Category	Total (n = 196)	Complication (n = 89)	No Complication (n = 107)	p-Value
Age [years] (median (Q1, Q3))	56 (42, 67)	60 (48, 69)	51 (38, 63)	0.01
Female	86 (46%)	44 (49%)	47 (44%)	0.40
Caucasian	185 (99%)	89 (100%)	105 (98%)	0.93
Functional Status				0.002
Independent	137 (92%)	56 (62.9%)	89 (83.1%)	
Partially Independent	10 (6.7%)	9 (10.1%)	1 (0.9%)	
Dependent	2 (1.3%)	2 (2.2%)	1 (0.9%)	
Unknown	36 (19.3%)	22 (24.7%)	16 (15.1%)	
ASA Status				<0.001
1	41 (22%)	10 (11%)	33 (31%)	
2	115 (61%)	54 (61%)	65 (61%)	
3	31 (17%)	25 (28%)	9 (8.4%)	
Current Smoker	24 (13%)	8 (9.0%)	17 (16%)	0.14
Disseminated Cancer	7 (3.7%)	6 (6.7%)	5 (4.7%)	0.60
Tumor Location				0.44
Appendicular	148 (79%)	65 (75%)	87 (81%)	
Axial	39 (21%)	22 (25%)	20 (19%)	
Tumor Type				0.33
Bone	41 (22%)	27 (30%)	17 (16%)	
Soft Tissue	146 (78%)	62 (70%)	90 (84%)	
Charlson Comorbidity Score > 5	24 (13%)	18 (20%)	11 (10%)	0.05
Radiotherapy	(n = 187) *	(n = 85) *	(n = 102) *	<0.001
None	118 (63%)	39 (46%)	79 (77%)	
Neoadjuvant	64 (34%)	42 (49%)	22 (22%)	
Adjuvant	5 (2.7%)	4 (4.7%)	1 (1.0%)	
Chemotherapy	(n = 187) *	(n = 85) *	(n = 102) *	0.01
None	164 (88%)	69 (81%)	95 (93%)	
Neoadjuvant	17 (9.1%)	13 (15%)	4 (3.9%)	
Adjuvant	3 (1.6%)	2 (2.4%)	1 (1.0%)	
Sandwich	3 (1.5%)	1 (1.2%)	2 (2.1%)	

* Numbers for radiotherapy and chemotherapy are based on the number of patients and not on the number of surgeries performed. This table provides a comprehensive overview of the postoperative complications observed in the study cohort, broken down by various categories including tumor type, treatment modality, demographic factors, functional status, and specific complication types.

Table 10. Summary of the types of infections.

Type of Infection	Number	Percentage (%)
Surgical Site Infections	8/196	4.1
Pneumonia	2/196	1.0
Sepsis	2/196	1.0
Wound Dehiscence (Deep)	7 /196	3.6
Wound Dehiscence (Superficial)	7/196	3.6
Venous Thromboembolism	4/196	2.0
Allograft Failure	1/196	0.5
Prosthesis Failure	1/196	1.0
Flap Failure	1/196	0.5
Blood Transfusion	17/196	8.7
Reoperation	10/196	5.1
Re-Admission	6/196	3.1

3.7. Risk Factors of 30-Day Postoperative Morbidity

Our analysis identified several independent risk factors associated with complications within 30 days post-surgery.

Applying a multivariable regression model and after adjusting for the known prognostic factors age and dignity, patients with ASA 3 compared to the ASA 1 category and patients with bone tumors compared to soft tissue tumors were at increased odds of suffering from a complication, OR 3.74 (95% CI; 1.24, 12.0), $p = 0.02$ and OR 2.26 (95% CI; 1.03, 4.93), $p = 0.04$, respectively. Furthermore, the odds of a postoperative complication increased with the number of erythrocyte concentrates administered, OR 2.62 (95% CI; 1.53, 6.06), $p = 0.005$.

Conversely, the Charlson Comorbidity Index (CCI) and patient functional status were not significantly associated with the occurrence of complications. Additionally, neither neoadjuvant radiotherapy nor systemic therapy was linked to a higher rate of postoperative morbidity. This highlights the specific clinical and surgical factors that more directly influence outcomes in our patient cohort (Table 11).

Table 11. Univariable logistic regression analysis for 30-day postoperative complications.

Variable	Odds Ratio (95% CI)	*p*-Value
Age	1.0 (0.98, 1.01)	0.06
Gender (Male vs. Female)	1.15 (0.60, 2.24)	0.71
Tumor Type		
-Bone (vs. Soft Tissue)	2.46 (1.18, 5.06)	0.02
Presence of Metastasis	4.09 (1.18, 14.8)	0.03
Tumor Classification		
-Sarcoma (vs. benign)	2.87 (1.31, 7.02)	0.01
Radiotherapy		
-Neoadjuvant (vs. adjuvant vs. none)	1.18 (0.59, 2.32)	0.60
Systemic Therapy		
-Neoadjuvant (vs. adjuvant vs. none)	2.27 (0.84, 5.87)	0.01
ASA Status		
-ASA 2 (vs. ASA 1)	1.05 (0.44, 2.69)	0.92
-ASA 3 (vs. ASA 1)	4.38 (1.62, 12.7)	0.01
Charlson Comorbidity Index (CCI)	1.13 (0.96, 1.33)	0.14
Functional Status	2.29 (0.91, 5.85)	0.07
Number of Erythrocyte Concentrations	3.00 (1.67, 7.24)	0.01

This table presents the results of univariable regression analyses assessing the risk factors for 30-day postoperative morbidity.

3.8. Association between Charlson Comorbidity Index and 30-Day Postoperative Morbidity

Our analysis showed that the Charlson Comorbidity Index (CCI) does not significantly predict the occurrence or severity of complications within 30 days post-surgery. Both the occurrence of complications and their severity were not statistically influenced by the CCI, with odds ratios of 1.30 ($p = 0.14$) and 1.09 ($p = 0.54$), respectively. This suggests that the CCI, despite its broad usage in predicting long-term mortality, may not be a reliable indicator of short-term postoperative complications in this patient population (Table 12) (Figure 1).

Table 12. Association of Charlson Comorbidity Score with 30-day postoperative morbidity.

Outcome	Odds Ratio (OR)	95% Confidence Interval (CI)	*p*-Value
Occurrence of Complications	1.13	0.96,1.33	0.14
Complication Severity	1.09	0.83–1.43	0.54

This table shows the results of a univariable logistic regression with the occurrence of complications as the dependent variable and the results of a proportional odds model with the complication severity as graded by Clavien-Dindo as the dependent variable.

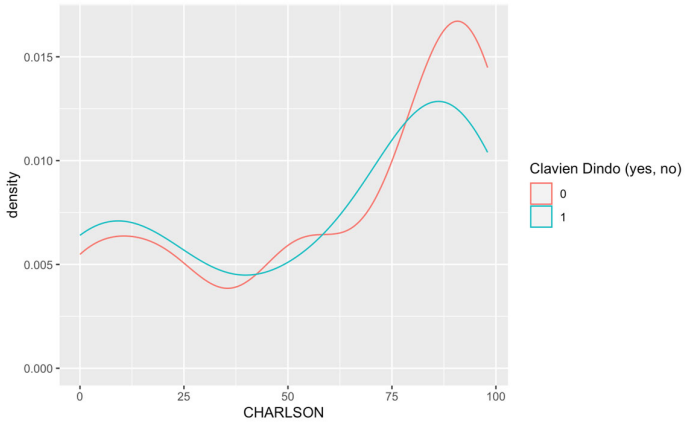


Figure 1. This density plot reveals no association of the Charlson Comorbidity Index with the 30-day postoperative morbidity rate according to Clavien-Dindo.

4. Discussion

This study provides a comprehensive evaluation of postoperative outcomes in musculoskeletal tumor surgeries, uncovering significant predictors of surgical morbidity through a detailed analysis. Our results indicate that surgical reconstruction and ASA 3 status are strongly associated with increased complication rates. Furthermore, the bone tumor is identified as a critical factor that elevates postoperative morbidity. This study also underscores the impact of multiple erythrocyte transfusions on increasing morbidity, emphasizing the need for meticulous blood management and surgical planning. These findings advocate for the implementation of specialized risk management strategies, aiming to refine surgical interventions and enhance patient outcomes in the complex landscape of musculoskeletal tumor surgery [3,7,14].

Our examination extends beyond identifying risk factors to analyzing their implications within the surgical context, focusing particularly on reconstructive surgeries, erythrocyte transfusion requirements, and critical patient risk factors. In line with findings from Gallaway et al. and Gonzalez et al. [1,13], our research confirms that reconstructive surgeries significantly elevate postoperative complications, illustrating the complex surgical decisions that impact patient outcomes. Similarly, our emphasis on erythrocyte transfusions as a risk factor for increased morbidity parallels observations from Gonzalez et al. [1], who noted complications related to low hematocrit levels, suggesting a shared concern across studies about blood management in surgical procedures. Our analysis further aligns with Gallaway et al. [13] regarding the critical influence of bone tumor presence on postoperative outcomes, affirming that these inherent patient conditions significantly contribute to morbidity, consistent with their reported findings. However, a unique aspect of our study is the detailed exploration of ASA 3 status as a modifiable preoperative assessment parameter, which has been less emphasized in similar studies but is crucial for tailoring surgical and anesthetic strategies to mitigate risks.

Despite these similarities, our study also highlights a gap in the literature regarding standardized approaches to measuring and reporting these risk factors, especially compared to the uniform assessment methods evident in studies like those by Gallaway

et al. and Gonzalez et al. [1,13]. Conversely, Hoftiezer et al., analyzing factors associated with 30-day morbidity following upper extremity surgery, did not associate findings from above but linked an increased BMI, increased operative time, flap reconstruction, and tumor size > 5 cm with 30-day postoperative complications [15]. This disparity regarding parameters to be analyzed and findings underscores the necessity for more consistent and comprehensive methodologies to assess and report 30-day morbidity in musculoskeletal tumor surgery research, fostering better comparability and reliability of outcomes across studies.

The key insights derived from our analysis of 30-day postoperative morbidity in musculoskeletal tumor surgeries emphasize the need for refined surgical protocols and robust preoperative assessments. Given the heightened risks associated with ASA 3 status, bone tumors, and reconstructive surgeries, personalized surgical planning becomes imperative. Our findings suggest that such plans should incorporate targeted preoperative assessments and tailored intraoperative strategies to effectively manage these identified risks. Additionally, the significant role of erythrocyte transfusions in elevating morbidity rates calls for the development of stringent blood management protocols, potentially including preoperative optimization of hemoglobin levels and judicious intraoperative transfusion practices [16]. Future research should focus on enhancing predictive models for postoperative complications by integrating these and other clinical variables. This would not only refine the accuracy of risk assessments but also aid in developing specific interventional strategies aimed at minimizing complications. Prospective multicenter studies are necessary to validate our findings and to explore the effectiveness of these tailored approaches in diverse surgical settings. Moreover, our results underscore the importance of considering both inherent and modifiable risk factors in the surgical management of musculoskeletal tumors, suggesting a multidimensional approach to patient care that adapts to the specificities of each case. These comprehensive efforts will not only advance our understanding of the complex dynamics in musculoskeletal tumor surgeries but also lead to more effective and personalized treatment plans that significantly improve patient outcomes, aligning with the evolving standards of care in the field [6,14,17].

Our study, while providing insightful observations on musculoskeletal tumor surgeries, is not without limitations. The retrospective nature of our data collection introduces inherent biases, including potential selection biases and limitations in data completeness that may affect the findings' generalizability. Moreover, this study's focus on a single tertiary care center may not fully represent the wider patient population typically encountered in other settings, which could influence the applicability of our results to different healthcare environments. Additionally, the specificity of the patient demographics and tumor types included may limit the ability to generalize our conclusions universally. Future studies could address these limitations by incorporating a multicenter approach and a more diverse patient cohort to enhance the robustness and applicability of the findings.

5. Conclusions

In conclusion, this study highlights the importance of tailored surgical planning and rigorous preoperative assessments in reducing postoperative morbidity in musculoskeletal tumor surgeries. Key findings reveal that surgical reconstruction, ASA 3 status, bone tumor presence, and erythrocyte transfusions significantly influence outcomes, emphasizing the need for personalized treatment strategies. Despite its insights, this study's limitations underscore the necessity for broader, multicenter studies to confirm these findings and refine risk stratification methods. Future research should focus on developing predictive models that integrate clinical and benchmarking data to optimize surgical outcomes in this complex field.

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Article

Quality of Sarcoma Care: Longitudinal Real-Time Assessment and Evidence Analytics of Quality Indicators

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Simple Summary: This article comprehensively defines, assesses and analyzes quality indicators of sarcoma care. A novel interoperable digital platform is presented that gathers information from physicians (work-up, therapy and MDT information) as well as patients (PROMS/PREMS) consecutively and instantly when a new event occurs, which thereby automatically provides evidence of the quality of care on all aspects. As the platform analyzes annotated real-time world information, predictive modelling and value-based health care may become a reality, thereby giving rise to precision health care in the future.

Abstract: Sarcomas represent a large group of rare to very rare diseases, requiring complex management with a transdisciplinary approach. Overall progress has been hampered because of discipline, institution and network fragmentation, and there is no global data harmonization or quality standards. To report on and improve quality, a common definition of quality indicators (QIs) of sarcoma care as well as the capacity to assess longitudinal real-time data is required. An international advisory board of world-renowned sarcoma experts defined six categories of QIs, totaling more than 80 quality indicators. An interoperable (web-based) digital platform was then created combining the management of the weekly sarcoma board meeting with the sarcoma registry and incorporating patient-reported outcome measures (PROMs) into the routine follow-up care to assess the entire care cycle of the patient. The QIs were then programmed into the digital platform for real-time analysis and visualization. The definition of standardized QIs covering all physician- (diagnostics and therapeutics), patient- (PROMS/PREMS), and cost-based aspects in combination with their real-time assessment over the entire sarcoma care cycle can be realized. Standardized QIs as well as their real-time assessment and data visualization are critical to improving the quality of sarcoma care. By enabling predictive modelling and introducing VBHC, precision health care for a complex disease is on the horizon.

Keywords: interoperable digital platform; quality indicators; real-time assessment; value-based health care; integrated practice unit; sarcoma; data annotation

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1. Introduction

Sarcomas constitute a large group of rare cancers, and their treatment is multidisciplinary and complex. There are a series of evidence- and consensus-based sarcoma guidelines available for the appropriate work-up and treatment of bone and soft tissue sarcomas. Several recent studies examined the compliance of such guidelines, as well as its positive association with clinical outcomes [1–5]. Due to low adherence, sarcoma treatment

is preferentially regionalized to dedicated networks because specialized multidisciplinary sarcoma teams (MDT) provide improved management and care with better adherence to guidelines compared with patients who are treated outside of such networks [6–12]. However, regionalization of care alone does not yet guarantee quality of care, mainly because quality indicators of work-up and treatment have not yet been established at large, and a tool for their large-scale assessment with the possibility of real-life monitoring is lacking [13].

While access to an MDT- or sarcoma-integrated practice unit (IPU) care network plays a pivotal role with respect to quality care, health care costs are constantly rising, despite the fact that the increasing costs may not necessarily match the added quality [14]. Identification of the most effective ways to organize, manage, finance and deliver high-quality care (which is summarized as health services research) to reduce non-compliance to CPG and improve patient safety and outcomes will become increasingly important in the near future. Effective on April 2021, for example, Switzerland introduced a new law regarding the quality and economics of patient care, which commits all care providers to measure quality and to introduce a quality management system, which lays the foundation for value-based health care (VBHC).

VBHC was introduced more than 15 years ago by Porter et al. and is defined by the quality and outcome divided by the total costs over the entire longitudinal health care cycle [15–17]. It transforms a fee-for-service legacy system into a value-based system of shared values, vision, transparency and trust, thereby moving from quantity to quality and from volume to value. Meanwhile, VBHC is a widely accepted instrument to improve quality of care while reducing health care costs [18,19]. There are several important pre-requisites for VBHC. First, an integral information technology platform is required, which allows the preferably real-time interoperable data exchange of IPUs over the entire globe. Second, VBHC requires the definition of quality indicators (QIs) and its assessment. Third, the established quality ultimately then has to be associated with the costs of the entire longitudinal care cycle.

A strategy for evaluating robust information on QIs is the harmonization of data by real-time prospective assessment [20,21]. This requires an interoperable digital platform, ideally between sarcoma networks and their global databases, which represents a digital mirror of prospective patient data in real time and allows the instant visualization of the data. However, it is commonly believed that within current silo hospital structures in many centers (such as data management, "added monodisciplinary" approach and currently available clinical information systems) the digital requirements widely surpass the financial preconditions to achieve such necessary data information.

As far as sarcoma treatment is concerned and to the best of the authors' knowledge, there is no comprehensive definition of quality indicators of shared sarcoma care (beyond local-recurrence-free survival, disease-free survival, metastasis-free survival and overall survival) described in the literature. At this point, their real-time structured assessment, specifically in relation to healthcare costs, has never been realized. Herein, we provide an interoperable digital platform solution focusing on the QIs of sarcoma care.

2. Materials and Methods

2.1. Description of the Interoperable Digital Platform

SSN has established a cloud-based, transparent, harmonized, transdisciplinary, multi-institutional, prospective, real-world-time data sarcoma registry including absolute (not only sarcoma diagnosis but also all patients who undergo a biopsy for suspicion of sarcoma) patient numbers with a focus on the assessment of quality indicators (QI) of sarcoma care, covering the entire longitudinal care cycle. For this purpose, the management of the weekly multidisciplinary team (MDT)/sarcoma board (SB) meeting was coupled with the data registry. To ensure the quality and completeness of all MDT/SB decisions, every new patient and any new event or treatment change is required to be presented to the MDT/SB. Importantly, the patient has to give written consent to the collection and anonymous

use of their data. For each patient presented at the MDT/SB, the treating physician of a given discipline enters the respective information. For example, the surgeon fills in the details of surgery, the radiation oncologist enters the relevant data for radiation therapy, the pathologist and radiologist enter the respective data etc. This may include some 3–5 min for a single treating physician. This is a critically important step because regular clinical information systems most often do not allow for the collection of structured data, which is pivotal for analysis. This shared and structured data collection approach assures minimal time effort and the highest possible data quality. Furthermore, because all data are discussed together at the MDT/SB and because the discussion allows open questions (such as the surgical margin) to be addressed, this meeting that includes all treating physicians is used as a collective data quality check. This setup assures the highest possible data quality in real time, including the decisions on subsequent treatments. Based on the entered data, the interoperable digital platform is programmed to calculate and automatically visualize the QIs in diagrams, tables or figures. In addition, while the MDT/SB assures data inclusion regarding all active treatments, the interoperable digital platform requests PROMS electronically from patients under follow-up and without evidence of disease at predefined intervals. This guarantees longitudinal data coverage over the entire cycle of care for all patients.

2.2. QI and Tools

Using a modified Delphi approach, the Swiss Sarcoma Network (SSN) international advisory board consisting of world-renowned sarcoma experts (A.L., J.B., A.G. and J.M.) defined holistic quality indicators of sarcoma patient care. It encompasses six categories of care aspects (Table 1), totaling more than 80 QIs (Tables 2–7). To guarantee real-time data assessment over time, the patients fill out patient-reported outcome/experience measures (PROMS/PREMS) (Table 7) either at the outpatient visit or online in the case of telemedicine consultations, depending on type of treatment they had and the time point of follow-up. Overall, >385 variables are routinely assessed using the interoperable digital platform (Figure 3). The data are hosted at the Federal Institute of Technology in Switzerland (Leomed, ETH Zurich, Switzerland; https://sis.id.ethz.ch/services/confidentialrese;researchdata; accessed on 20 October 2022) to ensure the highest level of data protection with respect to interinstitutional exchange, political independence, and continuous technology developments. The interoperable digital platform allows the automated extraction of data to be used for calculations of QIs, thereby generating real-world evidence [22,23]. The digital platform allows for instant analysis and visualization, basic statistics and figure creation. The QI analysis of sarcoma care parameters can be customized according to, for example, time period, type of dignity, planned and unplanned (whoops) resections, institution, in real time and interactively. Its modular setup allows the extension and adaptation of the parameters as more data will be collected.

Table 1. Overview of groups of quality indicators.

QI FOR MULTIDISCIPLINARY TEAMS (MDT)
1. Sarcoma work-up of patients
2. MDT/SB management
3. Therapy (incl. surgery, radiation-, chemotherapy)
4. Complexity of sarcoma therapy
5. Clinical metrics outcome (physician based)
6. PROMS/PREMS (patient based)

Table 2. Sarcoma work-up.

QUALITY INDICATORS: SARCOMA WORK-UP
• was imaging performed before biopsy • time from first patient contact to biopsy • which type of biopsy was performed • time from biopsy to MDT/SB presentation • time from biopsy to SB presentation • was biopsy performed before initiation of treatment? separated according to type of treatment • was there metastasis at presentation • time from MDT/SB presentation to initiation of treatment (incl. analysis depending on type of therapy

Table 3. MDT/SB management.

QUALITY INDICATORS: MDT/SB MANAGEMENT
• how many patients were presented per month/per year • how many presentations took place per month/per year • how many first presentations • how many follow-up presentations • how many bone lesions—superficial/deep soft tissue lesions were presented • how many malignant—intermediate—benign lesions were discussed • how many decisions on: - surgery - radiation therapy - combination radiation therapy–surgery - combination chemotherapy–surgery - combination surgery–radiation therapy–chemotherapy • how many decisions were realized/executed? - Overall - surgery - radiation oncology - chemotherapy • how many patients were presented over entire cycle of care

Table 4. Therapy.

QUALITY INDICATORS: THERAPY
• % margin status (R0, R1, R2) at definitive surgery • surgical, pathological, consens • % amputations • % preoperative radiation therapy (yes/no) • % postoperative radiation therapy (yes/no) • % neoadjuvant chemotherapy (yes/no) • % adjuvant chemotherapy (yes/no)

Table 5. Complexity of therapy.

QUALITY INDICATORS: COMPLEXITY OF THERAPY	
• surgical complexity STS	Cancers March 2022
• surgical complexity bone sarcoma	Age, grading/type of lesion, prior RT, chemo/whoops, size of lesion, location, resected structures, reconstructed structures, involved disciplines
• surgical complexity visceral sarcoma	Age, grading/type of lesion, prior RT, chemo/whoops, size of lesion, location, resected structures, reconstructed structures, involved disciplines

Table 5. *Cont.*

QUALITY INDICATORS: COMPLEXITY OF THERAPY	
• radiation oncology complexity treatment	Aim of RT (curative, locally curative, palliative, definitive, unknown); RT technique (IMRT, VMAT, SRT, 3DCRT, 2DCRT, unknown; RT type (photons, protons, electrons, brachytherapy (transient, permanent), conventional, other, unknown); total dose/number of fractions; GTV/PTV; Grade III/IV toxicities;
• systemic treatment complexity	Aim of systemic therapy (curative intent pre/postop, additive, maintenance, palliative); number of curative/palliative cycles planned/executed; time to next treatment (TTT); reasons for discontinuation (completed, discontinued (toxicity, PD, planned, patient's wish, death); Grade III/IV toxicities

Table 6. Outcome.

QUALITY INDICATORS: OUTCOME
• local recurrence within 1st year after tumor resection
• local recurrence overall
• systemic recurrence with 1st year of treatment initiation
• systemic recurrence overall
• latest follow-up: NED, AWD, DOD, DOR, no assessment possible; lost to followup, unknown)
• in case of RT: % vascular disorders (lymphedema, ROM, fibrosis); skin disorders (hyper-,hypopigmentation); bone disorders (osteonecrosis)
• in case of chemotherapy: % therapy during last 3 months of life.

NED, no evidence of disease; AWD, alive with evidence of disease; DOD, dead of disease; DOR, death of other reasons.

Table 7. PROMS/PREMS.

SARCOMA QUALITY INDICATORS	PROMS/PREMS
• work-up/regular f-up	-WHO-ECOG -EQ-5D -EQ-VAS -work ability index
• biopsy	-biopsy
• surgery	-MSTS upper/lower extremity -TESS upper/lower extremity
• radiation oncology	-visceral -local effects of RT
• chemotherapy	-EORTC-QLQ-C30 -MDASI
• therapy focused	-cancer therapy satisfaction -satisfaction with RT -control preferences
• Physican related	-CARE
• Institution focused	-satisfaction with institution

2.3. Objectives

In this study, we assessed and described the selection of Qis relating to the sarcoma work-up as well as EQ-5D (a PROM) in a four-year period using the interoperable digital platform.

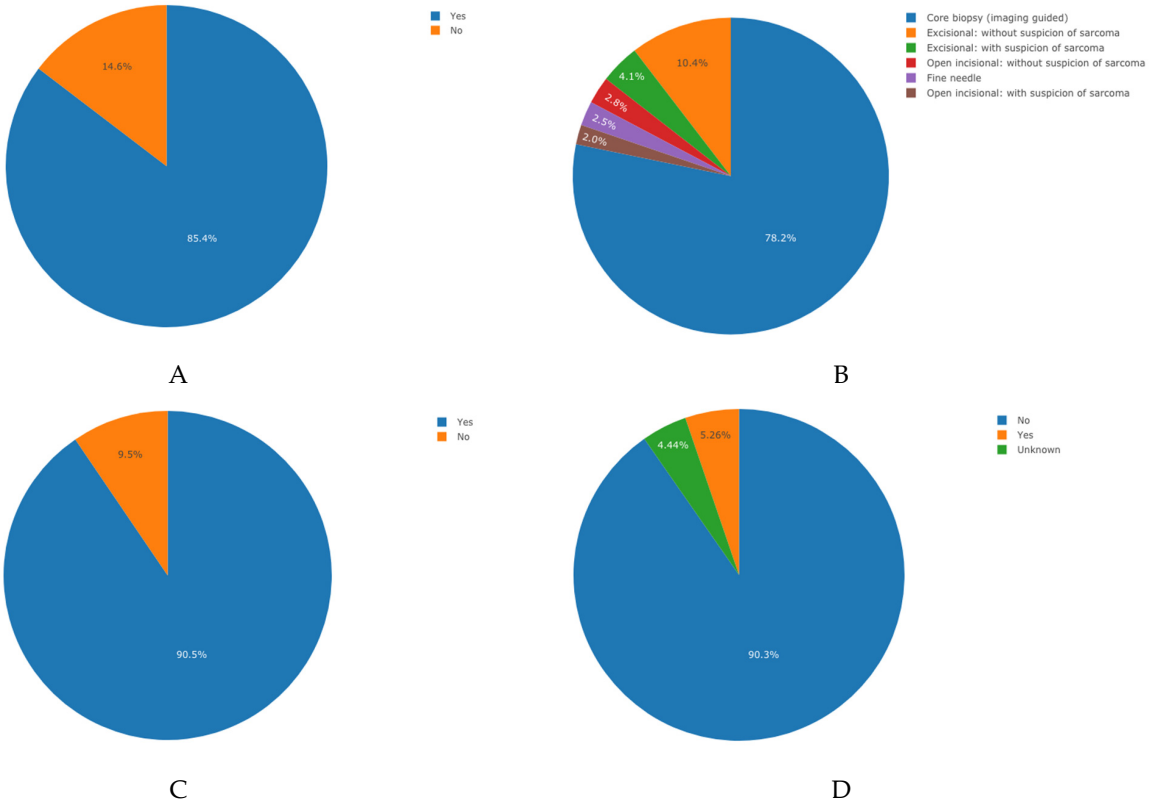
3. Results

3.1. Definition of Quality Indicators of Sarcoma Care

The quality indicators of sarcoma care as defined herein encompass six categories, including the work-up of sarcoma patients, the management of the MDT/SB meeting, type of therapies, the complexity of therapy, outcome measures and PROMS/PREMS (Table 1). Each single category contains a subset of parameters (Tables 2–7) that define the respective category.

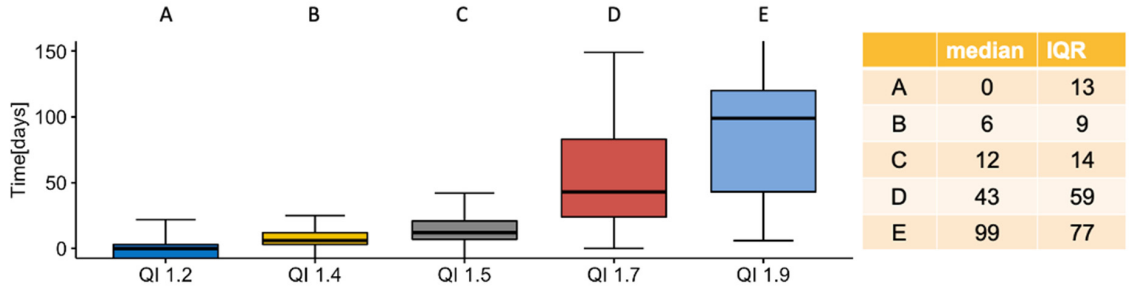
3.2. Quality Indicators of Sarcoma Work-Up

The detailed results of the Qis work-up are summarized in Figures 1 and 2 for 1308 patients with suspected (n = 719, 55%) and (n = 589, 45%) confirmed sarcoma presented within the SSN over a four-year time period (1 January 2018 until 31 March 2022). With respect to the QI sarcoma work-up as an example for all other quality indicators, it was observed that n = 1117 (85.4%) of all patients underwent radiological imaging before performing a biopsy. On the interactive website of the interoperable digital platform, this number can be instantly further analyzed and visualized according to, for example, diagnostic categories, diagnoses, anatomic regions, institution etc. to define how the respective parameter of interest may differ from the mean of the category of interest (Figure 1). This enables the discovery of strengths and weaknesses of each referral network, institution or discipline and may not only specifically define areas of improvement but also provide a benchmark for comparison with other sarcoma networks on an international level (including adjustment to the tumor characteristics and complexity of therapy). Similarly, analyzing the time from the first biopsy to first contact within the sarcoma IPU, we find a median of 0 days and an interquartile range of 13 days, which implies that half of all patients underwent the biopsy performed at the same day as the first contact or present with the biopsy, defining the efficiency of this specific part of the work-up process. With information regarding structured data on the work-up, a cost tag can be attributed to each specific step, thereby generating the effective cost for a given aspect of treatment.



(**a**)

Figure 1. *Cont.*



	median	IQR
A	0	13
B	6	9
C	12	14
D	43	59
E	99	77

(**b**)

Figure 1. (**a**) Pie chart analysis for four of the nine quality indicators of the sarcoma work-up; (**A**), was imaging performed before biopsy? (**B**), which type of biopsy was performed? (**C**), was biopsy conducted before initiation of treatment? (**D**), was metastasis present at diagnosis? (**b**) Box plot analysis for five of the nine quality indicators of the sarcoma work-up; A, time from first patient contact to biopsy, B, time from biopsy until establishment of diagnosis, C, time from biopsy until sarcoma board presentation, D, time from diagnosis to initiation of therapy and E, time from sarcoma board presentation to initiation of treatment.

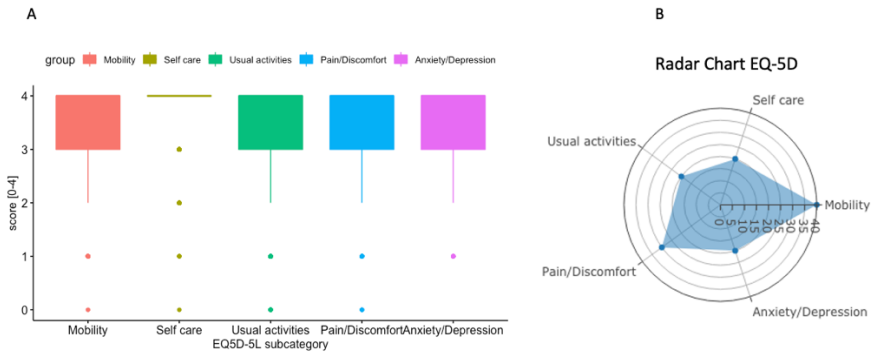


Figure 2. (**A**) Box plot summary of EQ-5D including 511 consecutive patients. (**B**) Radar chart summary of one single patient representing the five dimensions of EQ-5D.

3.3. HRQOL-EQ-5D

In the time period from the 1 October 2021 to the 31 March 2022, 511 EQ-5D questionnaires were routinely assessed in the outpatient clinic, including all patients with suspected and confirmed sarcoma, as summarized in Figure 2 [24]. These results show that the consecutive assessment of health-related quality of life as assessed by EQ-5D scores in the routine outpatient clinic is feasible. Analogous to the QIs, each subcategory can be analyzed longitudinally over time and/or by event of treatment according to clinical metrics using the interactive website. A radar chart (Figure 2B) is provided to assist the interpretation of the results of the discussion with the patient.

4. Discussion

Today's competition in health care is often not aligned with shared value, and financial success of various health care stakeholders may not necessarily equal success for the patient. Because of rising health care costs and the uncontrolled growth of unstructured medical data, the creation of a novel ecosystem with data interoperability focusing on quality care evaluated from practices and patient outcomes is pivotal. The existing misalignment can be overcome with structured data collection, global data harmonization and interactive data assessment with real-time analysis to create evidence-based information.

Existing databases for sarcoma research may often underestimate the true prevalence of sarcoma. This is explained by their dependence on administrative or billing data, insufficient data coding or the use of preexisting documented hospital diagnoses codes, which are reasons why the expansion on real-world evidence-based patient-focused data

sets is mandatory [20]. Furthermore, routine structured assessment and analysis of QIs play an integral role in establishing a novel ecosystem with interoperable and harmonized data exchange to improve the quality of care for sarcoma patients. The six categories of QIs span the entire cycle of care for any given disease of the patient with sarcoma suspicion and are thereby representative for the quality of sarcoma care. To the best of the authors' knowledge, this represents an entirely novel approach that generates absolute numbers including all patients with suspicion of sarcoma (not only with confirmed sarcoma diagnosis).

Herein, we focus on two aspects of QIs to present the feasibility and routine acquisition of the setup: the QI 1 work-up and one of the PROMS (EQ-5D) (Table 1). The QI sarcoma work-up consists of eight questions, which cover the key aspects of preparing a patient for treatment. Detailing the work-up is important, particularly with respect to the historically unchanged and unacceptably high rate of unplanned ("whoops") resections, where more precise data may foster the understanding of why these still occur today. Additionally, the QI 1 work-up includes a second review by an expert sarcoma pathologist, which is a critical and established quality indicator, but it still does not represent common practice mainly because the structure of many current databases simply does not automatically generate such information. Obviously, the definitions always remain debatable but can easily be expanded by further aspects if sarcoma experts deem it necessary. For this purpose, the sarcoma academy (www.sarcoma.academy; accessed 20 October 2022) was founded to enable inter-disciplinarily exchange of cases and to discuss and update the QIs on the global level. The analysis of quality indicators as presented herein summarizes the routine assessment of 1308 patients over a four-year period of one single MDT/SB network and may provide a benchmark for future national and international comparisons.

HRQoL questionnaires are increasingly recognized as a pivotal tool for reporting outcome measures in the medical practice [18,19]. In oncology specifically, the EORTC-QLQ-C30 and the EQ-5D are widely recognized and were introduced for sarcoma patients years ago [25,26]. However, their routine clinical use for sarcoma patients in daily practice has not yet been shown, and there is also not a reference score for all sarcoma entities and respective anatomic locations available. In the current study, our digital platform allows the consecutive assessment of all outpatient visits in daily routine practice. We currently assess the EQ-5D at each single clinical visit, and the EORTC-QLQ-C30 is assessed in addition for all patients who underwent chemotherapy. Overall, the six QI categories cover the entire cycle of patient care, which is further detailed by the single aspects. This setup allows the identification of weak and strong areas, thereby facilitating improvement in sarcoma care within an MDT/SB. It further allows benchmarking and comparison of treatment quality among various MDT/SB in distant geographic areas, which directly benefits the patient. As such, a global definition and comparison of sarcoma shared care becomes possible, which enables us to define areas of improvement based on harmonized data and evidence analysis. Importantly, through global harmonization of data quality, transdisciplinary and structured data can be assessed independent of the location and become interchangeable, and multi-institutional international collaboration on a rare disease is greatly facilitated. It is envisioned that herewith, a sarcoma quality score for a respective MDT/SB network (the center itself and its associated regional network) can be defined and introduced for international benchmark comparisons while importantly respecting the complexities associated with treatment. This may greatly impact the quality of international trials through the generation of more robust data and improved care quality for the patient. Having information regarding structured data on the entire cycle of care including the work-up enables a cost tag to be attributed to each specific step, which thereby generates an effective cost for a given aspect of treatment.

Cost increases in health care is a universal problem. Porter et al. introduced the concept of value-based health care (VBHC) [16,17,27]. Herein, shared value is defined by the quality of patient care and outcome divided by the total cost over the entire cycle of care [28,29]. The prerequisite to introduce VBHC to create a new ecosystem is the definition of quality. Because the digital interoperable platform encompasses the entire cycle of care

and because each structured QI parameter can be attributed a cost tag, it will become possible for the first time to determine the entire costs of the treatment for a given disease and patient (Figure 3). Above all, cost containment will be based uniquely on quality measures with such a setup, which enables the introduction of VBHC through disruption of the current ecosystem. Importantly, this has great potential to achieve cost containment for the benefit of the patient as well as a sustainable health care system [30].

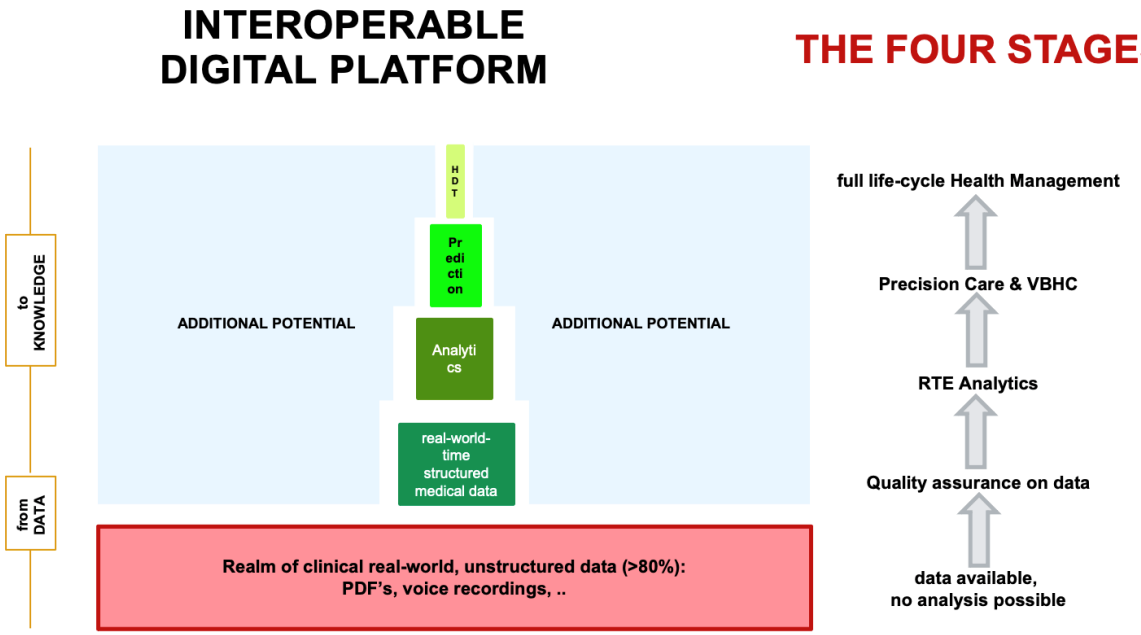


Figure 3. The interoperable digital platform is designed to receive longitudinal, absolute, routine, structured, real-world-time data from daily clinical routine practice. The MDT/SB fulfills the purpose of data quality control. Analytics of these data generate real-time evidence, which is used for precision modelling (through artificial intelligence and machine learning approaches) as well as value-based health care (through attribution of cost tags with structured data). Abbreviations. RTE, real-time evidence; VBHC, value-based health care; HDT, human digital twin.

Data are considered the key driver for the evolution from one-size-fits-all to precision medicine [21,31]. Predicting outcomes has been recognized as a major focus in today's health care, and currently, nomograms are still routinely used in daily sarcoma practice [32,33]. However, these are most often based on retrospective data, sometimes even more than 20 years old, without harmonized data acquisition and definitions and with all institutions independent from each other. Although validation has been performed, calibration curves imply wide ranges of survival predictions and therefore may imperfectly mirror reality. Therefore, because the technical infrastructure is now able to integrate a common, internationally defined and harmonized data language into daily practice, real-time prospective data acquisition may be regarded as today's standard and daily routine. Focusing data acquisition on quality standards, the patient can transparently monitor the quality of the treatment according to international guidelines and quality standards on his own. Having such structured quality data available at a large scale, predictive outcome analytics to individualize treatment decisions based on outcome prediction becomes a reality (Figure 3). As of now, we have integrated clinical data (to represent physician-based data), PROMS & PREMS (to represent patient-based data) as well as data of the costs of the work-up and treatment of patients (to represent health care cost). In the future, we will integrate multi-omic (genomics, epigenomics, proteomics, metabolomics, etc.) functional tumor profiling data for clinical decision support such as realized with the TumorProfiler®or through semantic web technologies [34]. The combination of clinical data and

bioinformatics data allow predictive outcome analytics as a standard of care in the very near future, and digital twin computing (DTC) becomes reality.

Obviously, the exchange and security of patient data remains a constant challenge for global collaboration, as the different laws on data privacy and security issues are usually country specific. However, and because the assessment of quality of sarcoma care—which is in strong contrast to Alphabet, Amazon or Alibaba—focuses not on the individual patient's data but is aggregated, the exchange of anonymized data with the respective patient's consent such as is widely practiced by pharma companies is becoming a reality. Furthermore, one may argue that extrapolating on health care data from a small country with an intricate network of small hospitals in semi-autonomic political areas within close distances and a BIP of close to 12% may not be representative for other countries with different geographies and demographies. However, as previously mentioned, the QIs were determined by sarcoma experts from different countries and from the view of the patient, which is independent of where health care is requested and is therefore considered similar worldwide. Furthermore, the presented QIs may not be considered comprehensive. The system is set up such that any new parameter may be modularly integrated into the interoperable digital platform.

5. Conclusions

It has been recognized for decades that the most pressing questions can only be answered through international collaboration. This has, however, not yet materialized due to the lack of means and technology. The interoperable digital platform takes advantage of current technological opportunities, which defines a common language focused on the quality of sarcoma care, allows real-time assessment over the entire care cycle, strengthens the collaboration of IPUs and transparently integrates and visualizes quality analytics to realize an international exchange. It may ultimately pave the way to realizing precision medicine through predictive modelling and introducing VBHC for a complex disease, which may serve as a role model for other diseases.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: https://www.swiss-sarcoma.net/ (accessed on 22 November 2022).

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Article

Unlocking the Power of Benchmarking: Real-World-Time Data Analysis for Enhanced Sarcoma Patient Outcomes

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Simple Summary: Benchmarking is a crucial tool for healthcare providers to improve quality and efficiency, especially for complex conditions like sarcomas. Sarcomas are a type of cancer that require a multidisciplinary approach to treatment. However, despite adherence to international guidelines, differences in the processes used by these boards can affect patient outcomes and treatment costs. This study compared two multidisciplinary teams/sarcoma tumor boards and established an interoperable digital platform, Sarconnector®, for real-world time (RWT) data assessment and automated analysis. Differences were obtained in various areas, such as first-time presentations, follow-up presentations, primary sarcomas, biopsies and chemotherapy indications. By identifying areas of improvement and making data-driven decisions on the meta-level, healthcare providers can optimize resources and improve patient outcomes. Benchmarking with the RWT harmonized data approach provided by the Sarconnector® can help healthcare providers achieve better outcomes for their patients and improve the overall effectiveness of the healthcare system.

Abstract: Benchmarking is crucial for healthcare providers to enhance quality and efficiency, notably for complex conditions like sarcomas. Multidisciplinary teams/sarcoma boards (MDT/SBs) are vital in sarcoma management, but differences in their processes can affect patient outcomes and treatment costs, despite adherence to international guidelines. To address this issue, this study aimed to compare two MDT/SBs and establish an interoperable digital platform, Sarconnector®, for real-time-world data assessment and automated analysis. The study included 983 patients, 46.0% of whom female, with a median age of 58 years, and 4.5% of patients presented with metastasis at diagnosis. Differences were observed in the number of first-time presentations, follow-up presentations, primary sarcomas, biopsies and chemotherapy indications between the two MDT/SB. The results highlight the importance of benchmarking and utilizing a harmonized data approach, such as the RWT approach provided by the Sarconnector®, to standardize and evaluate quality and cost metrics. By identifying areas of improvement and making data-driven decisions on the meta-level, healthcare providers can optimize resources and improve patient outcomes. In conclusion, benchmarking with the RWT harmonized data approach provided by the Sarconnector® can help healthcare providers improve the overall effectiveness of the healthcare system and achieve better outcomes for their patients in terms of both outcomes and costs.

Keywords: IELAS-RWTD/E (interoperable electronic longitudinal absolute structured real-world time data/evidence); MDT/SB (multidisciplinary team/sarcoma board meeting); VBHC (value-based healthcare); AI/ML (artificial intelligence/machine learning); CROMS (clinician-reported outcome measures); PROMS (patient-reported outcome measures); PREMS (patient-experienced outcome measures); IPU (integrated practice unit); SPDT (sarcoma patient digital twin)

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1. Introduction

Surgery is the mainstay treatment in sarcoma care [1,2]. While many standards have been described in sarcoma surgery, such as surgical margins, multidisciplinary approaches, preoperative planning, appropriate surgical techniques with adequate postoperative care and regular follow-ups, and importantly, multidisciplinary team meetings, the overall quality definitions of sarcoma surgery have not been addressed [3–8]. In a pivotal landmark paper and based on an international consensus jury approach, Domenghino et al. proposed a framework to evaluate the quality of surgical interventions and to identify areas for improvement, with the potential to improve the assessment of surgical interventions and facilitate the sharing of best practices [9]. The authors highlight the importance of data management, with data-management systems being designed to capture comprehensive and accurate data on surgical outcomes, including clinical outcomes, patient-reported outcomes and complications of therapy. Data need to be interoperable and allow the integration of data from multiple sources, including electronic health records, registries and administrative databases [10–12]. Specifically, the consensus jury suggests assessing a multilayer outcome to compare results from one's own practices, processes, or outcomes to those of other organizations or practices in the same field, both nationally and internationally, to ultimately allow the establishment of a benchmark as a powerful tool that can be used in many surgical disciplines to improve quality and performance and to establish best practices and standards of care.

Benchmarking in surgery or in healthcare in general is considered difficult for a variety of reasons and has only scarcely been reported up to now [9,13–15]. However, besides the potential of quality improvement through improvement of clinical practices, it allows the establishment of standards of care, identifying best practices and outliers, while also easing resource allocations and regulatory compliances [13,16]. Domenghino et al. suggest building the benchmark based on outcome parameters assessed at different time points, on the routine assessment of PROMS and PREMS in clinical care, and on the record of individual and global morbidity according to the Clavien–Dindo classification and the Comprehensive Complexity Index [9,17–20].

In today's healthcare system, the traditional fee-for-service model creates misaligned incentives where providers incentivize the delivery of a high volume of services rather than focusing on outcome [21,22]. Porter et al. introduced the value-based healthcare (VBHC) principle to better align incentives with outcome, to focus on patient needs, to emphasize outcome over volume, to encourage continuous improvement and to promote transparency and accountability [23–26]. He defined the value of healthcare as the ratio of quality to cost implying that to increase the value of healthcare, the quality of care delivered to patients has to increase, while also reducing the cost of that care. By measuring outcomes, therefore, areas of improvement are not only identified but also drive quality-improvement initiatives to improve patient outcomes. Therefore, to create a sustainable healthcare system and to realize VBHC, every effort has to be taken to define quality of care and to create opportunities to benchmark it and scale it over the geography [27–30].

Obviously, the definition of quality in patient outcomes to establish a benchmark as outlined above involves a shear amount of data, which on top has to address data governance, data integration, enabling analytics and data interoperability to share and to encourage collaboration, as well as ethical and legal considerations [11,31–35]. Modern strategies involving AI and ML approaches will revolutionize current approaches [12,33,36–39]. However, although machine-learning approaches to extract comprehensive data from electronic health records are on the horizon [40], a structured data frame for a given medical condition is necessary, allowing for standardization, interoperability, data analytics, security, transparency, collaboration and further improvements to enable data harmonization over the geography. Above all, real-time follow-up over the entire care cycle, including both clinician and patient perspectives is highly preferable, should be integrated by an interoperable data platform, which ultimately allows federated exchange and learning [41–43].

With respect to sarcoma, our group has recently established the spectrum of sarcoma surgery, the complexity scores for the surgery of soft tissue tumors, as well as the quality indicators of sarcoma care [44–46]. These consists of six groups, namely the MDT/SB-management, therapy-related parameters including surgery, radiation oncology and chemotherapy, the complexity of sarcoma therapy, physician-based clinical metrics (summarized as CROMS; clinician-reported outcome parameters), as well as patient-based outcome and experience measures (PROMS/PREMS). We have also introduced the sarcoma-specific instrument to longitudinally assess health-related outcomes of the routine care cycle from sarcoma patients' perspective [47,48]. To realize VBHC [49], it is our strategy to integrate the outlined data complexity by establishing real-world time data exchange, introducing an interoperable platform to benchmark outcome and to align quality with costs.

Therefore, this article addresses the need to define quality indicators and establish benchmarking in sarcoma surgery and care. Our study fills the gap by proposing a framework implemented through an interoperable digital platform. We present a dataset of parameters for benchmarking sarcoma care, enabling the harmonized comparison of multidisciplinary teams and their (surgical) outcomes on the meta-level. This contribution is significant as it facilitates the assessment and improvement of (surgical) interventions, promotes best practices, and establishes standards of care. Additionally, our study aligns with the principles of value-based healthcare, emphasizing patient outcomes, continuous improvement, and cost reduction. By integrating data complexity on the meta-level and introducing an interoperable digital platform, we pave the way for sustainable healthcare systems and improved patient outcomes in sarcoma care.

Herein, we introduce the Sarconnector® (BF&PH, Zurich, Switzerland) as an interoperable digital platform to pave the way for the benchmarking of sarcoma care through real-world time data assessment of automated analysis. We report the dataset of parameters to define the outcome and quality indicators used for benchmarking and present as the proof of principal of assessing meta-level data (as opposed to the more familiar ground-level data) the comparison of two independent MDT/SBs with its automated data analysis.

2. Materials and Methods

2.1. Study Objectives

The primary objective of this study was to compare the demographics and basic treatment plan of two independent MDT/SBs to set the stage for prospective, large-scale, electronic, structured, longitudinal over the entire care cycle, with consecutive and absolute patient numbers, real-world time data assessment, as well as its automated analysis to create evidence regarding sarcoma care. The second objective was to establish and integrate an interoperable digital platform herein called Sarconnector®, which fulfills all the outlined requirements and allows its use in the daily routine work process.

2.2. Study Population

Data from patients diagnosed with sarcoma and presented at two independent MDT/SB sarcoma centers (MDT/SB-A and MDT/SB-B) were consecutively included and prospectively collected over 15 months. They both included one main tertiary referral University hospital each and its associated hospitals and networks. At both of these MDT/SB, more than 100 newly diagnosed patients with sarcomas each year are being discussed, thereby qualifying as internationally representative sarcoma centers [3]. For both MDT/SB, the same interoperable digital platform was used to assess the information of the patients. For both MDT/SB, it is a prerequisite to have a pathology reference review available to review all relevant imaging studies, and to have all 8 disciplines participating at the respective weekly meetings. All newly diagnosed patients, all patients after completion of each treatment step (for example, if combination therapy is decided on, the patient has to be presented after completion of preoperative radiation therapy and before surgery) or

patients with a change to the treatment plan other than previously decided on are required to be presented at the MDT/SB.

2.3. Sarconnector®

The interoperable digital platform is introduced elsewhere [46,47]. It is now expanded to the Sarconnector®, which presents with a front end as well as a back end (Figure 1). The front end includes both the data entry and the real-time data visualization. The core of the back end bases on the SQL database language with the R program to perform statistical analysis. Data are introduced either through the hospital or cloud server using API data exporter tools and interactive shiny apps. RWTD/E assessment is made possible through the combination of the weekly MDT/SB and the interoperable platform, as well as through PROMS/PREMS assessment by patients during their life-long follow-up [46,47]. Besides PROMS/PREMS, the Sarconnector® also includes clinical metrics (so-called CROMS) and health economics as data dimensions (Figure 2). Because of the RWTD assessment set-up, personalized and automated analytics can also be carried out in real-time.

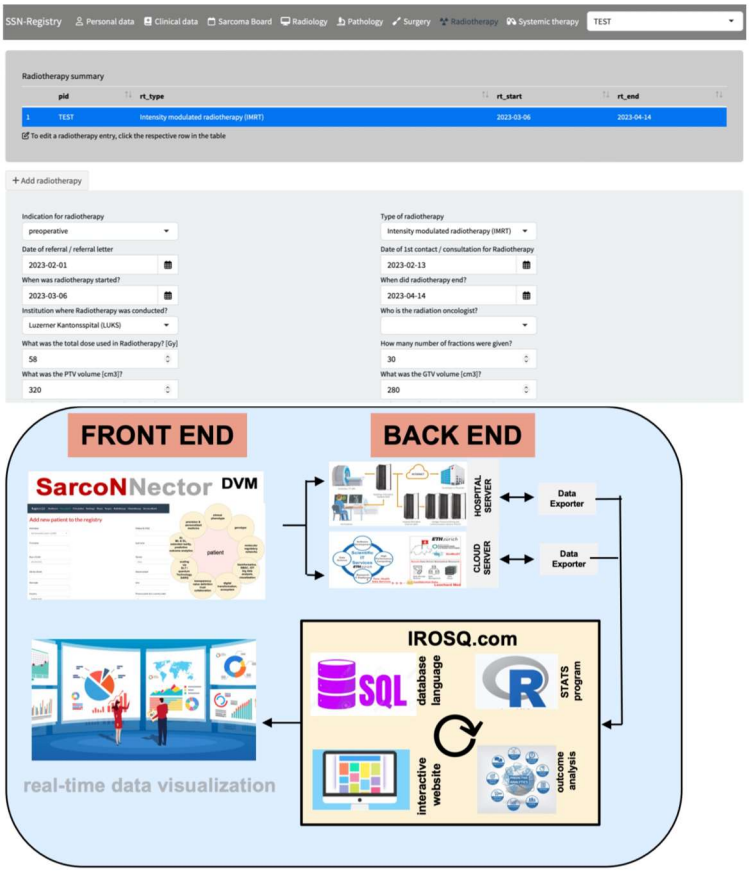


Figure 1. The Sarconnector® as an interoperable digital platform to allow IELAS-RWTD/E. An integrated practice unit (IPU) with an interoperable digital platform is a prerequisite to assessing IELASRWTD/E. A data quality guarantor creates the link between the interoperable digital platform, herein referred to as the Sarconnector®, which combines the assessment of data and simultaneous analysis with descriptive, inferential, non-/parameter and Bayesian statistics, with a great focus on exploratory data analysis and visualization. The front end consists of an easy-to-use data entry site, which simultaneously allows visualization of the data. The core of the back end is based on the SQL database language with the R program to perform statistical analysis.

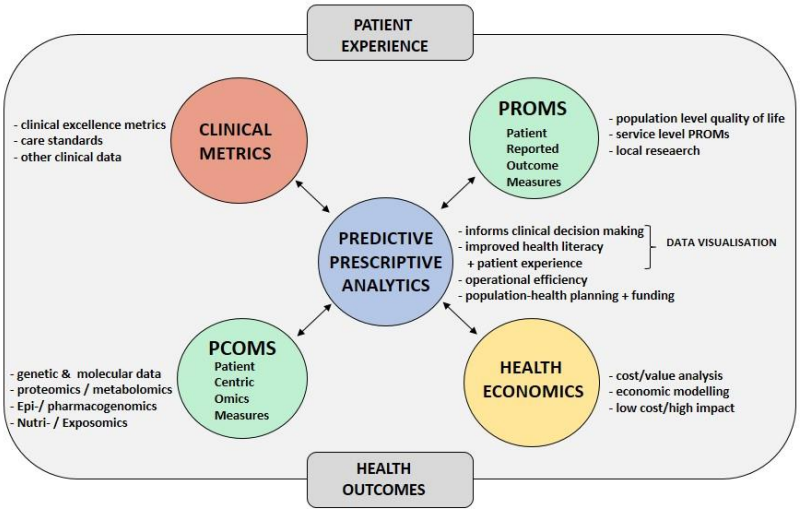


Figure 2. The Sarconnector® includes all data dimensions. This interoperable digital platform (Sarconnector®) includes all relevant physician-based, work-up, therapy and follow-up data, as well as patient-based PROMS and PREMS. To associate costs with outcome, it also includes health economics data. Based on these data, AI/ML approaches can be applied for predictive and prescriptive outcome modelling, ultimately enabling the sarcoma patient digital twin.

The Sarconnector® is designed to synthesize meta-level data to integrate multiple MDT/SB. As such, it provides not only object- or ground-level data, but specifically meta-level data, which yields higher-level analysis that is concerned with the structure, organization or properties of a lower level, related to higher-level thinking. It analyzes the quality indicators for a specific MDT/SB separately but can also integrate the data over several MDT/SB, thereby establishing a benchmark not only for a respective institution with its associated network, but also for a country or continent.

The flowchart of data processing by the Sarconnector® ("Driving precision in sarcoma care: real-world time data, value-based benchmarking, and digital twinning") can be summarized as follows: (A.) Collection of real-world time data over the entire care cycle: data related to sarcoma care, including clinical-reported outcome measures (CROMS), patient-reported outcome measures (PROMS), patient-reported experience measures (PREMS) and quality indicators (QIs), are collected from various sources, such as electronic health records, surveys and patient feedback; (B.) Storage of data on an interoperable digital platform: the collected data are stored securely on a digital platform that allows for interoperability, ensuring compatibility and data exchange between different systems and stakeholders; (C.) Automated analysis on the platform with immediate front end display: the platform employs automated analytical tools and algorithms to process the data and extract relevant insights. This involves statistical analysis, data mining and machine-learning techniques to identify patterns and trends; (D.) Benchmarking and quality indicators: the analyzed data are compared against predefined quality indicators specific to sarcoma care. These indicators include measures such as survival rates, recurrence rates, patient satisfaction scores, adherence to treatment guidelines, etc.; (E.) Assessment of sarcoma care quality: based on the benchmarking results, an assessment can highlight areas of strength and areas that require improvement; (F.) Value-based healthcare assessment: evaluating the value provided by the care process, this assessment takes into account the outcomes achieved relative to the resources used. It considers the effectiveness, efficiency and patient-centeredness of the care provided, aiming to optimize the overall value delivered to patients; (G.) Iterative improvement loop: the assessment findings are used to identify areas for improvement in the sarcoma care process. The healthcare team can take corrective actions, update protocols and implement interventions to enhance the quality of care provided; (H.) Predictive AI/ML modelling: the collected real-world time data are leveraged to develop predictive models using artificial intelligence and machine-learning techniques. These models can

forecast future outcomes, identify high-risk patients and support personalized treatment decisions, enhancing the decision-making process; (I.) Composition of the sarcoma patient digital twin: over time, as more data are collected and analyzed, the information is utilized to create a digital twin of sarcoma care. This digital twin serves as a virtual representation that can stimulate the behavior of the care process, predict outcomes and support decision making.

2.4. Statistical Analysis

Descriptive statistics were used to describe baseline patient characteristics. Categorical variables are presented as N (%), while numerical variables are presented as median (range). Fisher's exact test was performed to test for differences in chemotherapy and biopsy proportions between the two MDT-SBs. Statistical analysis was performed using the R statistical program.

3. Results

3.1. Basic Data and the Sarconnector®

Overall, there were 983 patients included in this study, of which 452 (46.0%) were female, with a median age at diagnosis of 58.0 (range, 1.0 to 59.0) years. Table 1 summarizes the dignity as well as the anatomic location of the lesions. There were 44 (4.5%) patients who presented with metastasis at diagnosis.

Table 1. This table summarizes all relevant basic demographic data of the patients included in this study. The numbers are separately listed for each MDT/SB, as well as overall.

	Overall N = 983	**MDT/SB-A N = 610**	**MDT/SB-B N = 373**	***p*-Value**
Female	452 (46.0%)	283 (46.4%)	169 (45.3%)	0.74
Age at diagnosis	58.0 (1.0, 95.0)	60.0 (8.0, 93.0)	56.0 (1.0, 95.0)	0.001
Bone tumors				<0.001
Chondrogenic	44 (4.5%)	24 (3.9%)	20 (5.4%)	
Osteogenic	19 (1.9%)	6 (1.0%)	13 (3.5%)	
Vascular	18 (1.8%)	14 (2.3%)	4 (1.1%)	
Others/Unknown	81 (8.2%)	60 (9.8%)	21 (5.6%)	
Soft-tissue tumors				
Adipocytic	201 (20.5%)	141 (23.1%)	60 (16.1%)	
(Myo-)fibroblastic	117 (11.9%)	59 (9.7%)	58 (15.6%)	
Fibrohistiocytic	33 (3.4%)	11 (1.8%)	22 (5.9%)	
Muscle tumors	82 (8.3%)	51 (8.4%)	31 (8.3%)	
Undifferentiated/unclassified	87 (8.9%)	50 (8.2%)	37 (9.9%)	
Others	301 (30.6%)	194 (31.8%)	107 (28.6%)	
Primary tumor site				0.37
Appendicular	558 (56.8%)	352 (57.7%)	206 (55.2%)	
Axial	367 (37.3%)	220 (36.1%)	147 (39.4%)	
NA	58 (5.9%)	38 (6.1%)	20 (5.4%)	
Metastasis at diagnosis	44 (4.5%)	26 (4.3%)	18 (4.8%)	0.75

The Sarconnector® presents an intuitive, self-explanatory front end, separated according to the respective disciplines (Figure 1). For each discipline, a minimal dataset of relevant parameters are requested to enter. The case report form is provided in the supplementary data (SUPP). At the top, it provides a summary of what type of, e.g., radiation therapy was performed. Specifically, besides the type of radiation performed, it also includes the use of a flab, the critical tumor volume/gross tumor volume (CTV/GTV) volumes, and the color wash. Because all disciplines assess their respective information regarding work-up and therapy, these parameters can be analyzed in relation to each other.

3.2. Comparison of Two MDT/SB

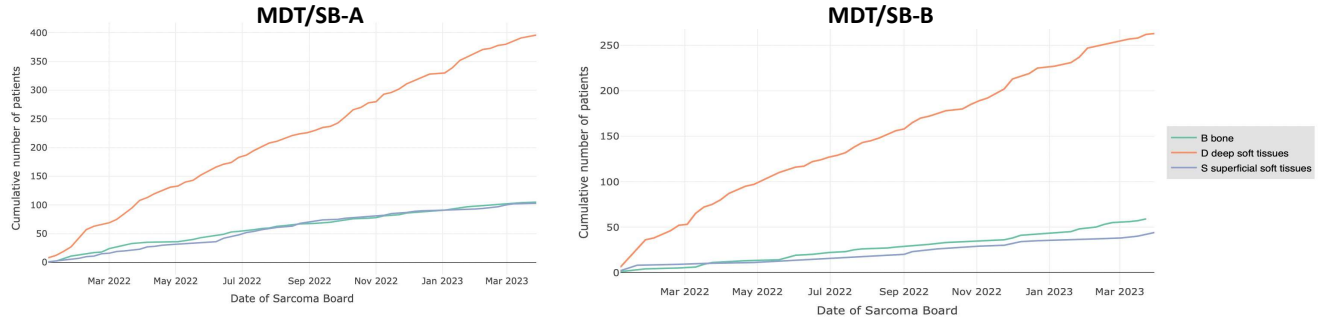
A basic data benchmark framework of consecutive patients over a 15-month period of two MDT/SBs were assessed for comparison (Table 2). While there were twice as many first-time presentations in MDT/SB-A compared with MDT/SB-B, there were equal follow-up presentations for both MDT/SBs. Patients with primary sarcomas were more numerous in MDT/SB-A than in MDT/SB-B, but together, they totaled 321 patients. An important difference relates to the number of biopsies, which are twice as much in MDT/SB-A as opposed to -B. This might be explained partly by the increased number of benign lesions being presented to the MDT/SB-A. While the indications for surgery and radiation therapy are comparable, the indications for chemotherapy differ between the two MDT/SBs. There are important differences pointing towards different strategies with respect to work-up and therapy. For example, there was a statistically significant difference in the proportion of biopsies performed. In the MDT/SB-A, 523/610 (85.7%) patients received a biopsy, but only 259/373 (69.4%) patients did in MDT/SB-B, $p < 0.0001$. Likewise, 23/330 (6.9%) patients with a sarcoma in MDT/SB-A were treated with chemotherapy, while 83/304 (27.3%) of sarcoma patients in MDT/SB-B were treated with chemotherapy, $p < 0.0001$.

Table 2. This table summarizes all relevant oncological data of the patients included in this study. The numbers are separately listed for each MDT/SB as well as overall.

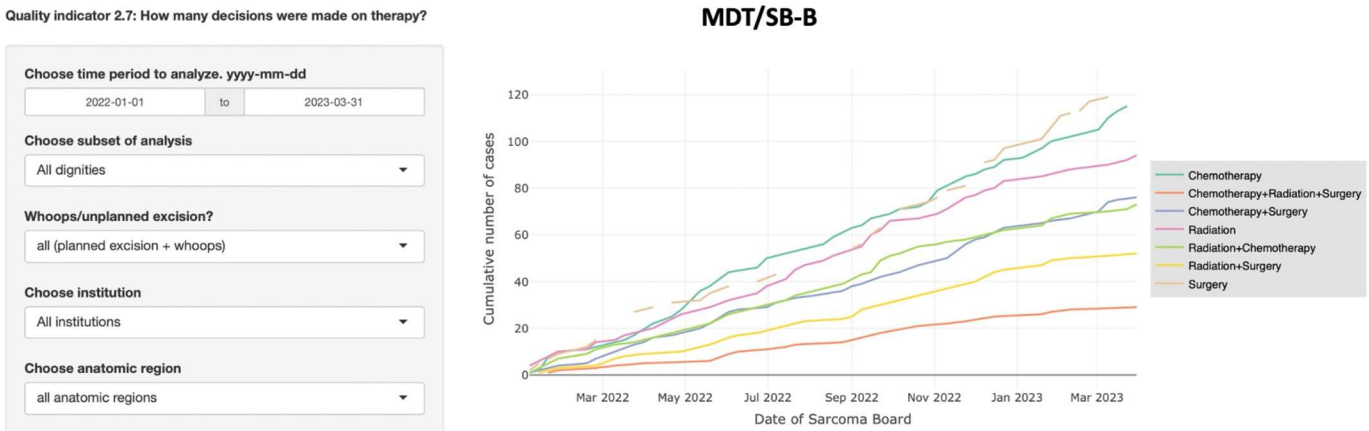
	OVERALL	**MDT-SB/A**	**MDT-SB/B**	***p*-Value**
Total number of patients	983	610	373	<0.001
Total number of presentations	1556	914	642	<0.001
	OVERALL	MDT-SB/A	MDT-SB/B	*p*-value
1st time presentations	650	416	234	<0.001
Follow-up presentations	833	431	402	<0.001
Dignity: 1st time/fup presentation	650/833	416/431	234/402	<0.001/0.17
Benign	120/70	105/54	15/16	<0.001/<0.001
Intermediate	135/50	61/77	74/3	<0.001/<0.93
Malignant	186/548	99/256	97/292	<0.001/<0.001
Simulator	43/20	35/13	8/7	0.01/0.26
Metastasis	10/4	10/4	0/0	0.02/0.13
Blood	53/11	9/1	44/10	<0.01/0.005
Others	103/30	97/26	6/4	<0.01/<0.01
Localization: 1st time/fup presentation	650/833	416/431	234/402	<0.001/0.17
Bone	117/141	77/76	40/65	0.67/0.58
Deep soft tissues	431/579	269/290	162/289	0.26/0.15
Superficial soft tissues	95/103	70/62	28/41	0.11/0.07
NA	7/10	0/3	4/7	0.02/0.21
1st time & intermediate/malignant	321	160	161	0.99
Bone	48	20	28	0.27
Deep soft tissues	224	111	113	0.90
Superficial soft tissues	49	29	20	0.17
Total number of biopsies	782	523	259	<0.001
Bone	133	82	51	0.19
Deep soft tissues	518	348	170	0.81
Superficial soft tissues	131	93	38	0.31
Indications for surgery	393	244	149	0.77
Bone	70	38	32	0.17
Deep soft tissues	259	161	98	0.99
Superficial soft tissues	64	45	19	0.16
Indications for radiotherapy	98	46	52	0.48
Bone	5	2	3	0.99
Deep soft tissues	73	33	40	0.65
Superficial soft tissues	20	11	9	0.46
Indications for chemotherapy	106	23	83	<0.001
Bone	28	9	19	0.18
Deep soft tissues	70	14	56	0.62
Superficial soft tissues	8	0	8	0.20

3.3. Interactive Data Analysis and Visualization

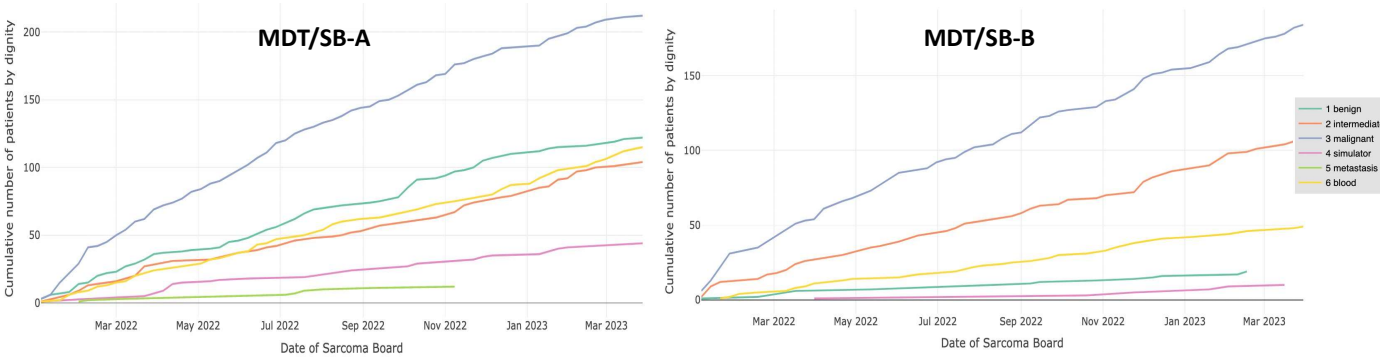
The Sarconnector® allows the interactive comparative visualization of the basic data with respect to a given time period, according to anatomic location, tumor biology or dignity of the tumor, and according to therapy, side by side for the respective MDT/SB (Figure 3a–d). The incidence of diagnosis or type of therapy is visualized over time to easily compare subgroups. Visualization of data is critically important to define subgroups for detailed analysis. Importantly, based on the selection of the subgroups to be defined for analysis, the system links the graphs with the respective raw data such that further detailed analysis can be carried out.



(**a**)

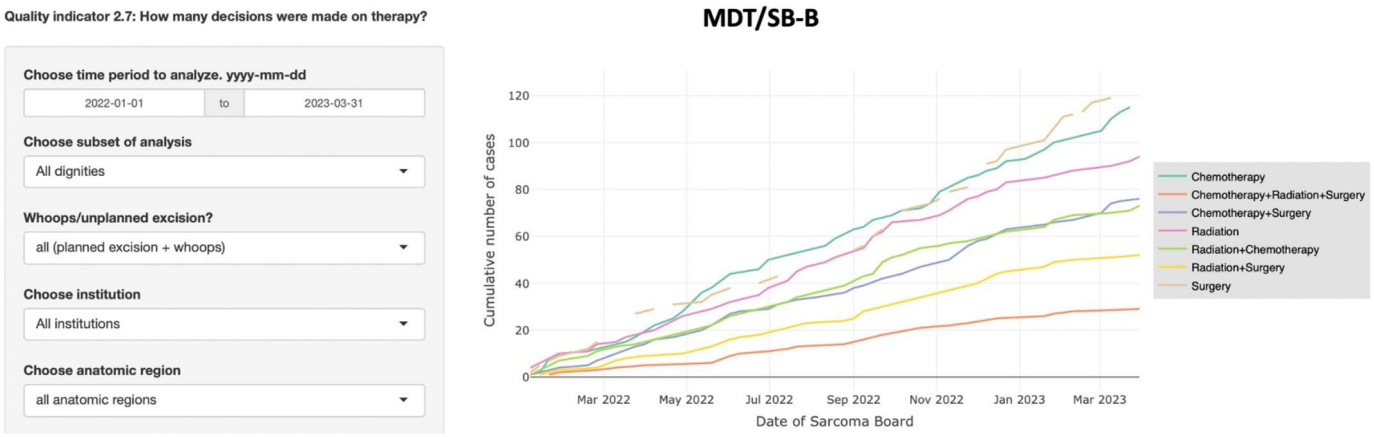


(**b**)



(**c**)

Figure 3. *Cont.*

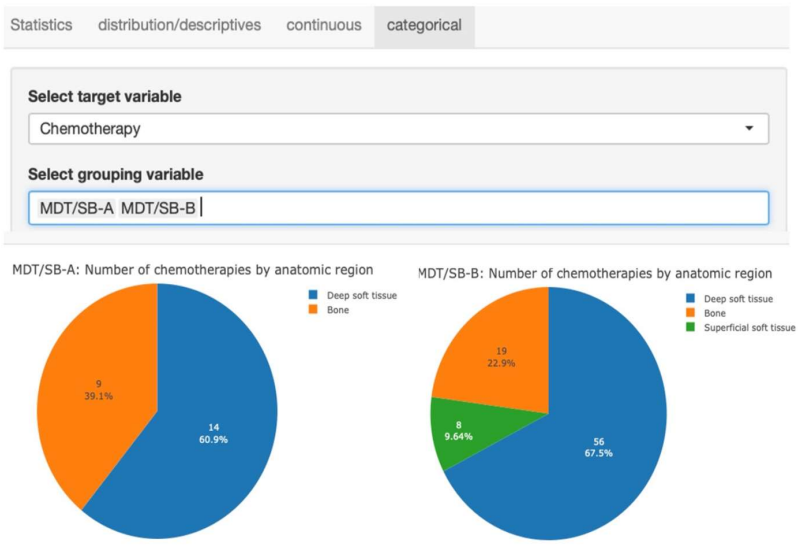


(**d**)

Figure 3. (**a**) These graphs show the cumulative incidence of patients presented at the MDT/SBs over a 15-month period, according to anatomic location of the tumor. (**b**) These graphs show the cumulative incidence of the patients presented at the MDT/SBs over a 15-month period, according to dignity of the tumors. (**c**) This graph shows the cumulative indications of patients presented at the MDT/SB-A over a 15-month period, according to the performed therapy. (**d**) This graph shows the cumulative indications of patients presented at the MDT/SB-Bs over a 15-month period, according to the performed therapy.

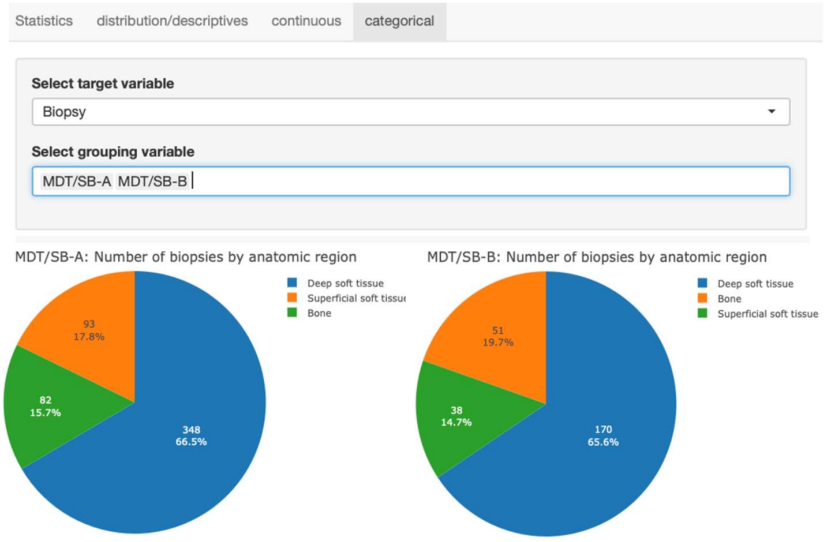
3.4. Automated Statistical Analysis and Visualization

The Sarconnector® allows the analysis of any subgroup parameter, the performance of basic statistical tests, as well as advanced statistical techniques (such as Cox regression, competing risk analysis). As a first step of the workflow, the appropriate statistical measure to analyze the data is chosen. For example, a Shapiro–Wilk normality test and Levene's test for equal variances are performed. Since these tests might suffer from low power [50], the researcher can also visually assess normal distribution by inspecting normal Q-Q plots and histograms. In the next step, the appropriate test is automatically chosen and performed. Furthermore, summary statistics (such as means and standard deviations of the compared samples or Kaplan–Meier estimates) and the corresponding figures are produced, which can be used in scientific publications (such as this one). The Sarconnector® therefore facilitates the conduction of clinical studies (Figure 4).



(**a**)

Figure 4. *Cont.*



(**b**)

Figure 4. (**a**) There was a statistically significant difference in the proportion of biopsies performed. In the MDT/SB-A, 523/610 (85.7%) patients received a biopsy, but only 259/373 (69.4%) patients did in MDT/SB-B, $p < 0.0001$. (**b**) There was a statistically significant difference in the proportion of chemotherapies performed. In the MDT/SB-A, 23/330 (6.3%) patients with a sarcoma were treated with chemotherapy, and 83/304 (27.3%) patients were in MDT/SB-B, $p < 0.0001$.

Figure 4 shows an interactive statistics tool of the Sarconnector®, which allows the performance of statistical tests (such as the *t* test) for continuous and categorical variables and the drawing of figures for publications automatically; (Figure 4a.) biopsy and (Figure 4b.) chemotherapy are shown as representative examples.

4. Discussion

We herein present a novel approach to handling and harmonizing medical data, thereby mirroring sarcoma patient care in real-world time and comparing respective sarcoma centers/IPUs. Large amounts of data are being assessed trans-disciplinarily and trans-institutionally, as well as across centers using the Sarconnector®, which is designed to determine quality indicators of sarcoma care and to provide a quality-management system. It is important to realize that the Sarconnector® does not simply collect data on the object-level but on the meta-level. Herein, we report the comparison of two large sarcoma centers in terms of how patients are being cared for to be subjected for meta-level data analysis. For example, we found important differences regarding the work-up approach of biopsies, as well as of therapeutic approaches, such as the indication to use chemotherapy. This provides unexpected insights about providing sarcoma care of different healthcare ecosystems, with potentially important consequences for both quality and longitudinal cost of care, thereby allowing the establishment of a benchmark. The Sarconnector® with its numerous critical care parameters being harmonized, interoperable and benchmarked over the geography not only allows automated evidence-based insights from the entire care cycle of an individual patient, but also ultimately paves the way for value-based precision care, which may represent the main strength of the novel meta-level approach as presented herein.

Obviously, there are also limitations to consider. The findings reported herein heavily rely on the availability and accuracy of the data collected. Missing or incomplete data could impact the analysis and potentially introduce biases. Also, two large sarcoma centers may not fully represent the diversity of sarcoma care across all healthcare ecosystems. Further, while the Sarconnector® identifies associations between different care approaches, it may not establish causality. Confounding factors that were not accounted for in the

analysis could influence the observed differences. And while we are focusing on sarcoma care herein, benchmarking might not cover all aspects of healthcare delivery or other medical conditions. Last but not least, while this approach presented herein is novel and comprehensive, there might be challenges or complexities in the implementation and widespread adoption of such a system in RWT healthcare settings.

In healthcare, benchmarking targets define the standard approach to improve patient outcomes, including the establishment of the best achievable real-world postoperative outcomes [15]. Ideally, defined parameters are reproducible, objective and universal [51]. The purpose of benchmarking is to stimulate the genuine endeavor for perfection, rather than judge a unit or physician performance [13,15,52,53]. An international jury consensus approach identified benchmarking as one of the key elements to reporting and improving the quality of surgical interventions and medical care [9]. To realize benchmarking, CROMS, PROMS/PREMS and complications of (surgical) treatments as outcome parameters have to be assessed both nationally and internationally. Why do we need benchmarking? By comparing their own performances with peers, best practices can be identified and learning experiences maximized. The best outcome can be defined and be adopted for standard practices. By comparing clinical practices and outcomes, not only can best practices be identified, but so can new and innovative ways to improve patient care. Benchmarking helps recognize outliers performing exceptionally well or poorly, and subsequently then helps investigate the reasons for their performance. By identifying areas where resources can be best utilized, resource allocation is handled more efficiently. As presented herein, biopsies or chemotherapies may be performed too often or not, but having the opportunity to align with outcome will enable the system to optimally allocate resources. In the context of accreditation and certification programs, healthcare providers comply with regulatory requirements and demonstrate the quality of care provided. Benchmarking in medical care and specifically cancer care, however, is not widespread. Furthermore, it has to be distinguished from standard of care, which generally refers to accepted practices, protocols and guidelines for providing medical treatment for a particular condition or disease [1,2]. Such standards are established based on the best available scientific evidence and expert consensus and are often used as a benchmark or reference point for evaluating the quality of care. In contrast, benchmarking involves comparing the performance of healthcare providers or healthcare systems against established standards or against each other. The standard of medical care provides a set of guidelines and expectations for how medical care should be delivered, while benchmarking medical care involves comparing actual performance against those standards to identify areas of improvement and drive quality improvement. In both herein presented MDT/SBs, the provided care is based on guidelines; nevertheless, important differences in practicing do exist, emphasizing the importance of introducing a benchmark tool in addition to the established guidelines. While there are no benchmarks reported for sarcoma care, there are sparse studies in the literature on cancer care and some on surgical disciplines. The international cancer benchmarking partnership (ICBP) is a collaboration of researchers and clinicians from several countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway, Sweden and the United Kingdom) that aims to investigate and explain differences in cancer survival between countries [54,55]. This partnership compares cancer survival rates and stage at diagnosis across different countries using a standardized methodology in order to identify factors that contribute to variations in cancer outcomes [55]. The ICBP's mission statement is to provide policymakers, health professionals and the public with information about international variations in cancer survival and factors that might contribute to it in order to improve outcomes. To achieve this mission, the ICBP conducts research and analysis on cancer survival rates, stage at diagnosis and other related factors across participating countries. While this approach is laudable, it only concentrates on specific aspects of sarcoma care, while the herein presented approach is holistic. Nolte et al., exploring the link between policies and cancer survival, found a positive correlation with improvements in survival over time across various cancer sites analyzed [53]. Perera et al. developed an evidence-based benchmark

rate for cancer surgery used to provide a new template for high-income and emerging economies to rationally plan and assess their cancer surgery provisions [56]. Wind et al. explored the possibilities to benchmark cancer centers by structuring cancer care into pathways, reducing variability in clinical practices and improving patient outcomes [16]. They were successfully establishing and testing a benchmark tool that was pivotal to organizing cancer care in an IPU (integrated practice unit) to yield multiple performance improvements [52]. While benchmarking approaches are sparse for the musculoskeletal system [57], they are fairly common in visceral surgeries [58–62]. While these benchmarks focus on specific one-dimensional diseases, and while it is clear that policies will need to guide the transformation process, there are now efforts being undertaken to establish benchmarks for bottom-up use in more complex diseases [9,13,14]. With respect to sarcomas, there is only little information about benchmarking available [63–65], and they all refer to specific entities or surgeries without a holistic bottom-up approach including all basic parameters, underlining the necessity of our bottom-up approach as presented herein. Conversely, if it is the shared goal to benchmark quality and outcome, then it only makes sense to design a system including basic parameters that is designed to do so, i.e., to allow data harmonization and their scaling [44–48]. As shown herein (considering the discrepancies of performing biopsies or the indication to treat with chemotherapy among MDT/SBs and thereby identifying potential areas of differences in quality and costs), designing a system that allows not only the outcome but also the granular pathway of decisions, such as during an MDT/SB, is of critical importance. The Sarconnector® is designed to assess quality indicators, covering all the respective index and outcome parameters, and analyzes the pathway of decisions during MDT/SB to reproduce why which treatment was initiated. Taking into account the inclusion of long-term follow-up to incorporate outcome discrepancies, such an interoperable digital platform has the potential to ultimately become a sarcoma patient digital twin (SPDT) [40,66].

Data structures with their different types are obtained increased focus, and there is continued debate about its use [39,67]. Electronic health records (EHRs) are routinely used for clinical care and research. Clinical trials databases (CTDs) contain collected data during randomized trials. Administrative claims data representing billing codes and information submitted to insurance companies for reimbursement are usually again stored separately. There are also biobanks that store biological samples and associated data. Each data structure has its strengths and limitations [68]. The choice of data structure depends on the research question and the resources available for data collection and analysis. The advantage of real-world data includes the potential to capture real-world complexity, such as contextual factors and system interactions, which may be difficult to simulate through modelling alone [31,32]. Further, RWTD provides a rich source of information that can be used to calibrate and validate models [69,70]. RCTs are considered the gold standard for medical research as they involve randomization. Because these are typically conducted under highly controlled conditions, they can lead to limitations in terms of generalizability to the broader population and are usually associated with great costs. Conversely, RWTD provides a more comprehensive view of healthcare outcomes as it includes data collected from routine medical practice, electronic health records, administrative claims, and patient-generated data [40,67,69,71]. If incomplete or inaccurate data, confounding factors and selection biases are addressed with respective data structures, RWTD has the potential to complement and enhance the insights gained from RCTs [69,71–73]. An interoperable digital platform helps to overcome the limits by integrating data from various sources and standardizing data formats [74,75]. With an interoperable platform, data can be accessed, shared and analyzed more easily and efficiently. This may facilitate the identification of patterns and associations in the data that may not have been apparent otherwise. It improves the accuracy and completeness of data by reducing errors associated with data entry and enabling real-time capture [67]. If data are collected over time as we reported earlier [47], more accurate and timely information becomes available. Interestingly, an interoperable digital platform enables more extensive data analytics and modelling to

support decision-making processes, such as predictive modelling and machine-learning algorithms [39,74–76]. Integrating all common data sources and dimensions, coupled with the opportunity to analyze it concomitantly, enables the realization of real-world time evidence and prediction [77–79], and ultimately, the sarcoma patient digital twin (SPDT) [40,66].

The definition of outcome benchmarks with specific reference to quality indicators for a given disease, as well as an interoperable digital platform that includes economic data dimensions like the Sarconnector® does, represents the prerequisite for value-based healthcare, which aims to optimize the balance between health outcomes and costs [24,26,30,46]. VBHC incentivizes healthcare providers to deliver high-value care by linking reimbursement to quality indicators and promoting the use of shared decision-making tools that take into account patient preferences and values. In this context, the availability of RWTD/E with its associated analysis as presented herein plays a pivotal role. Because the Sarconnector® enables benchmarking sarcoma care and consequently the creation of a sustainable healthcare system, it is pivotal to support VBHC. Measuring and comparing performances across different healthcare providers or organizations becomes possible, while enabling the identification of best practices and areas for improvement in healthcare delivery is also made possible over time, which may lead to better outcomes and increased efficiency [21,80]. Variations in care delivery and outcomes may allow potential areas for cost savings and improved efficiency to be identified. Such tracking of performance over time allows for the evaluation of the effectiveness of interventions and the identification of trends. Health equity can be promoted by identifying and addressing disparities in healthcare. Benchmarking may also support VBHC by setting goals and targets for improving healthcare outcomes and reductions in costs, which can help to align incentives and motivate providers to improve performance [13,26,51,56]. High-performing providers may be used to inform patient decision making and help drive competition and innovation in the healthcare industry. The development of novel payment models makes it possible to incentivize high-value care, rewarding providers for delivering high quality at lower costs. It not only facilitates collaboration and knowledge sharing among healthcare providers and organizations, but it also supports the development of policies and regulations that promote the delivery of high-value care and encourage sustainability of the healthcare system. As presented herein by comparing two MDT/SBs and assessing consecutive and prospective RWT data, we found important differences regarding the number of biopsies and the number of chemotherapies performed for a comparable patient cohort. Both MDT/SBs treat their patients according to their best knowledge and available evidence. Nevertheless, the reported differences imply that depending on which sarcoma center/IPU a patient is being treated in, a patient may be over- or undertreated, or the set-up to deliver care may be differently organized. Independent of the situation, it is obvious that such differences have a direct impact on the financial burden. It also becomes obvious that the number per se of performed chemotherapies, for example, is merely a measure of volume but is not correlated with quality of care, which conversely can neither be associated with costs. The Sarconnector® is capable of identifying differences in delivering care between MDT/SBs from the same country and of even neighboring counties with partly overlapping patient populations. There are likely obvious differences in delivering care at different outcome qualities, but this is for certain at different costs. This is a somewhat unexpected finding, but it evidences the validity and the necessity of such a tool. Obviously, many more questions arise with these findings that need to be answered. We therefore believe that the Sarconnector® represents a powerful tool to develop a sustainable healthcare system.

5. Conclusions

In conclusion, benchmarking is a crucial tool for improving healthcare quality and efficiency with respective cost containment. The RWT data approach provided by the Sarconnector® offers a valuable method for evaluating quality and cost metrics in a standardized way, allowing for transparent comparisons between different healthcare providers.

This approach enables healthcare providers to identify areas for improvement and make data-driven decisions to optimize their resources and improve outcomes. By utilizing benchmarking and the RWT harmonized data approach, healthcare providers can move towards a value-based care model, where high-quality care is delivered at a reasonable cost. Ultimately, benchmarking with the RWT harmonized data approach provided by the Sarconnector® can help healthcare providers achieve better outcomes for their patients and improve the overall effectiveness of the healthcare system with respect to both outcomes and costs.

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Review

The Sarcoma-Specific Instrument to Longitudinally Assess Health-Related Outcomes of the Routine Care Cycle

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Abstract: Patient-based health related quality of life (HRQoL) measurements are associated with an improvement in quality of care and outcomes. For a complex disease such as sarcoma, there is no disease-specific questionnaire available which covers all clinically relevant dimensions. Herein, we report on the development of an electronically implemented, sarcoma-specific instrument to assess health-related outcomes, which encompasses a combination of generic questionnaires tailored to the respective disease and treatment status covering the entire longitudinal care cycle. An interoperable digital platform was designed to provide a node between patients and physicians and to integrate the sarcoma-specific HRQoL instrument with patient and physician-based quality indicators to allow longitudinal structured real-world-time data evidence analytics. This approach enables the prediction modeling of disease, and by attributing cost tags to quality indicators, treatment effectiveness for a given disease will be directly correlated with financial expenses, which may ultimately lead to a more sustainable healthcare system.

Keywords: sarcoma-specific HRQoL instrument (health-related quality of life); PROMs (patient reported outcome measurements); IELAS-RWTD/E (interoperable electronic longitudinal absolute structured real-world-time data/evidence); VBHC (value-based healthcare)

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1. Why Do We Need Patient Reported Outcome Measures (PROMs)?

Healthcare costs are constantly rising and impose great challenges [1]. Our healthcare system today is largely ignorant of incorporating treatment effectiveness and outcomes, and rising healthcare costs are leading us toward a wasteful and unsustainable trend [2].

Improving value in healthcare is meant to benefit patients, payers, providers and suppliers while increasing the economic sustainability of our healthcare system [3]. Therefore, there is a great need to improve patient-centered care [2] and to possibly redesign a novel healthcare ecosystem with particular focus on shared value [4]. Porter defined shared value as a multidimensional relationship between health outcomes and costs incurred to deliver these outcomes [3,5]. Obviously, there are differences in perceptions of value among patients and between patients and providers [6]. The definition of shared value in healthcare includes the clinical metrics as defined by the physicians as well as by the patients' voice as assessed by the quality of care. Considering the upcoming healthcare transition as projected for the next decade [7], the definition of quality of care becomes

pivotal because our current fee-for-service model will be replaced by a value-based on quality model. In such a model, PROMs are measures used to assess patients' health or quality of life and represent an integral part of patient-defined quality of care. They were introduced to assess treatment effectiveness and improve outcomes, and are meanwhile a pivotal part of value definition [8–14]. There are currently numerous PROMs to assess health-related quality of life (HRQoL). Specifically with regard to cancer, they were shown to be prognostic tools such as for outcome, for example in breast cancer, multiple myeloma, colon and lung cancers [15–18]. PROMs are generally used at the aggregate level for audit and benchmarking, real world evidence generation and as an input or predicted output for clinical tools and AI in health [11]. At an individual level, PROMs facilitate shared decision making, screen or monitor symptoms and provide timely care tailored to individual needs [11,12,19]. Meanwhile, however, it has become obvious that one single (as opposed to a multidimensional) PROM may not cover all aspects of health for a given disease at various timepoints. Further, the definition of which dimensions of disease are to be included is obviously critical. A real challenge to introduce PROMs is that today's healthcare personnel, including clinicians, are not formally trained to consider also the impacts of social determinants of health (SDOH) on health outcomes [17,20] while delivering care [21–23]. According to the County Health Rankings Model, SDOH, such as health behaviors, socioeconomic factors and physical environment, contribute to 80% of the clinical outcomes in a community. In contrast, clinical care contributes to the remaining 20% of clinical outcomes [21,24,25]. Clinicians rely heavily on biomarkers and diagnostic test results to guide their decision-making. Shared-decision making preference elicitation and documentation remain challenges in today's healthcare system, and preferences related to quality of life should be considered in treatment decision making [26]. To cover all healthcare dimensions, Khurana et al. developed a Whole Person Health Score (WPHS) that quantifies a person's health into six domains: physical health, emotional health, resource utilization, socioeconomics, ownerships, and nutrition and lifestyle [21]. The WPHS extends the physical health assessment by five more dimensions to cover all possible parameters impacting the course of a disease. Ideally, these six dimensions are represented when a HRQoL instrument is developed. An instrument covering all health dimensions for a given disease including the incorporation of the patients' view to define the shared value is of great importance to ultimately realize value-based healthcare (VBHC), which will be the base to create a sustainable healthcare system with cost control (Table 1). The question remains, however, how this is being realized specifically for sarcoma patients.

In this review, we first address the challenges of introducing PROMs in routine sarcoma patient care, to then, based on the literature, reason about the selection of which aspects need to be covered. In a further step, we describe a sarcoma-specific instrument which basically is composed of established PROMs. Last, we introduce the interoperable digital sarcoma platform which allows for simultaneous data assessment and its analysis.

Table 1. Summary of main challenges, bibliography included in this introduction and its added value.

Challenge	References	Added Value
Where do we want to go?	[8]	This article describes the transition from the current care to the future state of how our healthcare system will look like in 2030, specifically emphasizing the potential of digital transformation.
What is good health?	[18,21–26]	These articles define the social determinants of health and the delivery of care. Health behaviors, socioeconomic factors and physical environment contribute 80% to health outcomes, whereas clinical care only contributes the remaining 20% to clinical outcomes. For these reasons, the Whole Person Health Score was created.

Table 1. *Cont.*

Challenge	References	Added Value
What is the current problem?	[1,2,6,7,27]	Healthcare costs represent a seemingly unsurmountable problem, and lead us towards an unsustainable trend. While perceptions of value differ among patients and providers, shared decision-making regarding data assessment and documentation remain challenges specifically because most of the healthcare data are unstructured und therefore not ready for analysis.
Potential solutions?	[3–5]	Improving value benefits may lead to a sustainable health system. A novel ecosystem centers on the shared value being the multidimensional relationship between health outcomes and costs incurred to deliver these, as defined by the value-based healthcare principle. For these reasons, quality of care must be defined and assessed using structured data, to which then cost tags can be attributed which allows the definition of the entire costs of a given diagnosis over the entire care cycle.
Why are PROMS important?	[9–19]	These articles summarize how PROMS assess treatment effectiveness and outcome, and show that they can improve survival. PROMS have to be designed such that they cover the entire spectrum of the social determinants of health as suggested by WPHS but are nevertheless disease-specific.

2. Challenges to Introduce PROMs for Sarcoma Patients

Sarcomas represent an extremely heterogenous disease. While being rare or ultra-rare, they are composed of more than 175 distinct diagnostic entities, and occur at all possible anatomic sites of all age groups. Treatment is transdisciplinary, and while surgery is the mainstay of treatment, it is extremely complex because surgical techniques vary greatly from one anatomical site to others, and one surgeon nowadays is unable to cover the entire surgical spectrum of techniques at the required level [27]. Several disciplines together determine the successful outcome of the patients, and weekly multidisciplinary tumor board meetings have proven to be instrumental to achieve this [28–32]. While choosing a sarcoma instrument to define patient-defined quality of care, it cannot only focus on one single diagnostic or therapeutic aspect, but it must incorporate the sum of care provided by all disciplines because its success is determined by the sum of all treatments. As sarcoma patients need life-long follow-up for potential late effects associated with their disease, the assessment has to be designed longitudinally over the entire cycle of care, from the initial work-up of the patient, all types of treatment combinations, until last follow-up or death. If we want to assess the health of sarcoma patients using the WPHS framework, we need to assess a broad range of outcomes. There is already a multitude of PROMs for sarcoma patients available, both for assessing experience and outcomes of treatment [33–40]. Ideally, the information assessed through PROMs in sarcoma could be integrated in some overall sarcoma-specific instrument to define quality of care. The main prerequisites include the possibility of routine collection of data (as opposed to use in clinical trials only) as well as the allocation of PROMs that correspond to patients' clinical metrics such as anatomic location, diagnostic subtypes, type of therapies, age and gender as well as prognosis [36,37]. It currently remains an open question whether generic or cancer-specific questionnaires will push through [41]. Generic questionnaires alone (such as EQ-5D) may not specifically enough address the needs for a given disease at any given timepoint of the care cycle

such as sarcoma, while as opposed to a newly developed sarcoma-specific instrument, an established PRO may allow for cross-comparison among other diseases and benchmark comparisons to the standardized normal population.

3. Which PROMs Are Being Used for Sarcoma Patients?

In a scoping review, Almeida et al. mapped the reported PROMs in sarcoma patients from the available literature and how they were measured, focusing specifically on the nature, extension and reach of research related to PRO and what instruments were being used to assess these [33]. They stressed the importance that PROMs include multidimensional assessments of quality of life, that the evaluation be longitudinal, and that anatomic location should be instrumental to include. Although the assessment of different time points of the care cycle—with respect to different diagnostic procedures or treatments—would provide important information, the complexity of sarcoma as a disease may hinder such introduction and utilization of PROMs with common approaches. Almeida et al. therefore concluded that there must be a new and sarcoma-specific measurement strategy to mirror the quality of sarcoma care [33].

Martins et al. reported on the sarcoma measure (SAM) [34]. They defined 22 items reflecting physical, emotional, financial well-being as well as sexuality and coined the term "sanxiety" of sarcoma patients. The SAM is a patient reported experience measure that can be used in clinical practice for all patients irrespective of age, type of sarcoma or treatment status. Some criticize that it is impossible to have one sarcoma-specific measure that meets the needs of clinical practice, academia and industry [41]. Others put fourth that SAM is only an experience but no outcome measure [36,37].

Within the spectrum of mesenchymal tumors, there are diagnosis specific PROMs for desmoid patients. In the Profiles study, Schut et al. created a disease-specific, desmoid-type fibromatosis questionnaire (DTF-QoL) covering 173 questions (which takes up to one hour for the patient to fill out) and compares it to the well-established and generic EORTC-QLQ and EQ-5D questionnaires, which are currently under investigation. They foresee to use it longitudinally over the entire care cycle depending on their prospective findings upon the conclusion of their study [35,42].

Den Hollander et al. performed an exhaustive systematic literature review unravelling the heterogeneity of disease and sarcoma patients' health related quality of life [37], specifically focusing on the anatomic tumor location. They analyzed fifty-four different questionnaires, most often cancer-generic or generic HRQoL questionnaires. While they found that sarcoma patients in general reported lower HRQoL than the general population, they identified distinctive patterns with respect to symptoms, physical functioning, disability and psychosocial well-being depending on the tumor's location. They also found that other factors such as disease stage should be taken into account to prioritize patients' needs. These authors concluded that a sarcoma-specific strategy should be developed and used covering the heterogeneity of sarcoma, including anatomic location specific issues to improve personalized HRQoL assessment in clinical practice. As a follow-up on this, den Hollander et al. recently published a study protocol to develop a sarcoma specific instrument to develop a comprehensive list of HRQoL issues relevant to sarcoma patients, as well as a measurement strategy indicating which issues should be evaluated in certain subgroups [37]. While such an approach is extremely useful and will hopefully lead to customized measures, it will represent an entirely new instrument which cannot be cross-referenced with existing ones. Therefore, an alternative approach may include the introduction of a set of validated PROMs, which are already being used in many other cancer types and, importantly, for which there is most often information on the normal population available for comparison and benchmarking. These are designed to cover not only different dimensions of health, such as for example physical and mental health, but also the entire care cycle with customized measurements based on type of therapy performed and disease status. A sarcoma-specific instrument to cover the entire longitudinal care cycle using established PROMs would allow cross-referencing with patients with other

cancers as well as with the normal population, thereby greatly enhancing the establishment of quality standards and ultimately sustainable cost accounting in sarcoma care.

4. Sarcoma-Specific HRQoL-Instrument Based on Generic PROMs

The major challenge in defining a sarcoma-specific HRQoL instrument is the complexity of the disease itself and the respective multidisciplinary treatments at various timepoints, with greatly changing expectations from the patients' side over time depending on the disease status. In designing the sarcoma-specific HRQoL instrument, we addressed the following challenges: (1.) use of generic and well-established PROMs to allow benchmarking with other diseases as well as the normal population; (2.) to cover the main WDPS aspects such as physical and emotional health, resource utilization (which is specifically important in sarcoma patients with respect to rehabilitation), socioeconomic aspects, ownership, nutrition and health; (3.) longitudinal assessment from first time presentation until last follow-up or death; (4.) individualized assessment by assigning only PROMs relevant for treatment received as well as follow-up status (Table 2). The herein presented sarcoma-specific instrument includes a variety of PROMs for the baseline visit of the patient. It includes the disease specific physical (EQ-5D-5L) as well as the overall health (PROMIS Global-10; WHO-ECOG) questionnaires. For example, indicated pain level (disease specific) may not necessarily be caused by the soft tissue tumor at the forearm itself but by unrelated back pain (overall health related), which must be distinguished in the assessment. Emotional as well as socioeconomic factors are pivotal and are covered using specifically EQ-VAS, Brief Symptom Inventory (BSI-18) and the work ability index (WAI). As the biopsy is an invasive procedure, it has an important bearing on the patient and therefore must be addressed separately as well. We are currently developing a specific mesenchymal tumor biopsy PROM (MTBP) including 10 questions and this will be reported separately. Toronto Extremity Salvage scores (TESS) as well as Musculoskeletal Tumor Society (MSTS) scores were specifically designed for the extremities and are globally accepted and used. The Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) is in the process of establishing a specific PROM for visceral sarcoma surgeries and will be included here. With respect to radiation therapy, there are two PROMs introduced which evaluate patient-reported symptomatic toxicity (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) as well as the local effects by the patient (Local effects of radiation therapy). Medical oncologists often use the widely accepted HRQoL measure EORTC-QLQ30 specifically for randomized controlled trials. It provides a holistic overview and includes other well-established PROMs such as MDASI. Obviously, once the patient has completed the therapy and undergoes regular follow-up visits, different needs have to be addressed such as rehabilitation capacities. We are currently working on a synthesis of PROMs which bases on the presented PROMs herein, but with adapted weighting to address specifically emotional health, socio-economic factors, ownership and resource utilization such as rehabilitation capacities and potential.

This herein presented sarcoma-specific HRQoL instrument aims to address the specific needs and challenges of the sarcoma patient depending on disease status as well as type and time-point of therapy, or follow-up. This information will help to compare the different patients for a given time point or treatment type, but also to measure changes over time or effectiveness of new interventions for the individuum. Its design to assess the patient over the entire care cycle allows the personalized longitudinal assessment. Ideally, the patient receives the opportunity to monitor their own disease status and can objectively follow their own progress of disease development, which may enhance the transparent exchange with the physician.

Table 2. Sarcoma-specific HRQOL instrument: summary of established PROMs assigned at the different timepoints and for different treatment status.

Time Point of Assessment & Therapy Status	Type of PROM
Work-up at diagnosis Regular visits during therapy	WHO-ECOGPROMIS [43] EQ-VAS [44] EQ-5D-5L [45] BSI-18 [46] WAI [47]
Biopsy	Mesenchymal Tumor biopsy PROM * (MTBP)
Surgery	TESS (upper/lower extremity) [48] MSTS (upper/lower extremity) [49] Visceral (TARPSWG) *
Radiation Therapy	Local effects of therapy PRO-CTCAE
Chemotherapy	EORTC-QLQ-C30 [50,51]
Follow-up visits after completion of therapy	Combination of above

* in development; ROMS are assessed at each follow-up visit as suggested by Wilson et al. [52], Abbreviations: WHO-ECOG: World Health Organization–Eastern-Cooperative Oncology Group; PROMIS: Patient reported outcome measurement information system; EQ-VAS: EuroQuol Group visual analogue scale; BSI-18: Brief symptom inventory; TESS: Toronto extremity salvage score; MSTS: Musculoskeletal tumor society; TARPSWG: Transatlantic retroperitoneal sarcoma working group; PRO-CTCAE: Patient-reported outcomes Common terminology Criteria for adverse events; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer—Core quality of life questionnaire.

5. Interoperable Digital Platform: Data Assessment and Analysis

The large volume of data produced in healthcare overall and also proposed herein to be assessed with the PROMs presents a major obstacle and threat to routine practice [53]. As a consequence, there is a seemingly unsurmountable threshold to introduce a set of PROMs into routine medical practice, being used at best under standardized conditions such as in randomized controlled trials, and to assess these data several times for the same patients over time. Data management is a tremendous challenge, but the advent of digital transformation may lead to the disruption of current practices and will revolutionize healthcare in the decade to come. There is still an ongoing debate on whether PROMs are being assessed on paper versus electronically; although, it has been shown that the latter far exceeds the potential disadvantages, and manual analysis of paper PROMs is not affordable anymore given the current overall labor shortage [9,54–56].

Given the complexity of sarcoma as an extremely heterogenous disease with complex transdisciplinary treatment interactions, there is ideally an interoperable digital platform which integrates all diagnostic and treatment relevant aspects of sarcoma care (Figure 1). As such, the data generated from PROMs assessment can be analyzed in the context of all clinically relevant parameters such as disease status, exact pathological diagnosis, anatomic location as well as treatment decisions at the weekly multidisciplinary tumor board. Further, it also allows automatically tailoring (and therefore decreasing the time spent to fill out a questionnaire) the specific questions of a given PROM to the patient's specific situation. For example, if the patient on the EQ-5D-5L has "no emotional constraints", then it will not be necessary to fill out also the BSI-18 to assess the specifics of emotional constraints. As such, by individualizing the questionnaire to the patient's need, it will be more attractive for the patient to spend more or less time to answer all the questions. Another advantage includes the generation of automatic alerts for the patient by the interoperable digital platform. Having integrated, for example, the date of surgery (or any other treatment aspect), the system can send an alert to the patient at predefined intervals to assess the respective PROM over time. The interoperable digital platform is able, based on the patients' answers, to prepare or generate individualized reports for the regular clinical outpatient or telemedicine visits. We foresee that such an interoperable digital platform is able to integrate all patient

related information (i.e., clinical, molecular, as well as economic parameters) as well as all stakeholders of patient care and to generate IELAS-RWTD/E [57,58]. Therefore, the implementation of PROMs has to be viewed as an integral part of patient care to generate robust data to optimize treatment decisions for the patient, but also to define quality of care, which ultimately is the prerequisite for value-based healthcare, paving the way to establishing a sustainable healthcare system. In a next step, together with all physician-based data of clinical metrics, such an interoperable digital platform allows the holistic analysis of all data dimension parameters, thereby allowing the generation of IELAS-RWTD evidence, which can be instantly analyzed and visualized on a protected interactive website. Ultimately, through machine learning algorithms, such a set-up allows predictive and prescriptive outcome analytics, which is the prerequisite for the upcoming precision medicine era (Figure 1).

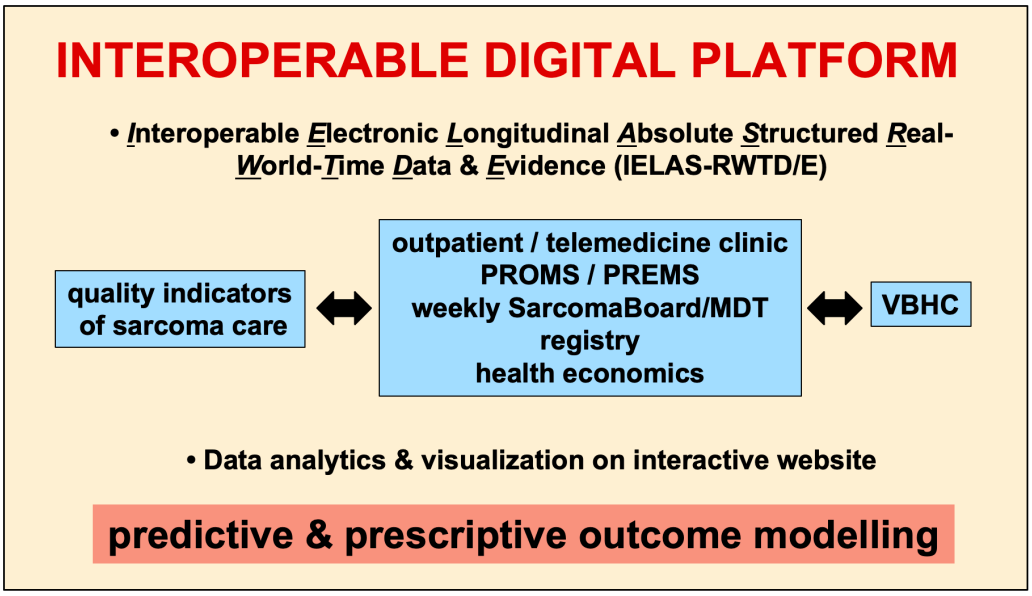


Figure 1. The interoperable digital platform integrates all available data of work-up, therapy and follow-up on the patient, based on quality indicators including the sarcoma-specific HRQOL instrument. It is the node of communication and exchange between patients and care providers of any level. It assesses and integrates routine, structured data in real-time of absolute and prospective patient numbers over time (IELAS-RWTD/E), which ultimately enables VBHC by attributing cost tags. The interoperable digital platform visualizes the descriptive data analytics on an interactive website, and ultimately allows predictive and prescriptive outcome modeling. PREMS: patient reported experience measures; MDT: multidisciplinary tumor board/Sarcoma Board.

6. Discussion

The patient's perception on quality of care and treatment effectiveness are meanwhile established predictors of outcome. The introduction of a sarcoma-specific HRQoL instrument therefore is indispensable, specifically for a complex disease requiring the interplay of multiple disciplines. The literature suggests that novel questionnaires be designed to better reflect the heterogeneity of sarcoma as a disease as well as its treatment because one single PROM does not cover all required needs.

Herein, an alternative approach to define a sarcoma-specific HRQoL instrument is presented using a sum of established generic PROMs which are assessed depending on the respective status of the longitudinal care cycle of the patient [8]. This approach allows comparison and benchmarking with other diseases and, importantly, with the normal population [59]. This is in contrast to the suggestion by Den Hollander et al. who develop an entirely novel sarcoma-specific questionnaire [37]. It will be very interesting to see which parameters this group will ultimately include in their questionnaire, and how it

will compare to the approach presented herein. Obviously, the implementation of this sarcoma-specific HRQoL faces some challenges. Both physicians and patients have to be trained for a novel ecosystem of data handling and assessment by on-site education during their outpatient visit. Similar to an iPhone use, the ease of self-explanatory handling of the program to enter the data does not really present a hurdle. Each patient (or telemedicine visit via a link) receives an iPad to enter the data and, if needed, receives instant support for program handling. Data themselves are stored and protected regarding ethical and legal issues, and only deanonymized data are used for exchange in the context of national and international comparisons, which is very important to scale globally and is also shown by others [60]. To achieve this, we have created the Sarcoma Academy to foster quality in sarcoma care by organizing monthly webinars (www.sarcoma.academy; accessed on 1 March 2023). The patient and their treating physician have access to their own data and represent the main contributors and also the main stakeholders. Once predictive modeling is realized, the results shall benefit the patient and his treatment.

In designing a sarcoma-specific HRQoL instrument, a holistic inclusion of all possible health dimensions is preferred. Ideally, it includes the entire longitudinal care cycle of routine care with the data dimensions as defined by WPHS, structured data which are instantly available for both patients and care providers, to ultimately achieve IELAS-RWTD/E analytics and precision outcome modeling [61]. Obviously, such a comprehensive amount of data cannot be handled with common approaches; a new ecosystem of data management is therefore required in healthcare. With the exciting opportunities created by digital transformation, the definition of different types of data will become increasingly important in the future. The interoperable digital platform is designed as a node for the integration of data generated from both the care providers, as well as the patients, to internationally exchange and scale to create evidence through analytics and, ultimately, knowledge. For this purpose, the interoperable digital platform presented herein allows *E*lectronic capturing of data which are *L*ongitudinal and prospective if they cover the entire care cycle, and *A*bsolute if they are all consecutive and not just a selection of patients is included. The assessment has to be designed so that all data will be *S*tructured instead of unstructured. *R*eal-*W*orld data refers to routine data assessment, and real-*T*ime refers to the instant availability of these *D*ata. The interoperable digital platform allows an automated analysis of these data, thereby creating *E*vidence. As such, it is designed to include all data dimensions as represented by IELAS-RWTD/E. Integrating all data dimensions of quality indicators of care from both the patients' and physicians' view sets the stage for an integral evidence analytics. Additionally, this in turn is the prerequisite for predictive modeling to individualize therapy in the future, thereby realizing precision care. Integrating the sarcoma-specific HRQoL instrument into an interoperable digital platform allows the analysis of each single parameter of the HRQoL instrument with clinical metrics such as specific type of diagnosis, anatomic localization and therapy aspects. It facilitates the coordinated exchange of information between patients and care providers to be transparently shared by both. The interoperable digital platform therefore provides not only information and knowledge for the physician but also for the patient. Such an interoperable digital platform can also be designed to be an integral part of an institutional electronic health record (EHR) system. It is foreseen that an EHR will be composed of many other disease specific interoperable digital platforms, as presented herein for sarcoma. In its entirety, such EHR is then able to not only provide information on the entirety of all medical care provided over the care cycle, but it also assesses the treatment effectiveness both from the physicians' and patients' perspectives with transparent real-time analytics. Further, attributing now a cost tag to each quantifiable structured data unit, the individual costs of treatment for a given disease can be determined longitudinally. This in turn allows the definition of shared value (which equals quality and outcome over costs of the entire longitudinal care cycle), as Porter et al. defined the concept of value-based healthcare [3,5].

In summary, a holistic approach in designing a sarcoma-specific HRQoL instrument includes the sum of multiple generic PROMs tailored to the specific steps of the entire

care cycle. While this, on the one hand, allows for comparison and benchmarking with other diseases as well as the normal population, the large data volume cannot be handled with standard approaches. A novel interoperable digital platform not only integrates both patient- and physician-based quality indicators but also allows IELAS-RWTD/E analytics, paving the way to precision medicine and value-based healthcare [62]. The holistic assessment of the health of sarcoma patients and survivors will contribute to tailoring care to patients' needs and, ultimately, improve health. Further, such an approach will be indispensable to associate treatment effectiveness with healthcare cost control, which is the prerequisite for a sustainable healthcare system.

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Article

Enhancing Healthcare for Sarcoma Patients: Lessons from a Diagnostic Pathway Efficiency Analysis

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Simple Summary: The total interval of the diagnostic pathway, which consists of the patient interval and the diagnostic interval, describes the time between the first symptom and the final diagnosis. Thus, it could be used as an efficiency marker of a healthcare system. The efficiency of the most expensive health care system in Europe, Switzerland, for bone and soft tissue sarcomas, as well as their benign representatives, has not yet been described. Sarcomas are rare and have a worse outcome than more common tumors. It is assumed that a short total interval leads to a better outcome. Finding out where to start in the total interval to achieve the greatest potential for optimization and to elicit healthcare efficiency is the goal of this study. We have done this by dividing the total interval into its components and looking at their length, as well as potential influencing factors. This revealed that the patient and secondary care interval represent bottlenecks with age, grade, localization, and size being influencing factors of the length of intervals and probability of sarcoma.

Abstract: Sarcomas, rare and with lower survival rates than common tumors, offer insights into healthcare efficiency via the analysis of the total interval of the diagnostic pathway, combining the patient interval (time between the first symptom and visit with a physician) and diagnostic interval (time between first physician visit and histological diagnosis). Switzerland's healthcare system, Europe's costliest, lacks research on treating rare conditions, like mesenchymal tumors. This study examines the total interval of the diagnostic pathway for optimization strategies. Analyzing a dataset of 1028 patients presented from 2018 to 2021 to the Swiss Sarcoma Board (MDT/SB-SSN), this retrospective analysis delves into bone sarcoma (BS), soft-tissue sarcoma (STS), and their benign counterparts. Demographic and treatment data were extracted from medical records. The patient interval accounted for the largest proportion of the total interval and secondary care interval for the largest proportion of the diagnostic interval. Age, grade, and localization could be elicited as influencing factors of the length of different components of the total interval. An increasing age and tumor size, as well as the axial localization, could be elicited as factors increasing the probability of sarcoma. The patient and secondary care interval (SCI) offer the greatest potential for optimization, with SCI being the bottleneck of the diagnostic interval. New organizational structures for care work-ups are needed, such as integrated practice units (IPU) as integral part of value-based healthcare (VBHC).

Keywords: sarcoma; benign bone tumor; benign soft-tissue tumor; total interval of diagnostic pathway; diagnostic interval; referral patterns; healthcare system; quality management system; MDT/SB-SSN; multidisciplinary Team/Sarcoma Board of the Swiss Sarcoma Network; RWTD/E; real-world-time data evidence

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1. Introduction

Several studies have examined the diagnostic interval of sarcomas, yet none have specifically characterized this interval within Switzerland, the European country with the highest healthcare costs [1]. This research gap underscores a critical need to comprehensively understand the diagnostic pathway for sarcoma patients in a healthcare system characterized by high costs and a unique geographical and cultural landscape.

Sarcomas are among the rare diseases with an incidence of 4.43 per 100,000 person-years for soft-tissue sarcoma (STS) and 0.91 per 100,000 person-years for bone sarcoma (BS) [2,3]. Apart from their mesenchymal origin, sarcomas exhibit remarkable heterogeneity, with more than 80 histological subgroups [4] and diverse ages at disease onset, sites of manifestation, and tumor progression aggressiveness. This complexity combined with the rather limited research on rare cancers leads to an incomplete understanding of sarcoma biology, diagnostic challenges, and less effective therapies and guidelines. Consequently, these factors contribute to the observed lower survival rates compared to more common cancer entities [5].

This situation underscores a relevant concern, as the lack of comprehensive insights presents a significant obstacle for implementing both national and international measures. To comprehend potential variations in the treatment of sarcoma patients within the Swiss healthcare framework, it becomes essential to scrutinize the structure of the healthcare system itself. Switzerland's healthcare system is upheld through a blend of public and private funding. Access to healthcare services necessitates mandatory health insurance for citizens, who are also liable for a significant portion of the healthcare expenses. The Swiss healthcare system is characterized by a high quality of care, great patient satisfaction, extensive patient autonomy in choosing medical service providers, and a wide range of medical service providers [1]. Consequently, patients do not necessarily have to seek a primary care physician first, but can go directly to a secondary care specialist, depending on their insurance model and preferences. The referral patterns of sarcoma patients in Switzerland remain uncharted. Hence, it remains uncertain if the substantial healthcare expenses also lead to a positive outcome in the shape of short diagnostic intervals for uncommon conditions, like mesenchymal tumors. This matter holds significance not just for patients but also for governmental bodies, with potential cost-saving implications.

The diagnostic interval (the time between the first physician visit and a histologically confirmed diagnosis) together with the patient interval (the time between the date of the first symptom and first consultation with a physician) collectively compose the total interval of the diagnostic pathway (the time from the first mesenchymal tumor-related symptom to the histological confirmation of the diagnosis) [6–8]. The diagnostic interval describes the referrals from primary care via secondary care to the tertiary care sector. Tertiary care involves specialized medical facilities, such as sarcoma centers for mesenchymal tumors. To counteract the complex nature of mesenchymal tumors, which leads to diagnostic challenges and suboptimal treatment courses and outcomes, the centralization or regionalization of diagnosis and treatment of sarcoma patients is advocated [9–12]. However, the feasibility of such centralization or regionalization depends on the availability of the necessary logistical capacity, including the presence of sarcoma specialists. Otherwise, there could be a backlog of patients in the tertiary care sector if referrals from the secondary care sector exceed its capacity.

Early diagnosis is essential for the patient outcome in many cancer entities [13]. This is also true for sarcoma patients, for whom early diagnosis has a positive impact on survival [14]. To ensure a timely diagnosis, it is crucial for the total interval of the diagnostic pathway to be minimized.

To optimally shorten the total interval of the diagnostic pathway, it is imperative to gain a comprehensive understanding of how primary, secondary, and tertiary care intervals are interrelated, what the referral structures are, and therefore, what type of physicians (hospital-based vs. practice-based) are involved in the diagnostic pathway for the diagnosis of a mesenchymal tumor. This aspect remains unexplored to date.

To address which components of the total interval of the diagnostic pathway could be improved and to identify the appropriate targets for optimization efforts, aiming to minimize the duration between the initial symptom onset and diagnosis for patients with mesenchymal tumors, as well as to determine which patients are more likely to have a malignant mesenchymal tumor, this study investigates the various components of the total interval of the diagnostic pathway. These include an evaluation of their length, potential factors influencing the length of intervals, as well as the likelihood of a diagnoses, and an analysis of the involvement of different physicians (hospital-based vs. practice-based).

2. Materials and Methods

2.1. Study Design

This study represents a retrospective analysis of a prospectively collected dataset (based on a prospectively collected, real-world-time datawarehouse/-lake; Sarconnector® (PH&BF, Zurich, Switzerland) that included bone sarcoma (BS) and soft-tissue sarcoma (STS) patients, as well as patients diagnosed with a benign bone tumor or benign soft-tissue tumor, at a sarcoma center (MDT/SB-SSN) with its associated network, including seven secondary and tertiary care medical institutions in Switzerland, which constitutes the Swiss Sarcoma Network (SSN).

2.2. Study Objective

The main objective of this study was to analyze the diagnostic pathway from the first symptom to the histologically confirmed diagnosis in terms of physicians involved, length of the total interval, patient interval, and diagnostic interval, consisting of primary, secondary, and tertiary care intervals, as well as possible influencing factors, such as age, gender, grade, and tumor localization, for the four subgroups, BS, STS, benign bone tumors, and benign soft-tissue tumors. The aim was to use these analyses to describe in which part of the total interval of the diagnostic pathway and for which patients the greatest potential for optimization exists.

2.3. Selection Criteria

All consecutive patients presented at the weekly MDT/SB-SSN with a diagnosis of STS, BS, a benign soft-tissue tumor, or a benign bone tumor from 1 January 2018, to 31 December 2021, were included in this study. The diagnoses, which were based on the WHO classification, were divided into benign and malignant, with intermediate tumors categorized as malignant.

Patients were excluded if records were incomplete. Records were considered incomplete if, for example, no conclusion could be drawn from the available medical records as to the date of the primary and secondary care physician visit (see Figure 1). Since in the Swiss healthcare system, a visit to a primary care physician is not obligatory in every case before a visit to a specialist, patients whose data regarding the primary care interval were not complete were included. This was done because it was not possible to distinguish between (1) the absence of physician-directed care and (2) no documentation of a physician visit in the primary care interval. Named patients were listed as not available (NA) in Figures 3 and 4 under the primary care interval. The same reasoning was used for missing data based on the secondary care interval. These patients were also listed as NA in Figures 3 and 4 under secondary care interval. If it was clear from the medical records that a primary or secondary care physician was not involved (e.g., because it was an incidental finding in the context of other examinations in the secondary care interval or because the referral letter from the general practitioner described it as such), the patients were listed in Figures 3 and 4 under the "Absence of physician-directed care".

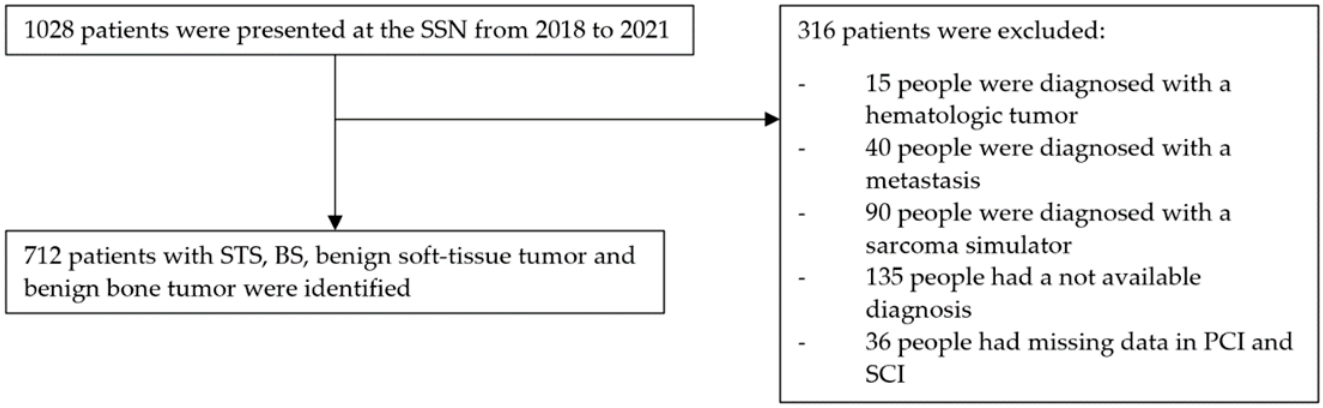


Figure 1. Flow chart of the patient inclusion progress.

2.4. Data Collection

Through a RWTD/E warehouse (Adjumed, Zurich, Switzerland) where the demographic and treatment-specific information of the patients from seven Swiss medical institutions are being collected, 1028 patients were identified. Data on age, sex, the WHO diagnosis, and anatomic region were also obtained from this warehouse. Information on the date of the first symptom that could be attributed to the benign or malignant mesenchymal tumor, the date of the first physician visit, the date of referral from primary to secondary care, the first visit to a secondary care physician, the referral to the sarcoma center in the tertiary care interval, and the date of a histologically confirmed diagnosis were extracted from the medical records. In addition, the medical records were used to determine whether the physician was a practice-based or hospital-based physician in primary and secondary care. Primary care physicians included general practitioners, gynecologists, ophthalmologists, pediatricians, and emergency room physicians. Secondary care physicians included all physicians who were not general practitioners. In PCI and SCI, both practice-based and hospital-based (e.g., physicians in an emergency department) physicians were included. The endpoint in the tertiary care interval was the sarcoma center, which was hospital-based in all cases in the included study population.

2.5. Definition of the Intervals

The definitions of the intervals were adopted from Soomers et al. [6] who adapted the standardized definition proposed by Weller et al. [7] and Olesen et al. [8]. The patient interval (PI) was defined as the time between the first noticed mesenchymal tumor-related symptom and first consultation with a medical doctor. The primary care interval (PCI) was defined as the time between the first physician visit and first secondary referral to a physician of the secondary care. Physicians were divided into practice-based and hospital-based. The secondary care interval (SCI) was defined as the time between the first secondary referral and referral to a specialist sarcoma center. Physicians were divided into practice-based and hospital-based. The timespan from referral to a specialist sarcoma center and the date of the histological diagnosis was defined as the tertiary care interval (TCI). Since the diagnosis of a benign or malignant bone or soft-tissue tumor can also take place outside a sarcoma center, the TCI values were sometimes negative. PCI, SCI, and TCI were summarized as the diagnostic interval (DI). The PI and DI resulted in the total interval of the diagnostic pathway (TIDP) (see Figure 2).

2.6. Statistical Analysis

Continuous variables are presented as the median (1st quartile, 3rd quartile), while categorical variables are presented as a number (percentage). Due to the low number of missing data, no missing data imputation was performed. To study the association between clinical variables (age, gender, histological grade, tumor localization, and size) and

a bone sarcoma versus soft-tissue sarcoma diagnosis or a benign versus sarcoma diagnosis, logistic regression models were created. To assess the association between clinical variables and the described intervals, linear regression was employed. The normal distribution of variables was assessed visually using histograms or QQ-plots. When continuous data were normally distributed, a t-test was performed, while a Mann–Whitney-U test was performed for non-normally distributed data. Differences between categorical variables were tested using a Chi-square test or using Fisher's exact test (if the expected value was below 5). A p-value < 0.05 was considered statistically significant. All analyses were conducted using R (version 4.3.1).

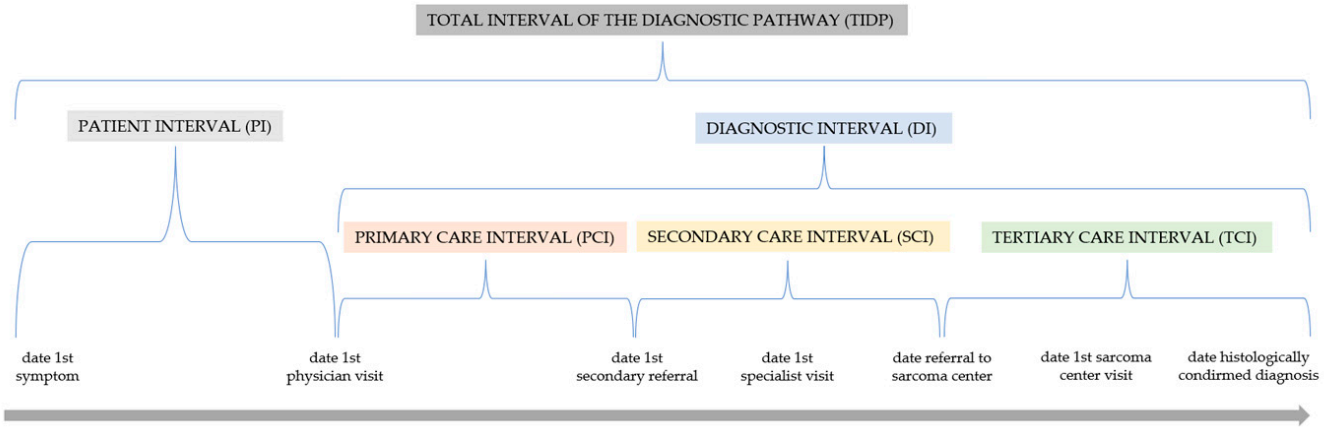


Figure 2. Time intervals from first symptom to the visit to a sarcoma center. Adopted from Soomers et al. 2020 [6]. Patient interval: time between date of first symptom and first visit to a physician. Primary care interval: time between first physician visit and first secondary referral to a specialized physician. Secondary care interval: time between first secondary referral and referral to a specialist sarcoma center. Tertiary care interval: time between referral to a specialist sarcoma center and the date of histological diagnosis. Diagnostic interval: time between first physician visit and histological diagnosis. Total interval of the diagnostic pathway (TIDP): time from first symptom to histological diagnosis.

3. Results

3.1. Diagnosis Probability Based on Patient and Tumor Traits (See Table 1)

Of the factors studied, age, localization, and size influenced the likelihood of bone sarcoma (BS) versus soft-tissue sarcoma (STS) and the likelihood of a benign versus malignant mesenchymal tumor. Most of the included patients (n = 356) were diagnosed with STS, especially deep STS (n = 296). The median age of the studied population was 56.0 years. With a 1-year increase in age, the likelihood of an STS compared with a BS increased by 3%, which was represented by the lower median age of patients with BS (44.0 years) and benign bone tumors (34.0 years). Similarly, the probability of a diagnosis of a malignant compared with a benign bone or soft-tissue tumor increased by 2% with a 1-year increase in age. The overall gender distribution was balanced (48.9% female), with more male patients (63.4%) having BS. However, gender did not affect the likelihood of being diagnosed with BS compared with STS or of being diagnosed with a malignant compared with a benign mesenchymal tumor. Among the sarcomas, grade G3 was the most common. Tumors were more frequently appendicular in location, although the distribution was more balanced in STS. An axial location increased the likelihood of an STS compared with a BS and of a malignant bone or soft-tissue tumor compared with a benign one. Malignant tumors tended to be larger than benign ones. The larger a tumor was, the more likely it was to be diagnosed as STS. The likelihood of a sarcoma compared with a benign tumor also increased with an increasing tumor size. In most subgroups, the number of cases decreased with an increasing tumor size.

Table 1. Diagnosis probability based on patient and tumor traits.

	OVERALL	BONE SARCOMA	LIKELIHOOD OF BONE SARCOMA VS. SOFT-TISSUE SARCOMA [a]			SOFT-TISSUE SARCOMA			LIKELIHOOD OF SARCOMA VS. BENIGN TUMOR [b]			BENIGN BONE TUMOR	BENIGN SOFT-TISSUE TUMOR		
			OR	95% CI	*p*-Value	Deep and Superficial	Deep	Superficial	OR	95% CI	*p*-Value		Deep and Superficial	Deep	Superficial
	n = 712	**n = 82**				**n = 356**	**n = 296**	**n = 60**				**n = 61**	**n = 213**	**n = 172**	**n = 41**
Age, years	56.0 (40.0, 68.0)	44.0 (19.0, 65.0)	1.03	1.02, 1.04	**<0.001**	60.0 (46.0, 72.0)	60.0 (46.0, 72.0)	61.5 (42.3, 74.3)	1.02	1.01, 1.02	**<0.001**	34.0 (23.0, 45.0)	55.0 (44.0, 63.0)	56.0 (44.0, 65.0)	54.0 (44.0, 61.0)
Female, (%)	348 (48.9%)	30 (36.6%)	1.09	0.82, 1.47	0.5	178 (50.0%)	145 (49.0%)	33 (55.0%)	0.87	0.64, 1.17	0.3	30 (49.2%)	110 (51.6%)	90 (52.3%)	20 (48.8%)
Grade												not applicable	not applicable	not applicable	not applicable
G1, (%)	74 (16.9%)	7 (8.5%)				67 (18.8%)	52 (17.6%)	15 (25.0%)							
G2, (%)	54 (12.3%)	5 (6.1%)	1.17	0.37, 4.07	0.8	49 (13.8%)	41 (13.9%)	8 (13.3%)							
G3, (%)	126 (28.8%)	26 (31.7%)	0.46	0.18, 1.03	0.07	100 (28.1%)	85 (28.7%)	15 (25.0%)							
NA	184 (42.0%)	44 (53.7%)				140 (39.3%)	118 (39.8%)	22 (36.7%)							
Region			2.91	2.11, 4.04	**<0.001**				2.34	1.67, 3.30	**<0.001**				
appendicular	469 (65.9%)	65 (79.3%)				193 (54.2%)	165 (55.7%)	28 (46.7%)				50 (82.0%)	161 (75.6%)	131 (76.2%)	30 (73.2%)
axial	243 (34.1%)	17 (20.7%)				163 (45.8%)	131 (44.3%)	32 (53.3%)				11 (18.0%)	52 (24.4%)	41 (23.8%)	11 (26.8%)
Size, mm	60.0 (34.3, 102.0)	60.0 (39.5, 85.0)	1.01	1.00, 1.01	**<0.001**	70.0 (32.0, 124.0)	86.0 (45.0, 130.0)	28.0 (20.0, 44.0)	1.00	1.00, 1.01	**0.001**	31.5 (11.5, 50.5)	60.0 (38.3, 97.3)	61.0 (39.0, 100.5)	54.0 (35.5, 79.5)
0–50 mm, n	247 (34.7%)	25 (30.5%)				106 (29.8%)	70 (23.6%)	36 (60.0%)				33 (54.1%)	83 (39.0%)	65 (37.8%)	18 (43.9%)
51–100 mm, n	179 (25.1%)	30 (36.6%)				67 (18.8%)	59 (19.9%)	8 (13.3%)				10 (16.4%)	72 (33.8%)	55 (32.0%)	17 (41.5%)

Table 1. *Cont.*

	OVERALL	BONE SARCOMA	LIKELIHOOD OF BONE SARCOMA VS. SOFT-TISSUE SARCOMA [a]			SOFT-TISSUE SARCOMA			LIKELIHOOD OF SARCOMA VS. BENIGN TUMOR [b]			BENIGN BONE TUMOR	BENIGN SOFT-TISSUE TUMOR		
			OR	95% CI	*p*-Value	Deep and Superficial	Deep	Superficial	OR	95% CI	*p*-Value		Deep and Superficial	Deep	Superficial
	n = 712	**n = 82**				**n = 356**	**n = 296**	**n = 60**				**n = 61**	**n = 213**	**n = 172**	**n = 41**
101–150 mm, n	91 (12.8%)	11 (13.4%)				50 (14.0%)	50 (16.9%)	0 (0%)				1 (1.6%)	29 (13.6%)	27 (15.7%)	2 (4.9%)
>150 mm, n	57 (8.0%)	1 (1.2%)				42 (11.8%)	41 (13.9%)	1 (1.7%)				0 (0%)	14 (6.6%)	13 (7.5%)	1 (2.4%)
NA	138 (19.4%)	15 (18.3%)				91 (25.6%)	76 (25.7%)	15 (25.0%)				17 (27.9%)	15 (7.0%)	12 (7.0%)	3 (7.3%)

[a]: The likelihood of STS (deep and superficial) vs. BS was determined. STS represented the reference. [b]: The likelihood of sarcoma (STS and BS) vs. benign mesenchymal tumors (benign bone and soft-tissue tumors) was determined. Sarcoma represented the reference.

3.2. Patient Interval (PI)

3.2.1. Length (See Table 2)

The patient interval (median, overall 90.0 weeks) was longer than the diagnostic interval (median, overall 46.0 weeks) in all subgroups. The patient interval was significantly shorter for deep STS (median, 8.3 weeks) than for superficial STS (median, 20.7 weeks) ($p = 0.01$). No such difference was observed between BS and STS. No differences in PI length were detected between benign bone and soft-tissue tumors or between superficial and deep soft-tissue tumors.

3.2.2. Influencing Parameters (See Table 3)

Of the potential influencing parameters investigated, age and localization, each showed a significant effect on the PI length in the benign bone and soft-tissue tumor subgroup, as well as in the overall population. An increasing age correlated significantly with a longer PI in the overall population and in soft-tissue tumors ($p = 0.047$ and $p = 0.04$, respectively). The PI was longer in benign bone tumors for an axial localization rather than for a appendicular localization ($p = 0.002$).

3.3. Diagnostic Interval (DI), Primary Care Interval (PCI)

3.3.1. Length (See Table 2)

The primary care interval was the shortest of the diagnostic intervals in all subgroups (median, overall 4.0 weeks). The subgroups of sarcomas showed comparable lengths of PCI, with BS (median, 0.6 weeks) having the median longest and superficial STS (median, 0.0 weeks) have the shortest, without statistical significance. Benign mesenchymal tumors also showed comparable lengths of the PCI, with bone tumors (median, 0.8 weeks) having the longest median and superficial soft-tissue tumors (median, 0.3 weeks) having the shortest, again without statistical significance. PCIs from benign mesenchymal tumors were slightly longer on average than comparable subsets of malignant mesenchymal tumors.

3.3.2. Influencing Parameters (See Table 3)

Of the potential influencing parameters investigated, only localization in the STS subgroup showed a significant effect on the PCI length. The axial tumor localization showed a significantly shorter PCI for STS compared to an appendicular localization ($p = 0.03$).

3.4. Diagnostic Interval (DI), Secondary Care Interval (SCI)

3.4.1. Length (See Table 2)

The secondary care interval accounted for the largest proportion of the diagnostic interval for sarcomas (median, overall 26.0 weeks). BS (median, 2.2 weeks) had significantly shorter SCIs than STS (median, 4.3 weeks) ($p = 0.005$); again, the SCI of deep STS (median, 3.9 weeks) was significantly shorter than that of superficial STS (median, 8.1 weeks) ($p = 0.01$). Among benign mesenchymal tumors, SCI represented the largest proportion of the DI for the benign soft-tissue tumor group (although this is likely due to deep soft-tissue tumors). For superficial soft-tissue tumors, the lengths of the SCI and TCI were comparable.

3.4.2. Influencing Parameters (See Table 3)

None of the potential influencing parameters investigated had a significant influence on the SCI of any subgroup.

Table 2. Length of patient, diagnostic, primary care, secondary care, tertiary care, and total interval in weeks.

	OVERALL	BONE SARCOMA		SOFT-TISSUE SARCOMA						BENIGN BONE TUMOR	BENIGN SOFT-TISSUE TUMOR				
				Deep and Superficial	Deep		Superficial				Deep and Superficial	Deep		Superficial	
	n = 712	n = 82	*p*-Value [c]	n = 356	n = 296	*p*-Value [d]	n = 60	n = 61	*p*-Value [e]	n = 213	n = 172	*p*-Value [f]	n = 41		
Patient Interval, weeks	90.0 (22.0, 284.0)	7.8 (2.7, 27.5)	0.46	8.8 (2.1, 29.0)	8.3 (2.0, 24.4)	**0.01**	20.7 (4.2, 130.6)	19.1 (4.3, 52.1)	0.17	21.6 (6.4, 109.6)	19.8 (6.3, 75.1)	0.22	29.9 (9.0, 176.4)		
Diagnostic Interval, weeks	46.0 (25.5, 95.5)	7.6 (3.1, 14.2)	0.89	6.7 (3.7, 13.3)	6.9 (3.9, 13.7)	0.22	5.7 (3.6, 9.3)	19.8 (6.8, 79.7)	**0.005**	6.0 (3.6, 13.4)	6.0 (3.6, 14.6)	0.35	5.6 (3.6, 9.5)		
Primary Care Interval, weeks	4.0 (0.0, 18.5)	0.6 (0.1, 6.5)	0.14	0.4 (0.0, 1.4)	0.4 (0.0, 1.3)	0.31	0.0 (0.0, 1.4)	0.8 (0.0, 44.9)	0.30	0.7 (0.0, 3.1)	0.7 (0.0, 4.4)	0.15	0.3 (0.0, 1.0)		
Secondary Care Interval, weeks	26.0 (12.0, 57.0)	2.2 (0.9, 6.6)	**0.005**	4.3 (2.1, 9.1)	3.9 (1.9, 8.1)	**0.01**	8.1 (4.9, 10.2)	2.6 (1.0, 10.7)	0.47	3.5 (1.6, 7.5)	3.9 (1.7, 10.0)	0.14	2.6 (1.5, 3.8)		
Tertiary Care Interval, weeks	14.0 (5.0, 26.3)	2.1 (1.0, 3.7)	**0.006**	1.3 (-0.6, 3.4)	1.6 (-0.2, 3.6)	**0.01**	0.9 (-3.3, 1.9)	3.1 (2.0, 8.1)	0.14	2.6 (1.8, 4.1)	2.6 (1.7, 4.0)	0.36	2.7 (1.9, 5.8)		
Total Interval, weeks	213.0 (84.0, 762.2)	22.8 (11.9, 56.7)	0.82	23.3 (10.4, 59.4)	20.9 (10.4, 55.3)	0.07	34.8 (12.3, 148.0)	100.5 (48.1, 206.6)	0.22	48.2 (17.7, 193.3)	43.0 (14.7, 150.6)	**0.04**	138.1 (29.1, 304.4)		

[c]: The *p*-value was calculated based on a Wilcoxon rank sum test with a continuity correction between STS (deep and superficial) and BS. [d]: The *p*-value was calculated based on a Wilcoxon rank sum test with a continuity correction between deep STS and superficial STS. [e]: The *p*-value was calculated based on a Wilcoxon rank sum test with a continuity correction between benign soft-tissue tumors (deep and superficial) and benign bone tumors. [f]: The *p*-value was calculated based on a Wilcoxon rank sum test with a continuity correction between deep benign soft-tissue tumors and superficial benign soft-tissue tumors.

Table 3. Influence of age, gender, grade, and localization on intervals.

	PI [g]			DI [h]									TI [l]		
				PCI [i]			SCI [j]			TCI [k]					
	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value
Overall (n = 712)															
Age	7.07	0.08, 14.05	**0.047**	−0.91	−3.36, 1.54	0.46	0.71	−2.31, 3.73	0.65	−0.28	−1.77, 1.21	0.71	6.79	−1.03, 14.61	0.09
Gender male	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference

Table 3. *Cont.*

	PI [g]			DI [h]									TI [l]		
				PCI [i]			SCI [j]			TCI [k]					
	Beta	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**
female	86.53	−185.00, 358.05	0.53	−45.41	−142.57, 51.74	0.36	46.20	−68.73, 161.13	0.43	−11.31	−67.84 45.22	0.69	168.90	−132.39, 470.11	0.27
Grade G1	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
G2	−392.10	−1039.97, 255.67	0.24	−17.17	−258.50, 224.15	0.89	17.17	−261.18, 295.52	0.90	−28.42	−149.59, 92.76	0.65	−498.92	−1140.89, 143.05	0.13
G3	−384.70	−911.59, 142.23	0.15	−77.84	−261.66, 105.98	0.41	−18.07	−240.93, 204.78	0.87	116.81	17.25, 216.36	**0.02**	−470.85	−994.55, 52.85	0.08
Localization appendicular	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
axial (head, neck, trunk)	−177.51	−463.87, 108.86	0.224	−46.46	−147.89, 54.97	0.37	−21.42	−141.14, 98.29	0.73	−84.47	−143.12, −25.82	0.41	−264.11	−583.97, 55.75	0.11
Bone sarcoma (n = 82)															
Age	5.61	−13.44, 24.66	0.56	−1.48	−10.59, 7.63	0.75	−0.14	−0.95, 0.68	0.74	−0.13	−0.39, 0.13	0.31	7.55	−12.71, 27.80	0.46
Gender male	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
female	88.12	−830.06, 1006.30	0.85	−53.64	−494.73, 387.45	0.81	2.72	−36.48, 41.93	0.89	−8.45	−21.05, 4.14	0.19	−42.57	−1017.19, 932.04	0.93
Grade G1	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
G2	−37.05	−2366.05, 2291.95	0.98	−107.67	−1167.15, 951.82	0.84	−37.95	−129.28, 53.37	0.41	−12.80	−42.96, 17.36	0.40	−122.40	−2409.75, 2164.95	0.92
G3	48.49	−1679.16, 1776.14	0.96	−90.88	−724.04, 542.28	0.77	−21.64	−82.91, 39.62	0.48	−16.05	−38.39, 6.30	0.16	−15.80	−1815.48, 1783.88	0.99
Localization appendicular	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
axial (head, neck, trunk)	−187.90	−1424.36, 1048.56	0.76	472.71	−88.70, 1034.13	0.10	−7.66	−51.97, 36.65	0.73	−2.06	−16.31, 12.19	0.77	−45.29	−1259.59, 1169.00	0.94
Soft-tissue sarcoma (n = 356)															

Table 3. *Cont.*

	PI [g]			DI [h]									TI [l]		
				PCI [i]			SCI [j]			TCI [k]					
	Beta	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**
Age	4.67	−6.17, 15.51	0.40	0.55	−1.51, 2.60	0.60	0.78	−3.91, 5.47	0.74	1.11	−1.71, 3.93	0.44	3.90	−6.60, 14.39	0.47
Gender male	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
female	−42.41	−427.41, 342.60	0.83	−24.30	−101.26, 52.67	0.53	−22.46	−189.49, 144.57	0.79	−16.93	−115.72, 81.87	0.74	−18.80	−391.39, 353.80	0.92
Grade G1	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
G2	−430.19	−1119.79, 259.41	0.22	−5.59	−157.29, 146.12	0.45	24.29	−291.39, 339.96	0.88	−28.36	−192.80, 136.07	0.74	−525.67	−1148.01, 96.67	0.10
G3	−420.90	−997.45, 155.64	0.15	−73.77	−194.34, 46.79	0.94	−17.01	−277.62, 243.60	0.90	134.37	−3.76, 272.50	0.06	−498.96	−1015.67, 17.75	0.06
Localizationappen	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
axial (head, neck, trunk)	−220.20	−604.58, 164.21	0.26	−84.99	−160.21, −9.77	**0.03**	−109.96	−275.68, 55.75	0.19	−112.59	−210.99, −14.18	**0.03**	−297.40	−672.92, 78.11	0.12
Deep soft-tissue sarcoma (n = 296)															
Age	5.03	−6.50, 16.57	0.39	1.43	−0.97, 3.84	0.24	0.72	−4.95, 6.38	0.80	0.63	−2.83, 4.10	0.72	4.06	−7.91, 16.02	0.51
Gender male	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
female	−77.25	−479.40, 324.89	0.71	−40.20	−128.01, 47.61	0.37	−18.11	−213.53, 177.31	0.86	−40.66	−158.05, 76.72	0.50	−66.69	−481.55, 348.17	0.75
Grade G1	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
G2	−222.90	−966.79, 520.90	0.56	−32.83	−218.91, 153.24	0.73	32.40	−354.26, 419.07	0.87	−54.82	−251.40, 141.76	0.58	−384.41	−1088.57, 319.74	0.28
G3	−302.30	−928.03, 323.33	0.34	−114.18	−260.68, 32.32	0.13	−21.76	−339.89, 296.37	0.89	141.65	−24.05, 307.35	0.09	−477.53	−1060.61, 105.54	0.11
Localization appendicular	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
axial (head, neck, trunk)	−292.70	−694.86, 109.40	0.15	−83.18	−169.70, 3.33	0.06	−124.82	−319.22, 69.58	0.21	−128.24	−245.63, −10.84	**0.03**	−314.20	−735.48, 107.05	0.14

Table 3. *Cont.*

	PI [g]			DI [h]									TI [l]		
				PCI [i]			SCI [j]			TCI [k]					
	Beta	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**
Superficial soft-tissue sarcoma (n = 60)															
Age	9.08	−22.59, 40.75	0.56	−3.20	−6.91, 0.52	0.09	0.13	−1.18, 1.43	0.84	2.71	−0.64, 6.06	0.11	3.61	−18.69, 25.91	0.75
Gender male	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
female	−244.50	−1550.78, 1061.81	0.71	62.06	−98.57, 222.68	0.43	−21.07	−73.30, 31.16	0.41	87.35	−47.66, 222.35	0.20	109.40	−765.23, 984.12	0.80
Grade G1	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
G2	−1031.80	−3045.04, 981.47	0.30	36.96	−205.08, 279.01	0.75	−18.82	−95.17, 57.53	0.61	102.78	−128.78, 334.35	0.38	−1004.50	−2403.36, 394.36	0.16
G3	−414.60	−2092.34, 1263.09	0.62	−9.45	−224.29, 205.39	0.93	−1.07	−68.84, 66.70	0.97	93.13	−100.01, 286.27	0.34	−352.70	−1545.67, 840.24	0.56
Localization appendicular	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
axial (head, neck, trunk)	−1.20	−1214.74, 1212.34	0.998	−91.68	−243.05, 59.69	0.22	−11.61	−61.93, 38.71	0.64	−52.58	−187.69, 82.53	0.44	−371.90	−1235.52, 491.64	0.39
Benign bone tumor (n = 61)															
Age	12.03	0.31, 23.75	**0.045**	0.3656	−17.12, 17.85	0.97	−12.059	−32.23, 8.11	0.23	−5.180	−16.54, 6.18	0.35	−11.95	−46.97, 23.06	0.48
Gender male	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
Female	30.04	−300.40, 360.48	0.86	−367.90	−798.01, 62.17	0.09	337.80	−253.09, 928.69	0.25	271.00	−145.74, 687.74	0.19	314.00	−1011.63, 1639.63	0.63
Grade	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable
Localization appendicular	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
axial (head, neck, trunk)	169.01	−229.74, 567.76	**0.002**	−211.10	−797.88, 375.62	0.46	−89.73	−908.39, 728.93	0.82	−119.60	−575.95, 336.65	0.59	−314.90	−1676.93, 1047.06	0.63
Benign soft-tissue tumor (n = 213)															

Table 3. *Cont.*

	PI [g]			DI [h]									TI [l]		
				PCI [i]			SCI [j]			TCI [k]					
	Beta	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**
Age	16.29	0.42, 32.15	0.04	0.756	−6.20, 7.715	0.83	5.24	−2.40, 12.87	0.18	0.2511	−0.84, 1.34	0.65	26.53	8.84, 44.22	0.004
Gender male	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
female	280.60	−243.33, 804.44	0.29	46.05	−172.08, 264.18	0.68	114.86	−124.11, 353.82	0.34	−23.45	−59.68, 12.79	0.20	515.70	−100.63, 1132.03	0.10
Grade	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable
Localization appendicular	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
axial (head, neck, trunk)	21.60	−594.30, 637.50	0.95	−17.69	−268.97, 233.60	0.89	234.58	−42.02, 511.18	0.10	5.99	−37.39, 49.38	0.79	180.70	−569.78, 931.19	0.64
Benign deep soft-tissue tumor (n = 172)															
Age	13.01	−2.12, 28.13	0.09	2.38	−3.62, 8.37	0.43	5.54	−3.47, 14.54	0.23	0.37	−0.94, 1.67	0.58	26.59	8.57, 44.61	0.004
Gender male	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
female	−1.82	−524.09, 520.46	0.995	144.49	−44.13, 333.12	0.13	127.00	−157.82, 411.82	0.38	−30.23	−75.17, 14.71	0.19	382.50	−285.27, 1050.29	0.26
Grade	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable
Localizationappendicular	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
axial (head, neck, trunk)	59.61	−569.86, 689.07	0.85	48.07	−174.99, 271.13	0.67	291.60	−39.66, 622.89	0.08	8.75	−45.72, 63.22	0.75	422.40	−398.51, 1243.35	0.31
Benign superficial soft-tissue tumor (n = 41)															
Age	43.61	−17.13, 104.36	0.15	−5.39	−36.71, 25.93	0.72	−0.16	−0.97, 0.64	0.67	−0.29	−1.11, 0.52	0.47	30.60	−23.82, 85.01	0.26

Table 3. *Cont.*

	PI [g]			DI [h]									TI [l]		
				PCI [i]			SCI [j]			TCI [k]					
	Beta	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**
Gender male	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
female	1364.80	−196.65, 2926.25	0.08	−316.80	−1170.00, 536.33	0.44	6.39	−15.79, 28.57	0.55	6.41	−16.34, 29.15	0.57	1137.60	−350.82, 2625.95	0.13
Grade	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable
Localization appendicular	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
axial (head, neck, trunk)	−302.60	−2074.28, 1469.01	0.73	−263.20	−1218.54, 692.14	0.56	−9.32	−33.62, 14.99	0.42	−6.88	−32.90, 19.14	0.59	−657.90	−2405.68, 1089.96	0.45

[g]: PI, patient interval. [h]: DI, diagnostic interval. [i]: PCI, primary care interval. [j]: SCI, secondary care interval. [k]: TCI, tertiary care interval. [l]: TI, total interval.

3.5. Diagnostic Interval (DI), Tertiary Care Interval (TCI)

3.5.1. Length (See Table 2)

Sarcomas showed significant differences between BS and STS and between deep and superficial STS in the length of the TCI. BS (median, 2.1 weeks) showed a significantly longer TCI than STS (median, 1.3 weeks) ($p = 0.006$). In STS, in turn, the TCI was significantly shorter for superficial STS (median, 0.9 weeks) than for deep STS (median, 1.6 weeks) ($p < 0.01$). Such differences in TCI were not observed for benign bone and soft-tissue tumors. TCIs of malignant mesenchymal tumors were slightly shorter on average than those of the comparable subset of benign tumors.

3.5.2. Influencing Parameters (See Table 3)

Of the potential influencing parameters investigated, grade and localization had a significant effect on the TCI length in the overall population and the STS subgroup. In the overall population, high-grade tumors had a significantly longer TCI ($p = 0.02$). Axial tumor localization showed a significantly shorter TCI for STS compared to an appendicular localization ($p = 0.03$). This was also reflected in the TCI of deep STS ($p = 0.03$).

3.6. Total Interval (TI)

3.6.1. Length (See Table 2)

Total intervals were shorter for sarcomas than for benign tumors. The shortest TI was observed for both malignant and benign tumors of deep soft-tissue tumors (median, 20.9 and 43.0 weeks, respectively). The same was true for superficial soft-tissue tumors, which had the longest TI of both malignant and benign tumors (median, 34.8 and 138.1 weeks, respectively). However, no significant differences in the length of the TI were observed between the subgroups of benign tumors and between the subgroups of malignant tumors.

3.6.2. Influencing Factors (See Table 3)

Of the potential influencing factors investigated, only age had a significant effect on the length of the TI, but this was only true for benign soft-tissue tumors and benign deep soft-tissue tumors. An increasing age correlated significantly with a longer TI for benign soft-tissue tumors and benign deep soft-tissue tumors ($p = 0.004$ and $p = 0.004$, respectively).

3.7. Involved Physicians in the Primary Care Interval (PCI) (See Figures 3 and 4)

The PCI showed differences between benign and malignant mesenchymal tumors with respect to the involvement of physicians, as well as their localization in hospitals and medical practices. For malignant tumors (87.50% to 95.12%), PCI physicians were involved more frequently on average than for benign tumors (79.65 to 87.80%). In this regard, PCI physicians were visited more often for BS (95.12%) and superficial STS (95.00%) than for deep STS (87.50%). Benign mesenchymal tumors showed a similar pattern. PCI physicians were seen most often for benign superficial soft-tissue tumors (87.80%) and benign bone tumors (86.89%) and slightly less often for benign deep soft-tissue tumors (79.65%). In the PCI, the physicians consulted were more often practice-based. For malignant mesenchymal tumors (9.65 to 26.92%), physicians were more often hospital-based relative to benign mesenchymal tumors (0.00 to 9.43%).

3.8. Involved Physicians in the Secondary Care Interval (SCI) (See Figures 3 and 4)

The SCI showed differences between benign and malignant mesenchymal tumors with respect to the involvement of physicians, as well as their localization in hospitals and medical practices. For malignant tumors (71.28 to 81.67%), SCI physicians were involved more frequently on average than for benign tumors (62.30 to 63.41%). Here, SCI physicians were more frequently involved in superficial STS (81.67%) than in BS (71.95%) or deep STS (71.28%). Benign mesenchymal tumors showed a similar pattern. SCI physicians were most frequently consulted for benign superficial soft-tissue tumors (63.41%), followed by benign deep soft-tissue tumors (62.79%) and benign bone tumors (62.30%). In SCI, physicians

consulted were more often hospital-based than in the PCI. In malignant mesenchymal tumors (73.47 to 83.41%), physicians were more often hospital-based relative to benign mesenchymal tumors (68.42 to 76.92%).

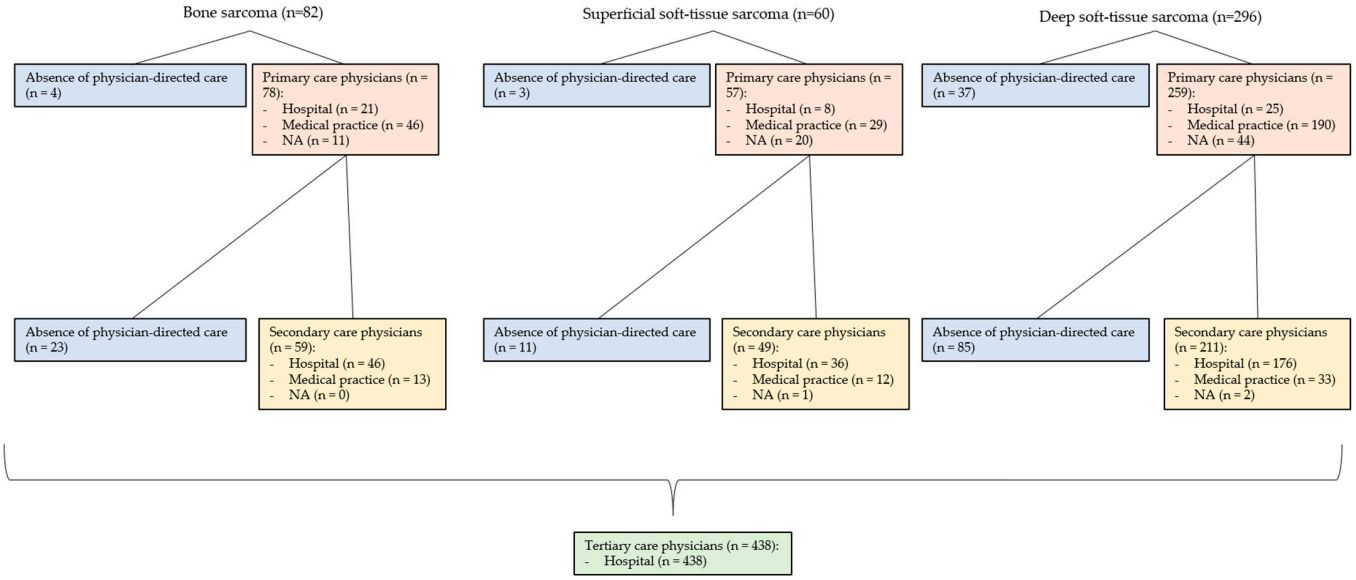


Figure 3. Referral pattern of bone sarcoma, superficial soft-tissue sarcoma, and deep soft-tissue sarcoma.

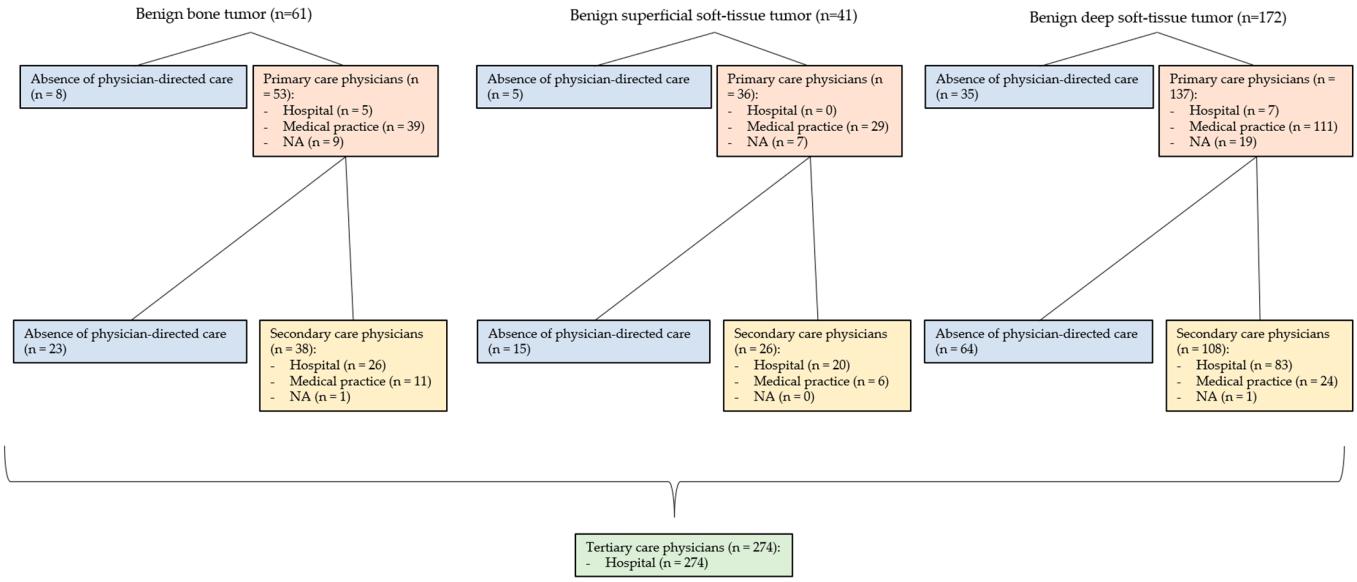


Figure 4. Referral pattern of benign bone tumors, benign superficial soft-tissue tumors, and benign deep soft-tissue tumors.

4. Discussion

This study addresses a significant gap in the literature by comprehensively analyzing the total interval for mesenchymal tumors in patients, particularly focusing on BS and STS, as well as their benign counterparts. The total interval of the diagnostic pathway, a complex measure influenced by diverse tumor-, patient-, and management-specific factors, has been dissected into its components. Notably, this study is the first to explore total intervals for benign mesenchymal tumors.

The patient interval emerges as a key determinant of the total interval of the entire diagnostic pathway, consistently occupying a major share across subgroups. Among malignant tumors, the secondary care interval assumes prominence in the diagnostic interval.

Age, grade, and localization were identified as factors influencing the interval durations of only some intervals, demonstrating the heterogeneity of mesenchymal tumors. A novel finding is the higher involvement of hospital-based practitioners in the diagnosis of sarcomas compared to benign mesenchymal tumors, possibly due to the more severe and urgent symptoms they exhibit that result in more frequent visits to the emergency ward. These insights contribute to a better understanding of the total interval in mesenchymal tumors.

The existing literature shows a wide range in the length of the different intervals of the diagnostic pathway of malignant mesenchymal tumors. The median values (including BS and STS) of the intervals in the present study are in the lower-to-middle range of values in the literature [15–40], indicating a rather efficient healthcare system, which, however, still has potential for optimization. The diagnostic pathway has not been previously analyzed for benign mesenchymal tumors; thus, no comparative values are available. As in the SURVSARC Study [41], the patient interval accounted for the largest proportion of the total interval in this study. This could also be observed in other cancer entities in the literature [42]. In particular, the patient interval accounted for a large proportion of the total interval for benign tumors, which is very important because the greatest potential for optimization lies in shortening the length of the patient interval. Important factors influencing the patient interval were patient age and tumor localization. Higher age has already been seen to be associated with longer intervals in some studies [16,19,27,29,30,43], although there are also studies that found no association [44] or even an opposite association [41]. In our study, there were 38 pediatric tumors (patient age, 2–18 years), 31 bone tumors (20 BSs, 11 benign bone tumors), 7 soft-tissue tumors (2 STSs; one superficial and one deep; 5 benign soft-tissue tumors, all with a deep location). The numbers were too low to compare pediatric with adult tumors.

In the diagnostic interval, the secondary care interval represented the largest proportion in terms of time. Already, Smolle et al. could show that examinations outside a sarcoma center led to a delay [45]. The visit to a GP compared to an emergency ward was associated with a longer primary care interval in the study by Goyal et al. [16]. The present study cannot confirm this; on the contrary, the primary care interval in which practice-based physicians were most frequently visited turned out to be particularly short, reflecting that GPs in Switzerland refer patients for bone and soft-tissue tumors in the shortest possible time. This is a very important finding: in the diagnostic interval, specialists outside a sarcoma center generate the bottleneck rather than primary care physicians. Axial localization leads to shorter patient and diagnostic intervals. Considering that the CNS is also axially located, symptoms are therefore already noticeable with small tumor masses, little room is left for surgery, and assuming that the treating physicians are aware of this, it becomes clear that faster action is required with an axially located tumor.

A longer total interval of the diagnostic pathway has been associated with lower survival by Bandyopadhyay et al. and Ferrari et al. [46,47]. In their study of primary pulmonary artery sarcoma, which had a median total interval of 14.3 weeks, Bandyopadhyay et al. showed a 46% increase in the odds of death when the length of the total interval was doubled [46]. Ferrari et al., in their study on STS in children and adolescents who had a median total interval of 8 weeks, showed a significant negative impact on survival with an increasing length of the total interval ($p = 0.002$) [47]. Translating this for the current examined cohort, where the median length of the total interval was 22.8 weeks for BS and 23.3 weeks for STS, it can be assumed that the survival rate could be increased by shortening the total interval of the diagnostic pathway. However, it is essential to note that a comprehensive investigation of this effect would be necessary. Moreover, aside from its direct impact on survival, a shorter total interval is also desirable due to its influence on patient well-being in cases where the diagnosis remains uncertain [48]. However, it must be taken into account that the patient interval accounts for a larger part of the total interval of the diagnostic pathway than the diagnostic interval.

The patient interval, which had a median duration of 90.0 weeks for this study's overall population, was nearly twice as long as the diagnostic interval, which had a median duration of 46.0 weeks and represented the largest delay in the total interval of the diagnostic pathway. This underscores that the primary issue does not lie with individual physicians, but rather with the referral process and therefore the structure of the healthcare system itself. The high investments in the healthcare system appear to be insufficient in promptly identifying sarcoma patients. The repeatedly mentioned complexity of the work-up and treatment of patients with sarcoma is greatly explained by the fact that sarcomas do not form a conventional medical discipline per se. Addressing the needs of sarcoma patients necessitates a comprehensive approach via a multidisciplinary team (MDT), and a physician head coordinating among disciplines is crucial. Integrated practice units (IPUs) could provide a solution. Here, the focus is on a problem rather than a discipline [49,50]. By bringing together different health professionals in a unified structured organization, challenges, like cumbersome referrals, could be surmounted, potentially leading to shorter intervals. Further, the patient interval could also be shortened by health professionals helping patients to recognize problems as such [51]. Subsequently, the diagnostic interval would also be shortened, as there would be no need for cumbersome referrals. Thus, the secondary care interval, which is the largest part of the diagnostic interval, could be optimized. In terms of value-based healthcare (VBHC), health outcomes, such as quality of life, could account for a larger share of costs by intercepting patients before they are plagued by unpleasant symptoms for a long time [52]. In addition, costs for nontargeted investigations could be saved. Therefore, reorganizing healthcare structures according to the VBHC principles may greatly enhance the work-up of sarcoma patients [51].

This study reflects the contact of patients with a sarcoma center; therefore, the numbers per subgroup are not balanced, which is a limitation of this study. For example, STS is many times more frequent than BS. This could have the consequence that effects of the investigated potential influencing factors did not show up in the smaller subgroups, although they would be present. In addition, a selection bias was found for those patients who presented at a sarcoma center. That is, someone thought of the possibility of a sarcoma diagnosis during the diagnostic interval and involved a sarcoma center. Patients for whom this possibility was not considered may never have been diagnosed with a mesenchymal tumor, thereby remaining within the diagnostic interval indefinitely.

Further investigation is needed to determine the reasons for the delays in the patient and secondary care interval. Regarding the patient interval, the perceived symptoms could be investigated, as well as the reasons that led to the consultation with a physician. Concerning the secondary care interval, a breakdown of the physicians visited in the primary and secondary care interval regarding their specialization, as well as the examinations performed, would be interesting to determine, on the one hand, to whom optimization approaches should be directed and, on the other hand, to determine the correlation of examinations performed with the length of the intervals. In this way, it would be possible to determine which investigations are appropriate and which could be dispensed with, thus saving costs. In addition, the correlation between patient outcome in this study population could be analyzed to confirm or reject the literary data correlating the outcome with the length of the total interval of the diagnostic pathway.

5. Conclusions

In Switzerland's efficient healthcare system, cost does not guarantee an expedited sarcoma diagnosis, possibly due to its multidisciplinary nature. Key factors, such as an older age, larger tumor size, and axial localization are associated with a higher malignancy risk, underscoring the need for shorter diagnostic intervals. Further research is essential for guiding clinicians with sarcoma suspicions. To improve patient outcomes through reduced total and diagnostic intervals, focus must be placed on shortening the patient and secondary care intervals. This necessitates targeted patient education and specialized physician training. In light of our findings, we advocate for the regionalization or centralization

of sarcoma care. While secondary care institutions need not be categorically excluded from sarcoma management, their involvement should be contingent upon active collaborations with a multidisciplinary team or sarcoma board from a tertiary care institution, particularly when complex treatments are required. Given these considerations, the logical next advancement for a sarcoma center is the establishment of Integrated Practice Units (IPUs), in alignment with Value-Based Health Care (VBHC) principles. IPUs offer the added benefits of transparently assessing and sharing treatment metrics and quality indicators within a collaborative network.

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Conflicts of Interest: The authors declare no conflict of interest.

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Article

Pain Accelerates, Swelling and Sensory Disturbances Delay Diagnosis in Mesenchymal Tumors

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Simple Summary: Sarcomas are rare tumors that can develop in bones or soft tissues. Recognizing them early is important because delays in diagnosis can lead to worse outcomes for patients. In our study, we looked at how different symptoms affect the time it takes for patients to be diagnosed with these tumors. We found that when patients experience pain, they tend to see a doctor sooner, leading to quicker diagnoses. However, symptoms like swelling or numbness often cause delays because patients or doctors may not realize they could be signs of a serious condition. Understanding which symptoms lead to delays can help improve education for both patients and healthcare providers, leading to earlier detection and better outcomes for people with sarcomas and similar tumors.

Abstract: Background/Objectives: The early diagnosis of mesenchymal tumors, including bone and soft tissue sarcoma and their benign counterparts, is crucial for improving patient outcomes. This study aims to analyze how different symptoms influence diagnostic timelines and identify factors contributing to delays in the diagnostic pathway. Methods: We conducted an analysis of 712 patients with mesenchymal tumors from the Swiss Sarcoma Network between January 2018 and December 2021. Symptoms were analyzed both individually, like pain and swelling, and by categories such as general, neurological and integumentary symptoms. Intervals of the total interval (TI) in the diagnostic pathway—including the patient interval (PI), primary care interval (PCI), secondary care interval (SCI) and tertiary care interval (TCI)—were assessed. Linear regression models estimated the impact of specific symptoms on these intervals. Results: Pain significantly reduced the PI and TI in patients with bone sarcomas (PI $\beta = -1787.5$; $p = 0.001$) and soft tissue sarcomas (TI $\beta = -442.1$; $p = 0.04$), prompting earlier medical consultation. In contrast, symptoms like growing swelling and sensory disturbances were associated with prolonged diagnostic intervals. Growing swelling lengthened the PI in benign bone tumors ($\beta = 382.98$; $p = 0.04$) and extended the TI in bone sarcomas ($\beta = 1637.4$; $p = 0.02$). Sensory disturbances delayed the PI and TI in superficial soft tissue sarcomas (PI $\beta = 1705$; $p = 0.02$; TI $\beta = 2037.6$; $p = 0.03$). Integumentary symptoms also led to significant delays in benign superficial soft tissue tumors. Conclusions: Pain accelerates the diagnostic process in mesenchymal tumors by prompting earlier consultation, while swelling and sensory disturbances contribute to delays across various diagnostic intervals. These findings highlight the need for increased awareness among patients and healthcare providers regarding the potential seriousness of

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these symptoms. Educational initiatives and optimized referral protocols are essential to reducing diagnostic delays and improving patient outcomes.

Keywords: mesenchymal tumors; sarcomas; diagnostic delays; pain; swelling; sensory disturbances; diagnostic intervals; early diagnosis; patient awareness; healthcare provider education

1. Introduction

Sarcomas are rare mesenchymal tumors with significant heterogeneity, encompassing both bone and soft tissue neoplasms that can range from benign to malignant and from superficial to deep-seated lesions. This diversity in histological subtypes—over 80 have been identified [1]—and anatomical presentations poses substantial diagnostic challenges. These challenges often result in delayed treatment initiation, which can lead to poorer patient outcomes—a common issue with rare cancers [2]. Early diagnosis is crucial for improving survival rates and enhancing the effectiveness of therapeutic interventions in sarcoma patients [3–5]. Therefore, understanding the diagnostic pathway and how various symptoms influence it is vital for improving patient care and outcomes. The non-specific nature of symptoms associated with mesenchymal tumors, such as pain, swelling and sensory disturbances, contributes significantly to diagnostic delays. Patients may not recognize the severity of these symptoms, leading to postponement in seeking medical attention [6]. Additionally, primary care physicians may misinterpret these symptoms due to the rarity and variable clinical presentations, further prolonging the time to accurate diagnosis [7–9]. These delays are particularly pronounced in the patient interval (from symptom onset to first medical consultation) and the secondary care interval (from specialist referral to referral to a sarcoma hub), which have been identified as major bottlenecks in the diagnostic pathway [10]. Despite existing research on diagnostic intervals, critical gaps remain unaddressed. Most studies have focused primarily on malignant tumors and common symptoms like pain and lumps, without providing a comprehensive overview of all symptom categories [6]. Benign mesenchymal tumors, as well as the differences between deep and superficial tumors, have been largely understudied. This lack of comprehensive symptom analysis limits the understanding of how various presentations impact the diagnostic process. Furthermore, while the centralization of care has been proposed to improve outcomes—studies have highlighted diagnostic discrepancies when non-specialist centers are involved [11,12]—there is a need for detailed analysis on how specific symptoms affect diagnostic timeliness across different healthcare levels. This study aims to address these gaps by examining how both benign and malignant mesenchymal tumors, as well as deep and superficial tumors, differ in symptom presentation and how these differences impact the diagnostic pathway. By exploring the symptoms, consulted physicians and diagnostic examinations of patients with mesenchymal tumors, we seek to assess their impact on the length of various diagnostic intervals: the patient interval, primary care interval, secondary care interval and tertiary care interval. This comprehensive approach will provide a more detailed understanding of the diagnostic process for sarcoma patients. Early diagnosis, as shown in studies on both general cancers [13] and sarcomas [10,14], significantly improves patient outcomes. Our findings could contribute to earlier detection strategies and more personalized approaches to management, ultimately improving patient outcomes in clinical practice.

2. Materials and Methods

2.1. Study Design

This study analyzed a prospectively collected dataset from the real-world-time data warehouse (RWTD/E-W) ShapeHub® (PH and BF, Zurich, Switzerland). The dataset comprises patients diagnosed with mesenchymal tumors, including soft tissue sarcomas (STS), bone sarcomas (BS), benign soft tissue tumors (BSTT) and benign bone tumors (BBT). The data were collected from sarcoma centers (MDT/SB-SSN) and their associated network, which includes seven secondary and tertiary care medical institutions forming the Swiss Sarcoma Network (SSN) in Switzerland. The study period spanned from 1 January 2018 to 31 December 2021.

2.2. Study Objective

The primary objective of this study was to analyze the symptoms of patients with mesenchymal tumors and to assess their impact on the length of various intervals of the diagnostic pathway: the patient interval (PI), primary care interval (PCI), secondary care interval (SCI) and tertiary care interval (TCI). This analysis was conducted across subgroups of STS, BS, BSTT and BBT. The study aimed to identify factors contributing to delays or efficiencies in each interval, with the long-term goal of optimizing diagnostic pathways to improve the timely detection and treatment of sarcomas and other mesenchymal tumors.

2.3. Selection Criteria

All consecutive patients presented at the weekly MDT/SB-SSN meetings with a diagnosis of STS, BS, BSTT or BBT between 1 January 2018 and 31 December 2021 were considered for inclusion. Diagnoses were established based on the World Health Organization (WHO) classification and categorized as benign or malignant, with intermediate tumors classified as sarcomas (see Figure 1).

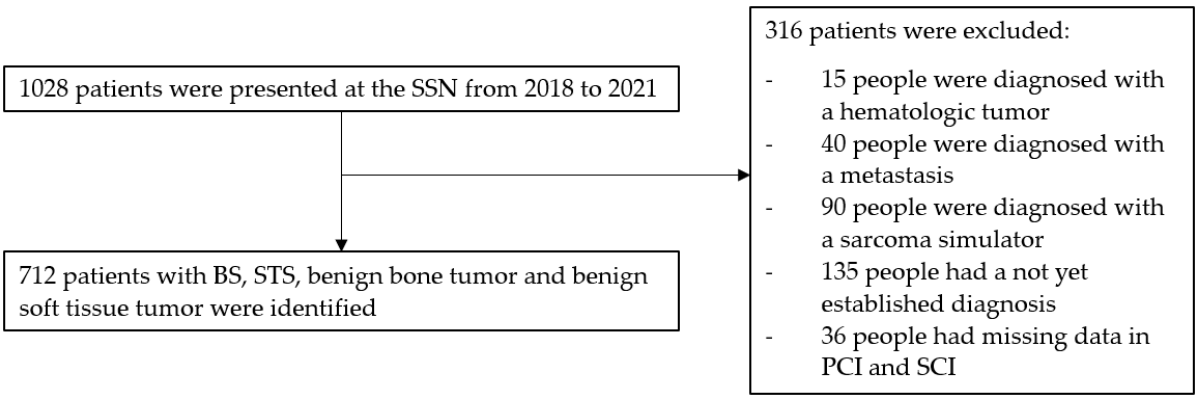


Figure 1. Flow chart of the patient inclusion progress.

Inclusion Criteria:

- Patients diagnosed with STS, BS, BSTT or BBT within the study period.
- Availability of complete medical records regarding documented symptom presentation and diagnostic timelines.
- Exclusion Criteria:
- Patients with incomplete medical records where key dates (e.g., first physician visit) could not be determined.
- Patients who received prior treatment for mesenchymal tumors before presentation to the SSN.
- Secondary mesenchymal tumors resulting from metastasis.

In the Swiss healthcare system, visiting a primary care physician is not mandatory before consulting a specialist. Therefore, patients with incomplete data regarding the PCI were still included, as it was not possible to differentiate between the absence of physician-directed care and missing documentation of a physician visit during the PCI. The same approach was applied to missing data in the SCI. If medical records explicitly indicated that no primary or secondary care physician was involved—such as incidental findings during other examinations or explicit statements in referral letters—these patients were categorized under "None" in the relevant intervals.

2.4. Data Collection

Data were extracted from a real-world-time data warehouse (RWTD/E) managed by Adjumed (Zurich, Switzerland), which aggregates demographic and treatment-specific information from patients across seven Swiss medical institutions. Initially, 1028 patients were identified. After applying the inclusion and exclusion criteria, 712 patients with complete medical records were included in the final analysis. The collected data encompassed the following:

- Demographic Information: Age, sex.
- Tumor Characteristics: WHO diagnosis, histological type, tumor grade (for malignant tumors), size, anatomical location (head and neck, superficial trunk, deep trunk, limb girdle, extremities and viscera) and depth (superficial or deep).
- Symptom presentation: Types of symptoms reported, classified into specific categories.
- Diagnostic Timelines:
    - Date of Symptom Onset: First symptom attributed to the mesenchymal tumor.
    - First Physician Visit: Date of initial medical consultation.
    - Referral Dates: Dates of referral from primary to secondary care and from secondary care to the sarcoma center/tertiary care.
    - Diagnosis Date: Date of histologically confirmed diagnosis.

2.5. Definition of the Intervals

- Patient Interval (PI): Time from symptom onset to the first medical consultation.
- Primary Care Interval (PCI): Time from the first medical consultation to referral to secondary care.
- Secondary Care Interval (SCI): Time from secondary care consultation to referral to the sarcoma center.
- Tertiary Care Interval (TCI): Time from sarcoma center consultation to histological diagnosis.
- Diagnostic Interval (DI): Sum of PCI, SCI and TCI, representing the time from the patient's first medical consultation to the histological diagnosis.
- Total Interval (TI): Sum of PI, PCI, SCI and TCI, representing the total time from symptom onset to the histological diagnosis.

2.6. Classification of the Symptoms

Symptoms were categorized based on relevant organ system or clinical domains to provide a structured and clinically meaningful framework:

- Circulatory: Symptoms related to the circulatory system (e.g., edema, cold foot, increased resting heart rate).
- Gastrointestinal: Symptoms related to the digestive tract (e.g., constipation, diarrhea, emesis, loss of appetite, abdominal distension).
- General Symptoms: Non-specific symptoms affecting overall health (e.g., pain, swelling (local increase in volume), fever, fatigue, night sweats, weight loss).

- Integumentary: Symptoms affecting the skin and related tissues (e.g., skin lesions, exophytic tumors, poorly healing wounds, discoloration, ulceration).
- Musculoskeletal: Symptoms related to muscles and bones (e.g., cramps, loss of strength, fasciculations, loss of function).
- Neurological: Symptoms related to the nervous system and sensory functions (e.g., headache, tinnitus, sensory disturbances).
- Respiratory: Symptoms related to breathing and the respiratory tract (e.g., dyspnea, coughing, voice changes).
- Urogenital: Symptoms affecting the urinary and reproductive systems (e.g., acute renal failure, hematuria, dysuria, postmenopausal bleeding).
- Incidental Findings: Unexpected findings detected during routine exams or follow-ups (e.g., incidental findings during cancer control or preoperative examinations), often retrospectively accompanied by symptoms like swelling or pain.
- Not Available (NA): Cases where symptom data were missing or unavailable.

Each symptom category was coded for statistical analysis. Patients presenting with multiple symptoms had each symptom recorded and analyzed accordingly.

2.7. Tumor Grading and Classification

The tumor grade was assigned based on the WHO classification system, applicable only to malignant tumors. Intermediate-grade tumors were classified as malignant for the purposes of this study. The tumor size was measured as the largest diameter recorded in imaging studies or surgical reports. The tumor location was categorized as appendicular (limbs) or axial (head, neck, trunk), and the depth was classified as superficial or deep based 175 on anatomical landmarks.

2.8. Statiscial Analysis

Continuous variables are presented as medians with interquartile ranges (IQR; 1st quartile, 3rd quartile), while categorical variables are reported as numbers and percentages. According to the study inclusion criteria, a complete case analysis was conducted. Previously analyzed interval lengths, including the patient, primary care, secondary care and tertiary care interval as well as the diagnostic and total interval, serve as baseline data in this study [10]. These intervals are examined here to assess the impact of symptom presentation on diagnostic timelines.

Differences between categorical variables were analyzed using Fisher's exact test. The association between specific symptoms and intervals of the diagnostic pathway was assessed using linear regression models. Beta coefficients (β) with 95% confidence intervals (CI) were calculated to estimate the effect size of symptoms on the PI, PCI, SCI, TCI and TI. A positive β indicated a lengthening of the interval, whereas a negative β indicated a shortening. Statistical significance was determined as a p-value of less than 0.05.

A priori-defined subgroup analyses were performed based on tumor type (malignant vs. benign), location (deep vs. superficial) and other relevant characteristics. All statistical analyses were conducted using R software (version 4.3.2).

2.9. Ethical Considerations

The study was approved by the local ethics committee (IRB approval number: BASEC—Nr. 2019-01107/NCT04300257), adhering to the guidelines of the Declaration of Helsinki. Given the retrospective nature of the study and the use of anonymized data, the requirement for informed consent was waived.

3. Results

3.1. Patient and Tumor Characteristics

3.1.1. Demographic Data

Age Distribution

In our cohort of 712 patients with mesenchymal tumors, the median age varied significantly across different tumor groups. Patients with BS had a median age of 44.0 years (interquartile range [IQR]: 19.0–65.0 years), indicating a younger population compared to other groups. STS patients exhibited a higher median age of 60.0 years (IQR: 46.0–72.0 years). BBT patients had a median age similar to BS at 34.0 years (IQR: 23.0–45.0 years), while BSTT presented in an older population with a median age of 55.0 years (IQR: 44.0–63.0 years). Notably, deep-seated tumors, both malignant and benign, tend to occur in older patients compared to superficial tumors (see Table 1).

Gender Distribution

The gender distribution also showed variation among tumor types. Females constituted 36.6% of the BS group, 50.0% of the STS group, 49.2% of the BBT group and 51.6% of the BSTT group. There was a slightly higher prevalence of certain tumors in one gender; for instance, STS had a marginally higher occurrence in males compared to females (see Table 1).

3.1.2. Tumor Characteristics

Tumor Grade (Applicable to Malignant Tumors Only)

Among the malignant tumors, tumor grading revealed that a significant proportion were high-grade neoplasms. In BS patients, 31.7% had grade G3 tumors, 6.1% had G2, and 8.5% had G1. Similarly, in the STS group, 28.1% were grade G3, 13.8% were G2 and 18.8% were G1 tumors. High-grade tumors were more prevalent in deep-seated sarcomas compared to superficial ones (see Table 1).

Tumor Location

BS were more frequently localized in the extremities (40.2%) and limb girdle (39.0%) compared to STS (30.3% and 22.8%, respectively). Similarly, benign tumors in the extremities were more common, with BBT (52.5%) showing a higher prevalence than BSTT (41.8%). However, BSTT (34.3%) and BBT (29.5%) were found comparably often in the limb girdle. Deep STS were predominantly located in the deep trunk (39.2%), whereas superficial STS were more frequently found in the superficial trunk (36.7%) and accounted for the highest proportion of tumors in the head and neck region (16.7%). Benign deep soft tissue tumors were less often localized in the deep trunk (19.8%) and superficial soft tissue tumors were less often localized in the superficial trunk (14.6%) compared to their malignant counterparts. Tumors in the viscera were observed only in the deep STS group (3.4%) (see Table 1).

Tumor Size

The median tumor size also differed among the groups. BS had a median size of 60.0 mm (IQR: 39.5–85.0 mm), while STS tumors were larger, with a median size of 70.0 mm (IQR: 32.0–124.0 mm). Benign tumors generally presented with smaller sizes; BBT had a median size of 31.5 mm (IQR: 11.5–50.5 mm), and BSTT had a median size of 60.0 mm (IQR: 38.3–97.3 mm). Notably, deep tumors were larger on average than superficial ones (see Table 1).

Table 1. Patient Characteristics by Tumor Groups.

	BS	**STS**			**BBT**	**BSTT**		
	***n* = 82**	**Deep and Superficial STS** ***n* = 356**	**Deep STS** ***n* = 296**	**Superficial STS** ***n* = 60**	***n* = 61**	**Deep and Superficial BSTT** ***n* = 213**	**Deep BSTT** ***n* = 172**	**Superficial BSTT** ***n* = 41**
Age, years	44.0 (19.0, 65.0)	60.0 (46.0, 72.0)	60.0 (46.0, 72.0)	61.5 (42.3, 74.3)	34.0 (23.0, 45.0)	55.0 (44.0, 63.0)	56.0 (44.0, 65.0)	54.0 (44.0, 61.0)
Female, (%)	30 (36.6%)	178 (50.0%)	145 (49.0%)	33 (55.0%)	30 (49.2%)	110 (51.6%)	90 (52.3%)	20 (48.8%)
Grade								
G1	7 (8.5%)	67 (18.8%)	52 (17.6%)	15 (25.0%)	not applicable	not applicable	not applicable	not applicable
G2	5 (6.1%)	49 (13.7%)	41 (13.9%)	8 (13.3%)	not applicable	not applicable	not applicable	not applicable
G3	26 (31.7%)	100 (28.1%)	85 (28.7%)	15 (25.0%)	not applicable	not applicable	not applicable	not applicable
NA	44 (53.7%)	140 (39.3%)	118 (39.9%)	22 (36.7%)	not applicable	not applicable	not applicable	not applicable
Region								
Head and Neck	2 (2.4%)	19 (5.3%)	9 (3.0%)	10 (16.7%)	4 (6.6%)	11 (5.2%)	6 (3.5%)	5 (12.2%)
Superficial Trunk	-	22 (6.2%)	-	22 (36.7%)	-	6 (2.8%)	-	6 (14.6%)
Deep Trunk	15 (18.3%)	116 (32.6%)	116 (39.2%)	-	7 (11.5%)	34 (16.0%)	34 (19.8%)	-
Limb Girdle	32 (39.0%)	81 (22.8%)	73 (24.7%)	8 (13.3%)	18 (29.5%)	73 (34.3%)	59 (34.3%)	14 (34.2%)
Extremities	33 (40.2%)	108 (30.3%)	88 (29.7%)	20 (33.3%)	32 (52.5%)	89 (41.8%)	73 (42.4%)	16 (39.0%)
Viscera	-	10 (2.8%)	10 (3.4%)	-	-	-	-	-
Size, mm	60.0 (39.5, 85.0)	70.0 (32.0, 124.0)	86.0 (45.0, 130.0)	28.0 (20.0, 44.0)	31.5 (11.5, 50.5)	60.0 (38.3, 97.3)	61.0 (39.0, 100.5)	54.0 (35.5, 79.5)
0–50 mm, *n*	25 (30.5%)	106 (29.8%)	70 (23.6%)	36 (60.0%)	33 (54.1%)	83 (39.0%)	65 (37.4%)	18 (43.9%)
51–100 mm, *n*	30 (36.6%)	67 (18.8%)	59 (19.9%)	8 (13.3%)	10 (16.4%)	72 (33.8%)	55 (32.0%)	17 (41.5%)
101–150 mm, *n*	11 (13.4%)	50 (14.1%)	50 (16.9%)	0 (0.0%)	1 (1.6%)	29 (13.6%)	27 (15.7%)	2 (4.9%)
>150 mm, *n*	1 (1.2%)	42 (11.8%)	41 (13.9%)	1 (1.7%)	0 (0.0%)	14 (6.6%)	13 (7.6%)	1 (2.4%)
NA	15 (18.3%)	91 (25.6%)	76 (25.7%)	15 (25.0%)	17 (27.8%)	15 (7.0%)	12 (7.0%)	3 (7.3%)

Legend: NA—not applicable.

3.2. Symptom Prevalence and Impact on the Diagnostic Interval

Analyzing symptom presentations across different tumor groups revealed significant variations in both prevalence (see Figure 2 and Tables 2 and 3) and their impact on diagnostic intervals (see Table A1). The median lengths of diagnostic pathway intervals are in Table A2 in Appendix A, serving as baseline data for symptom impact analysis.

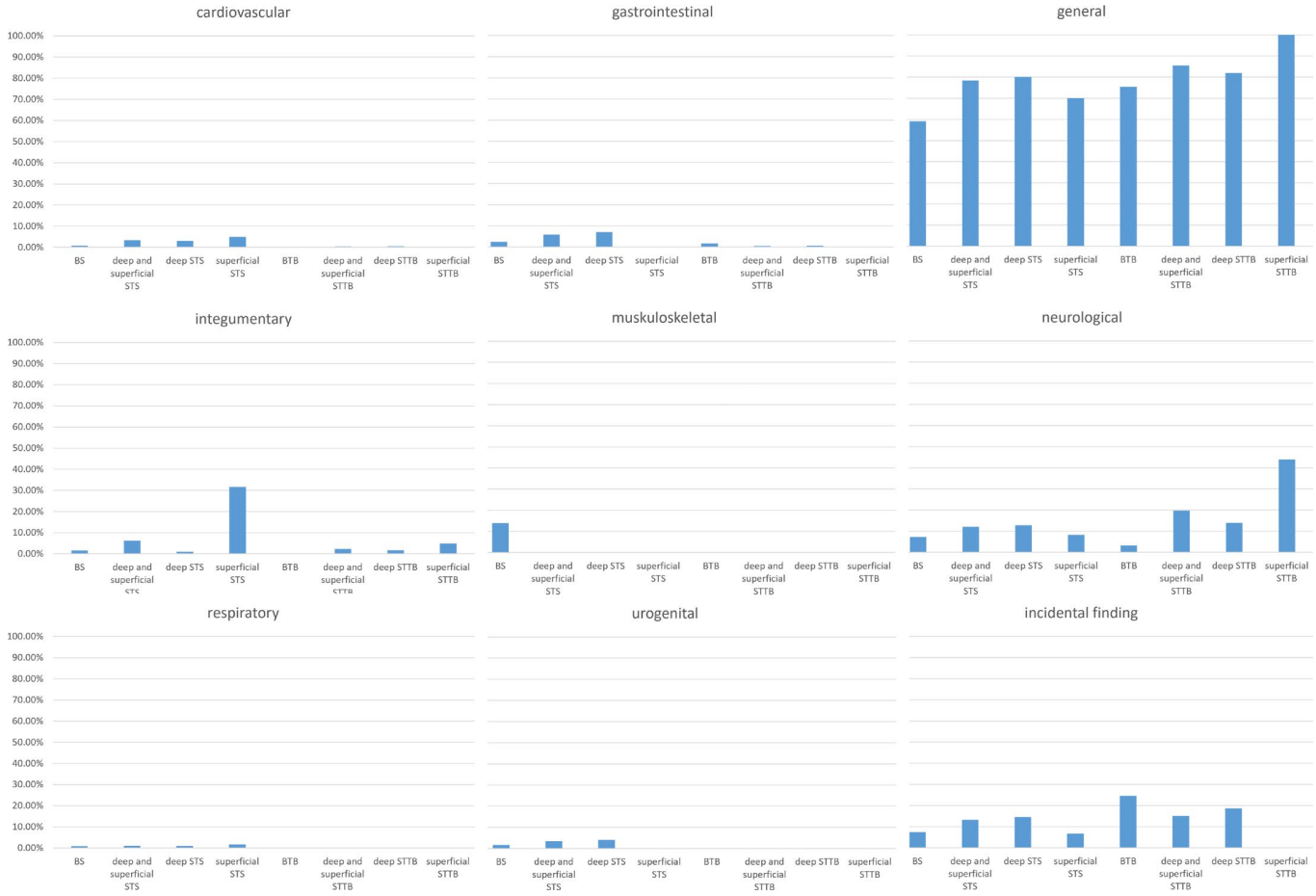


Figure 2. Distribution of Symptom Prevalence (%) Across Different Tumor Groups Categorized by Symptom Class: Circulatory, Gastrointestinal, General, Integumentary, Musculoskeletal, Neurological, Respiratory, Urogenital and Incidental Findings. For a detailed tabular representation and numerical data, please refer to Table A2 in Appendix A.

3.2.1. Circulatory Symptoms

Circulatory symptoms were more frequent in patients with STS, with bleeding reported in 5.0% of these cases, the highest among circulatory symptoms. These symptoms were almost absent in benign tumor groups. Notably, in patients with superficial STS, the presence of circulatory symptoms significantly lengthened the patient interval (PI) (β = 2324.5; p = 0.006) and the total interval (TI) (β = 2804.1; p = 0.01). This suggests that patients experiencing bleeding may delay seeking medical attention, possibly due to not associating this symptom with malignancy. Such delays highlight the need for patient education on the significance of bleeding as a potential indicator of serious underlying conditions (see Tables 2 and 3).

Table 2. More precise breakdown of symptoms per subgroup *.

	BS	STS			BBT	BSTT		
		Deep and Superficial STS	Deep STS	Superficial STS		Deep and Superficial BSTT	Deep BSTT	Superficial BSTT
	n = 82	*n* = 356	*n* = 296	*n* = 60	*n* = 61	*n* = 213	*n* = 172	*n* = 41
circulatory								
bleeding	0 (0.0%)	5 (1.4%)	2 (0.7%)	3 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
hematoma	0 (0.0%)	4 (1.1%)	3 (1.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
gastrointestinal								
constipation	1 (1.2%)	6 (1.7%)	6 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
increase in abdominal girth	0 (0.0%)	7 (2.0%)	7 (2.4%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.6%)	0 (0.0%)
loss of appetite	0 (0.0%)	5 (1.4%)	5 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
general symptoms								
difference in leg circumference	0 (0.0%)	7 (2.0%)	6 (2.0%)	1 (1.7%)	0 (0.0%)	2 (0.9%)	2 (1.2%)	0 (0.0%)
fatigue	0 (0.0%)	8 (2.3%)	8 (2.7%)	0 (0.0%)	0 (0.0%)	3 (1.4%)	3 (1.7%)	0 (0.0%)
fever	1 (1.2%)	4 (1.1%)	4 (1.4%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
growing swelling	9 (11.0%)	88 (24.7%)	67 (22.6%)	21 (35.0%)	7 (11.5%)	80 (37.6%)	57 (33.1%)	23 (33.1%)
night sweats	2 (2.4%)	6 (1.7%)	6 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
pain	65 (79.3%)	138 (38.8%)	131 (44.3%)	7 (11.7%)	43 (70.5%)	78 (36.6%)	68 (39.5%)	10 (39.5%)
swelling	25 (30.5%)	210 (59.0%)	165 (55.7%)	45 (75.0%)	21 (34.4%)	160 (75.1%)	120 (69.8%)	40 (69.8%)
weight loss	0 (0.0%)	16 (4.5%)	16 (5.4%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.6%)	0 (0.0%)
incidental finding								
incidental finding	9 (11.0%)	46 (12.9%)	42 (14.2%)	4 (6.7%)	15 (24.6%)	32 (15.0%)	32 (18.6%)	0 (0.0%)
incidental finding after trauma	3 (3.7%)	2 (0.6%)	2 (0.7%)	0 (0.0%)	8 (13.1%)	3 (1.4%)	3 (1.7%)	0 (0.0%)
incidental finding at control of cancerous disease	2 (2.4%)	26 (7.3%)	23 (7.8%)	3 (5.0%)	3 (4.9%)	7 (3.3%)	7 (4.1%)	0 (0.0%)
integumental								
discoloration	1 (1.2%)	7 (2.0%)	0 (0.0%)	7 (11.7%)	0 (0.0%)	3 (1.4%)	2 (1.2%)	1 (2.4%)
exophytic tumor	0 (0.0%)	7 (2.0%)	3 (1.0%)	4 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
pruritus	1 (1.2%)	2 (0.6%)	0 (0.0%)	2 (3.3%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (2.4%)

Table 2. *Cont.*

	BS	STS			BBT	BSTT		
		Deep and Superficial STS	Deep STS	Superficial STS		Deep and Superficial BSTT	Deep BSTT	Superficial BSTT
	***n* = 82**	***n* = 356**	***n* = 296**	***n* = 60**	***n* = 61**	***n* = 213**	***n* = 172**	***n* = 41**
skin lesion	0 (0.0%)	7 (2.0%)	3 (1.0%)	4 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ulcerating swelling	0 (0.0%)	5 (1.4%)	0 (0.0%)	5 (8.%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
musculoskeletal system								
loss of function	13 (15.9%)	17 (4.8%)	17 (5.7%)	0 (0.0%)	12 (19.7%)	12 (5.6%)	10 (5.8%)	2 (4.9%)
loss of strength	4 (4.9%)	4 (1.1%)	4 (1.4%)	0 (0.0%)	1 (1.6%)	4 (1.9%)	4 (2.3%)	0 (0.0%)
respiratory system								
change of voice	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
dyspnea	0 (0.0%)	2 (0.6%)	1 (0.3%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
neurological								
sensory disturbance	8 (9.8%)	40 (11.2%)	35 (11.8%)	5 (8.3%)	2 (3.3%)	42 (19.7%)	24 (14.0%)	18 (43.9%)
urogenital								
hematuria	1 (1.2%)	3 (0.8%)	3 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
pollakiuria	0 (0.0%)	4 (1.1%)	4 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NA	3 (3.7%)	16 (4.5%)	15 (5.1%)	1 (1.7%)	1 (1.6%)	3 (1.4%)	3 (1.7%)	0 (0.0%)

* A shortened version of Table 2 is presented here. The complete version of Table 2, which was used for the statistical analysis, is available upon request.

Table 3. Influence of symptoms and symptom classes on length of intervals ′°.

				DI								TI		
	PI			PCI			SCI			TCI				
	Beta	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**
Bone sarcoma (*n* = 82)															
Symptoms															
pain	−1787.5	−2812.4, −762.6	0.001	−226.4	−478.9, 26.1	0.08	−214.9	−457.9, 28.2	0.08	−8.0	−22.8, 6.8	0.29	−2556.8	−3788.5, −1325.2	<0.001
swelling	203.7	−628.0, 1035.4	0.63	176.0	−46.8, 398.8	0.12	174.7	−43.8, 393.1	0.12	−6.3	−19.5, 7.0	0.35	476.2	−579.1, 1531.6	0.37
growing swelling	1102.6	−74.7, 2280.0	0.07	433.2	124.1, 742.3	0.007	433.7	129.4, 737.9	0.006	2.5	−16.2, 21.2	0.79	1637.4	227.8, 3046.9	0.02
sensory disturbance	−300.7	1567.7, 966.2	0.64	549.5	209.6, 889.4	0.002	550.1	215.4, 884.8	0.002	−1.2	−22.5, 20.0	0.91	235.9	−1432.9, 1904.7	0.78

Table 3. *Cont.*

				DI								TI			
	PI			PCI			SCI			TCI					
	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value
Symptomclass															
circulatory	−477.9	−3888.7, 2932.8	0.78	43.7	−877.6, 964.9	0.93	39.5	−869.1, 948.1	0.93	−1.5	−51.4, 48.5	0.95	−631.2	4541.1, 3278.6	0.75
gastrointestinal	−481.3	−2475.9, 1513.3	0.63	−3.0	−542.3, 536.2	0.99	−4.5	−536.2, 527.1	0.99	−7.2	−42.7, 28.4	0.69	−628.1	−3414.2, 2157.9	0.65
general	457.3	−1970.1, 2884.7	0.71	73.6	−268.3, 415.5	0.67	67.3	−252.5, 387.2	0.68	−13.7	−34.6, 7.3	0.2	600.7	−3309.5, 4510.9	0.76
integumental	90.99	−2338.7, 2520.7	0.94	−71.3	−727.0, 584.4	0.83	−75.0	−721.5, 571.6	0.82	−4.1	−39.7, 31.5	0.82	−174.5	−2965.1, 2616.0	0.9
musculoskeletal	−385.8	−1338.7, 567.0	0.42	−40.7	−304.7, 223.3	0.76	−37.2	−296.8, 222.4	0.78	19.1	3.36, 34.7	0.02	−271.1	−1613.5, 1071.3	0.69
respiratory	−478.9	−3889.7, 2931.8	0.78	−71.9	−993.0, 849.3	0.88	−31.4	−940.0, 877.1	0.95	−2.5	−52.5, 47.5	0.92	−705.5	−4614.4, 3203.5	0.72
neurological	−319.7	−1522.9, 883.5	0.6	478.0	154.3, 801.6	0.004	477.9	159.2, 796.6	0.004	−3.1	−22.9, 16.8	0.76	99.8	−1460.6, 1660.2	0.9
urogenital	268.3	−2160.7, 2697.2	0.83	−37.9	−693.8, 617.9	0.91	−36.5	−683.2, 610.2	0.91	6.8	−28.8, 42.3	0.71	68.1	−2722.8, 2858.9	0.96
Soft tissue sarcoma (*n* = 356)															
Symptoms															
pain	−258.6	−574.7, 57.4	0.11	−50.5	−155.5, 54.5	0.35	−80.3	−200.8, 40.2	0.19	33.0	−80.1, 146.1	0.57	−442.1	−853.4, −30.8	0.04
swelling	−15.0	−348.0, 317.9	0.93	108.1	4.5, 211.6	0.04	134.6	15.8, 253.4	0.03	28.8	−82.5, 140.0	0.61	52.2	−383.3, 487.7	0.81
growing swelling	118.4	−230.5, 467.2	0.51	62.1	−55.9, 180.1	0.3	127.3	−8.4, 263.0	0.07	138.4	12.8, 264.1	0.03	235.2	−220.2, 690.6	0.31
sensory disturbance	120.4	−347.5, 588.3	0.61	−82.4	−244.2, 79.4	0.32	−99.8	−283.2, 83.6	0.29	166.1	−8.3, 340.6	0.06	163.3	−460.7, 787.3	0.61
Symptomclass															
circulatory	594.7	−216.2, 1405.6	0.15	−80.8	−350.1, 188.6	0.56	−98.3	−411.2, 214.7	0.54	58.9	−220.5, 338.3	0.68	415.7	−571.8, 1403.3	0.41
gastrointestinal	−54.5	−679.0, 570.0	0.86	−78.3	−284.8, 128.3	0.46	−99.2	−339.1, 140.8	0.42	121.1	−112.4, 354.6	0.31	−24.0	−852.7, 804.8	0.96
general	209.2	−280.0, 698.5	0.4	72.7	−53.5, 199.0	0.26	88.2	−58.2, 234.5	0.24	91.6	−42.0, 225.2	0.18	252.8	0−379.9, 885.6	0.43
integumental	−27.2	−638.4, 584.0	0.93	98.5	−123.4, 320.5	0.38	97.1	−167.9, 362.0	0.47	53.4	−157.4, 264.1	0.62	78.7	−669.0, 826.3	0.84
musculoskeletal	83.6	−555.1, 722.4	0.8	−61.0	−277.5, 155.5	0.58	−79.3	−324.9, 166.2	0.53	168.8	−64.3, 401.9	0.16	258.2	−595.3, 1111.6	0.55
respiratory	−267.8	−1658.2, 1122.6	0.71	−78.0	−538.7, 382.8	0.74	−98.9	−634.4, 436.6	0.72	−229.4	−686.2, 227.3	0.32	−673.1	−2287.0, 940.9	0.41
neurological	82.3	−371.6, 536.2	0.72	−83.3	−241.2, 74.7	0.3	−100.2	−277.6, 77.3	0.27	163.4	−8.6, 335.4	0.06	140.8	−474.5, 756.2	0.65
urogenital	−328.3	−1141.1, 484.5	0.43	−79.8	−349.2, 189.5	0.56	−101.3	−414.3, 211.6	0.53	122.4	−169.8, 414.6	0.41	−321.1	−1355.3, 713.1	0.54
Deep soft tissue sarcoma (*n* = 296)															
Symptoms															
pain	−204.0	−544.8, 136.7	0.24	−50.5	−164.9, 64.0	0.39	−85.4	−218.5, 47.7	0.21	36.6	−95.0, 168.2	0.59	−426.2	−878.8, 26.4	0.07
swelling	−164.4	−518.9, 190.1	0.36	109.5	−4.5, 223.6	0.06	142.0	9.7, 274.4	0.04	39.4	−92.0, 170.8	0.56	−114.0	−591.5, 363.5	0.64
growing swelling	65.1	−325.3, 455.3	0.74	26.7	−109.2, 162.5	0.7	111.2	−47.2, 269.5	0.17	162.1	6.8, 317.4	0.04	170.2	−355.5, 695.9	0.52
sensory disturbance	−95.7	−592.6, 401.2	0.71	−81.4	−259.4, 96.6	0.37	−102.3	−306.5, 101.8	0.33	181.9	−17.3, 381.2	0.07	−24.8	−691.6, 642.0	0.94
Symptomclass															
circulatory	−1.4	−928.6, 925.8	0.99	−79.5	−396.0, 237.0	0.62	−99.5	−473.0, 273.9	0.6	63.3	−269.5, 396.1	0.71	−112.3	−1211.4, 986.8	0.84
gastrointestinal	6.1	−616.2, 628.4	0.99	−78.3	−290.3, 133.7	0.47	−100.9	−350.9, 149.1	0.43	125.7	−127.6, 378.9	0.33	39.0	−800.9, 878.9	0.93
general	110.9	−486.1, 707.9	0.72	65.1	−79.9, 210.1	0.38	83.8	−85.6, 253.1	0.33	139.1	−27.2, 305.4	0.1	138.4	−678.4, 955.2	0.74
integumental	−300.6	−1886.9, 1285.8	0.71	−43.0	−585.1, 499.1	0.88	−57.7	−697.7, 582.3	0.86	50.2	518.6, 619.0	0.86	−397.0	−2270.8, 1476.8	0.68
musculoskeletal	146.1	−490.0, 782.1	0.65	−60.8	−282.8, 161.3	0.59	−80.8	−336.5, 175.0	0.54	174.0	−78.8, 426.7	0.18	325.2	−538.7, 1189.1	0.46
respiratory	−167.7	−1754.3, 1419.0	0.84	−76.7	−618.8, 465.4	0.78	−98.8	−738.7, 541.1	0.76	−321.4	−888.6, 245.9	0.27	−680.9	−2553.1, 1191.3	0.47
neurological	−119.6	−599.7, 360.5	0.62	−82.4	−255.6, 90.8	0.35	−102.7	−299.3, 94.0	0.31	178.7	−17.5, 374.8	0.07	−41.8	−698.5, 614.8	0.9
urogenital	−271.9	−1079.1, 535.3	0.51	−79.5	−355.1, 196.1	0.57	−102.5	−427.7, 222.7	0.54	126.2	−189.9, 442.3	0.43	−263.0	−1307.9, 781.8	0.62

Table 3. *Cont.*

	PI			DI								TI		
				PCI			SCI			TCI				
	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value	Beta	95% CI	*p*-Value
Superficial soft tissue sarcoma (*n* = 60)															
Symptoms															
pain	−230.3	−1429.3, 968.6	0.7	−87.8	−489.1, 313.5	0.66	−100.2	−507.8, 307.4	0.62	53.7	−176.1, 283.4	0.64	−215.0	−1630.1, 1200.1	0.76
swelling	743.1	−274.0, 1760.2	0.15	108.2	−164.4, 380.8	0.43	106.8	−178.6, 392.2	0.46	−35.1	−200.6, 130.5	0.67	804.1	−324.5, 1932.7	0.16
growing swelling	188.0	−634.0, 1010.0	0.65	204.2	−36.1, 444.4	0.09	206.2	39.2, 451.6	0.1	61.6	−92.1, 215.2	0.43	335.0	−627.6, 1297.5	0.49
sensory disturbance	1705.0	394.7, 3015.3	0.02	−87.8	−489.1, 313.5	0.66	−84.5	−492.4, 323.4	0.68	55.3	−259.8, 370.5	0.73	2037.6	199.2, 3876.1	0.03
Symptomclass															
circulatory	2324.5	682.96, 3966.10	0.006	−87.79	−595.32, 419.73	0.73	−94.42	−609.88, 421.04	0.71	39.66	−342.74, 422.056	0.84	2804.1	612.36, 4995.81	0.01
general	650.0	−274.7, 1574.7	0.16	108.2	−152.4, 368.7	0.41	108.7	−162.5, 379.9	0.42	−43.4	−202.4, 115.5	0.59	693.9	−368.2, 1756.0	0.2
integumental	−360.6	−1196.2, 475.0	0.39	163.5	−94.6, 421.7	0.21	175.5	−92.7, 443.7	0.2	57.3	−98.7, 213.3	0.46	−121.4	−1100.3, 857.5	0.8
respiratory	−665.7	−3655.0, 2323.6	0.66	−84.3	−946.3, 777.7	0.85	−98.4	−973.6, 776.8	0.82	44.0	−491.6, 579.5	0.87	−719.7	−3992.8, 2553.3	0.66
neurological	1705.0	394.7, 3015.3	0.01	−87.8	−489.1, 313.5	0.66	−84.5	−492.4, 323.4	0.68	55.3	−259.8, 370.5	0.73	2037.6	199.2, 3876.1	0.03
Benign bone tumor (*n* = 61)															
Symptoms															
pain	41.2	−270.3, 352.7	0.79	−83.9	−240.8, 72.9	0.29	−85.7	−242.0, 70.6	0.28	182.2	−375.7, 740.2	0.5	−308.5	−2010.2, 1393.2	0.71
swelling	241.1	−23.1, 505.4	0.07	77.4	−77.8, 232.5	0.32	73.6	−81.2, 228.4	0.34	−257.4	−777.0, 262.2	0.31	−341.8	−1913.9, 1230.3	0.65
growing swelling	383.0	17.8, 748.1	0.04	142.2	−76.06, 360.4	0.2	141.7	−75.9, 359.3	0.2	−143.4	−734.6, 447.7	0.61	301.1	−1401.0, 2003.3	0.71
sensory disturbance	108.4	−566.3, 783.1	0.75	−82.0	−475.5, 311.5	0.68	−85.7	−477.9, 306.6	0.66	−89.4	−937.5, 758.7	0.83	−10.5	−2429.0, 2408.1	0.99
Symptomclass															
gastrointestinal	−243.7	−1185.9, 698.6	0.61	−83.5	−635.0, 468.1	0.76	−87.1	637.0, 462.8	0.75	NA	NA	NA	NA	NA	NA
general	301.1	−249.3, 851.5	0.28	−24.3	−216.1, 167.6	0.8	−29.9	−221.1, 161.3	0.76	178.9	−982.6, 1340.5	0.75	NA	NA	NA
musculoskeletal	−120.1	−421.8, 181.5	0.43	−92.8	−270.4, 84.7	0.3	−95.9	−272.8, 81.0	0.28	−222.9	−807.1, 361.2	0.43	−915.8	−2550.0, 718.4	0.25
neurological	108.4	−566.3, 783.1	0.75	−82.0	−475.5, 311.5	0.68	−85.7	−477.9, 306.6	0.66	−89.4	−937.5, 758.7	0.83	−10.5	−2429.0, 2408.1	0.99
Benign soft tissue tumor (*n* = 213)															
Symptoms															
pain	−439.3	−962.4, 83.7	0.1	−11.0	−110.9, 89.0	0.83	−28.4	−131.3, 74.5	0.59	2.5	−40.7, 45.7	0.91	−388.7	−1094.6, 317.3	0.28
swelling	91.7	−663.4, 846.8	0.81	69.1	−43.4, 181.6	0.23	10.9	−103.7, 125.6	0.85	−25.2	−72.5, 22.0	0.29	203.4	−791.2, 1198.0	0.69
growing swelling	348.5	−176.0, 873.1	0.19	34.6	−67.6, 136.8	0.51	7.8	−97.8, 113.5	0.88	−34.6	−76.9, 7.7	0.11	377.3	−323.4, 1078.2	0.29
sensory disturbance	292.0	−323.8, 907.8	0.35	153.7	35.9, 271.5	0.01	134.3	10.3, 258.3	0.03	−41.0	−91.4, 9.5	0.11	584.0	−224.5, 1392.5	0.16
Symptomclass															
circulatory	−861.2	−4374.3, 2651.8	0.63	−69.1	−729.2, 591.0	0.84	−94.1	−788.5, 600.3	0.79	2.5	−254.9, 259.8	0.99	−1213.2	−5239.2, 2812.8	0.55
gastrointestinal	−870.3	−4383.3, 2642.7	0.63	−69.1	−729.2, 591.0	0.84	−61.9	−756.4, 632.6	0.86	NA	NA	NA	NA	NA	NA
general	NA	NA	NA	−24.3	−165.9, 117.3	0.74	−115.5	−254.1, 23.2	0.1	−44.6	−103.2, 14.0	0.14	NA	NA	NA
integumental	2447.1	898.8, 3995.5	0.002	−55.6	−438.8, 327.5	0.78	−73.8	−476.7, 329.2	0.72	30.7	−99.1, 160.6	0.64	2666.1	679.8, 4652.4	0.009
musculoskeletal	81.3	−863.8, 1026.4	0.87	114.6	−62.0, 291.2	0.2	98.5	−81.9, 278.8	0.28	13.0	−67.2, 93.2	0.75	562.0	−755.1, 1879.1	0.4
neurological	292.0	−323.8, 907.8	0.35	153.7	35.9, 271.5	0.01	134.3	10.3, 258.3	0.03	−41.0	−91.4, 9.5	0.11	584.0	−224.5, 1392.5	0.16

Table 3. *Cont.*

	PI			DI									TI		
				PCI			SCI			TCI					
	Beta	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**	**Beta**	**95% CI**	***p*-Value**
Benign deep soft tissue tumor (*n* = 172)															
Symptoms															
pain	−323.9	−878.3, 230.5	0.25	32.4	−46.9, 111.7	0.42	7.2	−81.6, 95.9	0.87	3.7	−48.7, 56.1	0.89	−208.8	−966.0, 548.4	0.59
swelling	−77.7	−816.0, 660.5	0.84	45.7	−40.6, 131.9	0.3	−12.3	−107.6, 83.0	0.8	−34.2	−88.9, 20.5	0.22	1.0	−971.2, 973.2	0.99
growing swelling	309.5	−259.8, 878.9	0.28	38.2	−45.5, 121.9	0.37	7.7	−86.5, 101.9	0.87	−58.7	−112.7, −4.7	0.03	383.3	−391.8, 1158.5	0.33
sensory disturbance	150.7	−587.2, 888.7	0.69	73.3	−35.9, 182.4	0.19	53.5	−70.9, 177.9	0.4	−88.6	−161.3, −16.0	0.02	399.6	−612.9, 1412.1	0.44
Symptomclass															
circulatory	−748.0	−4050.1, 2554.1	0.66	−49.9	−537.4, 437.6	0.84	−78.9	−634.5, 476.6	0.78	7.1	−279.0, 293.2	0.96	−1040.8	−4876.7, 2795.2	0.59
gastrointestinal	−757.1	−4059.1, 2544.9	0.66	−49.9	−537.4, 437.6	0.84	−46.8	−602.4, 508.9	0.87	NA	NA	NA	NA	NA	NA
general	NA	NA	NA	−47.9	−153.7, 58.0	0.37	−137.8	−249.3, −26.4	0.02	−52.1	−118.3, 14.2	0.12	NA	NA	NA
integumental	−370.3	−2290.9, 1550.4	0.7	−34.5	−380.3, 311.3	0.84	−61.7	−455.8, 332.3	0.76	5.6	−197.5, 208.7	0.96	−1061.9	−3783.6, 1659.9	0.44
musculoskeletal	89.9	−868.8, 1048.6	0.85	165.0	26.7, 303.4	0.02	144.1	−9.2, 297.3	0.07	15.6	−83.0, 114.2	0.76	771.7	−627.8, 2171.2	0.28
neurological	150.7	−587.2, 888.7	0.69	73.3	−35.9, 182.4	0.19	53.5	−70.9, 177.9	0.4	−88.6	−161.3, −16.0	0.02	399.6	−612.9, 1412.1	0.44
Benign superficial soft tissue tumor (*n* = 41)															
Symptoms															
pain	−579.5	−2123.0, 964.1	0.45	−225.5	−777.4, 326.5	0.41	−210.3	−724.4, 303.8	0.41	18.2	−12.7, 49.0	0.24	−466.4	−2612.5, 1679.6	0.66
swelling	1208.0	−3103.4, 5518.6	0.57	177.1	−1132.2, 1486.5	0.78	173.1	−1107.3, 1453.6	0.78	NA	NA	NA	NA	NA	NA
growing swelling	233.7	−1109.6, 1577.1	0.73	−47.2	−525.6, 431.3	0.84	−53.0	−512.9, 406.9	0.82	22.3	−1.5, 46.2	0.07	−60.0	−1784.0, 1663.9	0.94
sensory disturbance	213.6	−1130.1, 1557.3	0.75	290.6	−174.2, 755.5	0.21	287.9	−158.7, 734.6	0.2	7.8	−17.0, 32.6	0.52	376.7	−1319.7, 2073.0	0.65
Symptomclass															
integumental	6596.1	4350.1, 8842.2	<0.001	−165.8	−1475.3, 1143.8	0.8	−152.4	−1433.3, 1128.4	0.81	43.3	−4.8, 91.4	0.08	6216.6	3683.2, 8750.0	<0.001
musculoskeletal	399.9	−2697.3, 3497.0	0.8	−183.7	−1125.1, 757.7	0.69	−187.4	−1107.2, 732.5	0.68	3.7	−47.1, 54.5	0.88	−131.5	−3594.1, 3331.2	0.94
neurological	213.6	−1130.1, 1557.3	0.75	290.6	−174.2, 755.5	0.21	287.9	−158.7, 734.6	0.2	7.8	−17.0, 32.6	0.52	376.7	−1319.7, 2073.0	0.65

’ The influence of symptoms was analyzed across all sarcoma subgroups and intervals. Groups with insufficient symptom data to allow for statistically reliable analysis across all intervals (result NA) are not included in this table. ° For “symptoms”, “no pain/swelling/growing swelling” was used as a reference. For “symptomclass”, “no symptom of this class” was used as a reference.

3.2.2. Gastrointestinal Symptoms

Gastrointestinal symptoms were more common in deep malignant tumors, particularly deep STS, where constipation was reported by 2.0% of patients. These symptoms were almost absent in benign tumors. Gastrointestinal symptoms did not have a statistically significant impact on any interval of the diagnostic pathway (PI, diagnostic interval (DI) or TI), indicating that their infrequency and nonspecific nature may not significantly influence patient behavior or diagnostic processes (see Tables 2 and 3).

3.2.3. General Symptoms

General symptoms, including pain and swelling, were prevalent across several tumor types. Pain was reported by 79.3% of patients with bone sarcomas (BS), 44.3% with deep STS and 39.5% with benign superficial soft tissue tumors (BSTT). Swelling was observed in 75.0% of patients with superficial STS and was also highly prevalent in deep and superficial BSTT. Growing swelling was reported by 35.0% of patients with superficial STS and 37.6% with BSTT. In BS patients, pain significantly shortened the PI (β = 1787.5; $p < 0.001$) and the TI (β = 2556.8; $p < 0.001$), underscoring its role as a critical symptom prompting earlier medical consultation and facilitating timely diagnosis and treatment. Conversely, swelling did not significantly impact the PI but significantly lengthened the primary care interval (PCI) (β = 108.1; p = 0.04) and secondary care interval (SCI) (β = 134.6; p = 0.03) in STS patients. This indicates potential delays in referral and diagnosis due to underrecognition of the symptom's severity by primary and secondary care providers. Growing swelling significantly lengthened the PI in patients with benign tumors of bone (BBT) (β = 383.0; p = 0.04) and prolonged the PCI (β = 433.2; p = 0.007) and SCI (β = 433.7; p = 0.006) in BS patients, resulting in an extended TI (β = 1637.4; p = 0.02). These findings suggest that growing swelling may be perceived as less urgent, leading to delays in both patient presentation and progression through the healthcare system. Emphasizing the importance of the timely evaluation of enlarging masses is crucial to prevent diagnostic delays (see Tables 2 and 3).

3.2.4. Integumentary Symptoms

Integumentary symptoms, such as discoloration and ulcerating swelling, were more common in superficial STS, with discoloration reported in 11.7% and ulceration in 6.7% of patients. Discoloration was also reported in 2.4% of patients with benign superficial BSTT.

In patients with BSTT, integumentary symptoms significantly lengthened the PI (β = 2447.1; p = 0.002) and the TI (β = 2666.1; p = 0.009), with even longer delays observed in benign superficial STT (PI β = 6596.1; $p < 0.001$; TI β = 6216.6; $p < 0.001$). These substantial delays may be due to patients perceiving skin changes as benign or cosmetic issues, underscoring the necessity for public education on the potential seriousness of integumentary symptoms and encouraging prompt medical evaluation (see Tables 2 and 3).

3.2.5. Musculoskeletal Symptoms

Musculoskeletal symptoms like loss of function were primarily observed in BS (15.9%) and BBT (19.7%) and were rare in other tumor types. While these symptoms showed a tendency to shorten the PI in BS and BBT patients, they significantly prolonged the PCI in benign deep BSTT (β = 165.0; p = 0.02) and the tertiary care interval (TCI) in BS patients (β = 19.1; p = 0.02). This suggests the potential misinterpretation or underestimation of musculoskeletal symptoms by healthcare providers, highlighting the need for improved referral pathways and clinician education to reduce delays in diagnosis and treatment initiation (see Tables 2 and 3).

3.2.6. Neurological Symptoms

Neurological symptoms, particularly sensory disturbances, were most common in benign superficial BSTT (43.9%) and deep STS (11.8%). In superficial STS, neurological symptoms significantly lengthened the PI (β = 1705.0; p = 0.01) and the TI (β = 2037.6; p = 0.03), indicating delays in seeking medical attention.

Additionally, sensory disturbances significantly prolonged the PCI and SCI in BS (PCI β = 549.5; p = 0.002; SCI β = 550.1; p = 0.002) and benign BSTT (PCI β = 153.7; p = 0.01; SCI β = 134.3; p = 0.03). These findings suggest that neurological symptoms may be misattributed to less serious conditions, such as neuropathies or musculoskeletal issues, leading to delays in the diagnostic process. Enhancing awareness among patients and clinicians regarding the potential significance of neurological symptoms in the context of mesenchymal tumors is essential (see Tables 2 and 3).

3.2.7. Respiratory Symptoms

Respiratory symptoms were rare across all tumor types, with a slight peak in superficial STS, where 1.7% of patients reported dyspnea. Due to their low prevalence, respiratory symptoms did not have a significant impact on intervals of the diagnostic pathway (see Tables 2 and 3).

3.2.8. Urogenital Symptoms

Urogenital symptoms were slightly more frequent in BS and deep STS, with hematuria reported in 1.2% and 1.0% of patients, respectively. These symptoms did not significantly affect the diagnostic process, likely due to their rarity and nonspecific presentation (see Tables 2 and 3).

3.2.9. Incidental Findings

Incidental findings were more common in benign tumors, particularly in BBT (24.6%) and benign deep BSTT (18.6%). Such findings emphasize the importance of comprehensive evaluations and imaging studies, even when patients are asymptomatic. They present an opportunity for early detection and management, potentially preventing complications or disease progression (see Table 2).

4. Discussion

This study addresses a critical gap in the literature by comprehensively analyzing how various symptoms and symptom classes influence the intervals of the diagnostic pathway in patients with mesenchymal tumors, specifically focusing on bone sarcomas (BS), soft tissue sarcomas (STS) and their benign counterparts. Our findings reveal that pain emerges as a pivotal symptom that significantly reduces the patient interval (PI) and overall total interval in BS and STS patients by prompting earlier medical consultation. Conversely, symptoms like growing swellings, sensory disturbances and integumentary symptoms were associated with diagnostic delays, extending intervals such as the PI, primary care interval (PCI), secondary care interval (SCI) and tertiary care interval (TCI) in both malignant and benign tumors. Existing literature primarily emphasizes pain and lumps as the predominant symptoms reported by sarcoma patients [15–18]. However, their influence on intervals of the diagnostic pathway remains inconsistent. For instance, Brasme et al. identified pain as a factor that could lengthen the diagnostic pathway, suggesting that pain should be interpreted as a consequence of the tumor growth and size rather than a sole indicator [15]. In contrast, our studies align with studies by Pan et al. and Biscaglia et al., indicating that pain shortens the diagnostic timeline by prompting earlier consultation [17,18]. Sneppen et al. further refined this by distinguishing between constant

and intermittent pain, showing that constant pain leads to shorter delays compared to intermittent pain [16]. The discrepancy in these findings underscores the complexity of symptom interpretation in sarcoma patients. The acceleration of diagnosis in patients experiencing pain may be attributed to pain being perceived as an alarming and disruptive symptom, prompting patients to seek medical attention promptly [6]. Pain is often associated with more aggressive or rapidly growing tumors, which may heighten patient concern [7,17]. In contrast, symptoms like swelling or sensory disturbances might be perceived as benign or attributed to less serious conditions, leading to delays in seeking care [7,19]. Swelling may be considered a normal response to injury or overuse, and sensory disturbances might be misattributed to neuropathies or musculoskeletal issues [6]. Our study also highlights that the impact of these symptoms varies between tumor types and locations. For example, growing swellings significantly delayed diagnosis in both BS and benign tumors of bone (BBT), suggesting that patients may not recognize the urgency of this symptom regardless of malignancy status. Additionally, integumentary symptoms led to substantial delays in patients with benign superficial tumors, indicating that skin changes are often underestimated in their potential seriousness. These findings have important clinical and public health implications. Improving patient awareness about the significance of symptoms like swelling and sensory disturbances is crucial. Educational campaigns and patient education materials should emphasize that persistent or unexplained symptoms warrant medical evaluation. For healthcare providers, particularly in primary and secondary care, enhancing the recognition of potential sarcoma symptoms is essential. Training programs and clinical guidelines may reinforce the importance of considering mesenchymal tumors in differential diagnoses when patients present with these symptoms. Optimizing diagnostic pathways involves developing clear referral protocols to ensure timely evaluation by specialists. Implementing standardized guidelines for imaging and referral can help reduce delays. For instance, any persistent pain, increasing swelling or restricted movement lasting more than four weeks should prompt consideration of BS and warrant further radiological investigation, as suggested by Hardes et al. [20]. The European Society for Medical Oncology (ESMO) clinical practice guidelines recommend appropriate imaging modalities—such as MRI for STS and conventional X-rays followed by MRI for BS—before invasive procedures like biopsies are performed [21,22]. From a public health perspective, our findings support the need for policy initiatives that promote early detection strategies. The centralization of care within a hub-and-spoke-model, as highlighted by studies showing improved outcomes when patients are managed at specialized sarcoma centers [23–26], should be encouraged. Healthcare policies should facilitate resource allocation to support these centers and streamline referral processes. A major strength of this study is the comprehensive analysis of a large, prospectively collected dataset from multiple institutions within the Swiss Sarcoma Network. By including both benign and malignant tumors and considering a wide range of symptoms and diagnostic intervals, we provide a nuanced understanding of the diagnostic pathway in mesenchymal tumors. The novel approach of grouping symptoms into clinically relevant categories adds depth to the analysis and highlights specific areas where interventions could be targeted. However, there are limitations to consider. The potential selection bias inherent in focusing on patients referred to a sarcoma center suggests that someone along the diagnostic pathway had already considered the possibility of a sarcoma, which may not reflect the experiences of all patients with mesenchymal tumors. Additionally, the granular nature of our analysis resulted in smaller sample sizes within certain tumor subgroups and symptom classes, which may have limited the statistical power to detect some associations. The retrospective design and reliance on medical records may also introduce biases related to symptom reporting and documentation. For example, symptoms were listed in relation to the tumor disease

without screening for pre-existing conditions, such as peripheral neuropathy, that could explain symptoms like sensory disturbance. This unfiltered reporting approach may impact the specificity of symptom attribution to the tumor. The classification of "swelling" as a local increase in volume—excluding other common descriptors like "bulges, bumps and lumps"—may have led to deviations from the norm in tumor distribution and weakened comparability with other studies. Further research is warranted to delve deeper into how specific symptom characteristics influence diagnostic delays. For instance, distinguishing between types of pain (constant vs. intermittent) and their effects on PI and TI could provide more precise insights. Investigating whether these effects apply uniformly across all bone sarcomas or are limited to specific entities would enhance understanding. When considering tumor locations by body regions, the distribution in our study largely aligns with the literature. Minor differences include a slightly higher proportion of limb girdle tumors in BS and BSTT, as well as more deep trunk tumors in STS, while extremities are slightly less frequent. The occurrence of viscera tumors (2.8%) matches the rarity reported in the literature (<5%). These variations may reflect differences in patient population or classification criteria. Considering the broad range of tumor locations, from extremities to intraperitoneal regions and beyond, potential biases may have been introduced in assessing the effects of symptoms on diagnostic time intervals. Future studies could address this by examining the impact of symptoms on specific sarcoma subtypes and conducting a more detailed analysis of individual symptoms, such as "swelling". Additionally, focusing on how the tumor location influences the perception of symptoms could yield valuable insights and contribute to the refinement of diagnostic pathways. Exploring patient-related factors, such as personality traits and health-seeking behaviors, could identify groups at a higher risk for diagnostic delays. Qualitative studies examining patient perceptions of symptoms and barriers to seeking care would be valuable. Additionally, research focusing on healthcare providers is crucial. Surveys and educational assessments could determine the level of awareness among general practitioners and specialists regarding mesenchymal tumors and associated symptoms. Investigating systemic barriers within the healthcare system that contribute to delays, such as access to imaging modalities or specialist referrals, would inform policy interventions. Longitudinal studies assessing the impact of diagnostic delays on long-term patient outcomes, including survival rates and quality of life, are also essential to fully understanding the implications of our findings.

5. Conclusions

In conclusion, this study demonstrates that pain accelerates the diagnostic process in mesenchymal tumors by prompting earlier medical consultation, while symptoms like swelling and sensory disturbances contribute to significant delays across various intervals of the diagnostic pathway. These findings highlight the need for increased awareness among both patients and healthcare providers regarding the potential seriousness of these symptoms. Implementing educational initiatives, optimizing referral protocols and promoting early detection strategies are crucial steps toward reducing diagnostic delays and improving patient outcomes. Addressing these challenges requires a concerted effort from clinicians, policymakers and public health professionals to enhance the care of patients with mesenchymal tumors.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Table A1 presents the median lengths of each interval within the diagnostic pathway, including the patient interval (PI), primary care interval (PCI), secondary care interval (SCI), tertiary care interval (TCI), diagnostic interval (DI) and total interval (TI) [10]. These baseline measurements provide context for the subsequent analysis of symptom impact on interval length.

Table A1. Length of the patient, diagnostic, primary care, secondary care, tertiary care and total interval in weeks.

	Overall	Bone Sarcoma		Soft-Tissue Sarcoma				Benign Bone Tumor		Benign Soft-Tissue Tumor			
				Deep and Superficial	Deep		Superficial			Deep and Superficial	Deep		Superficial
	n = 712	*n* = 82	*p*-Value [a]	*n* = 356	*n* = 296	*p*-Value [b]	*n* = 60	*n* = 61	*p*-Value [c]	*n* = 213	*n* = 172	*p*-Value [d]	*n* = 41
Patient Interval, weeks	90.0 (22.0, 284.0)	7.8 (2.7, 27.5)	0.46	8.8 (2.1, 29.0)	8.3 (2.0, 24.4)	**0.01**	20.7 (4.2, 130.6)	19.1 (4.3, 52.1)	0.17	21.6 (6.4, 109.6)	19.8 (6.3, 75.1)	0.22	29.9 (9.0, 176.4)
Diagnostic Interval, weeks	46.0 (25.5, 95.5)	7.6 (3.1, 14.2)	0.89	6.7 (3.7, 13.3)	6.9 (3.9, 13.7)	0.22	5.7 (3.6, 9.3)	19.8 (6.8, 79.7)	**0.005**	6.0 (3.6, 13.4)	6.0 (3.6, 14.6)	0.35	5.6 (3.6, 9.5)
Primary Care Interval, weeks	4.0 (0.0, 18.5)	0.6 (0.1, 6.5)	0.14	0.4 (0.0, 1.4)	0.4 (0.0, 1.3)	0.31	0.0 (0.0, 1.4)	0.8 (0.0, 44.9)	0.30	0.7 (0.0, 3.1)	0.7 (0.0, 4.4)	0.15	0.3 (0.0, 1.0)
Secondary Care Interval, weeks	26.0 (12.0, 57.0)	2.2 (0.9, 6.6)	**0.005**	4.3 (2.1, 9.1)	3.9 (1.9, 8.1)	**0.01**	8.1 (4.9, 10.2)	2.6 (1.0, 10.7)	0.47	3.5 (1.6, 7.5)	3.9 (1.7, 10.0)	0.14	2.6 (1.5, 3.8)
Tertiary Care Interval, weeks	14.0 (5.0, 26.3)	2.1 (1.0, 3.7)	**0.006**	1.3 (−0.6, 3.4)	1.6 (−0.2, 3.6)	**0.01**	0.9 (−3.3, 1.9)	3.1 (2.0, 8.1)	0.14	2.6 (1.8, 4.1)	2.6 (1.7, 4.0)	0.36	2.7 (1.9, 5.8)
Total Interval, weeks	213.0 (84.0, 762.2)	22.8 (11.9, 56.7)	0.82	23.3 (10.4, 59.4)	20.9 (10.4, 55.3)	0.07	34.8 (12.3, 148.0)	100.5 (48.1, 206.6)	0.22	48.2 (17.7, 193.3)	43.0 (14.7, 150.6)	**0.04**	138.1 (29.1, 304.4)

[a]: The *p*-value was calculated by a Wilcoxon rank sum test with continuity correction between STS (deep and superficial) and BS. [b]: The *p*-value was calculated by a Wilcoxon rank sum test with continuity correction between deep STS and superficial STS. [c]: The *p*-value was calculated by a Wilcoxon rank sum test with continuity correction between benign soft-tissue tumors (deep and superficial) and benign bone tumors. [d]: The *p*-value was calculated by a Wilcoxon rank sum test with continuity correction between deep benign soft-tissue tumors and superficial benign soft-tissue tumors.

Table A2. Prevalence of Symptoms across Tumor Types.

Characteristic	BS	STS			BBT	BSTT		
		Deep and Superficial STS	Deep STS	Superficial STS		Deep and Superficial BSTT	Deep BSTT	Superficial BSTT
	n = 82	*n* = 356	*n* = 296	*n* = 60	*n* = 61	*n* = 213	*n* = 172	*n* = 41
Symptom class								
gastrointestinal	3 (3.7%)	21 (5.9%)	21 (7.1%)	0 (0.0%)	1 (1.6%)	1 (0.5%)	1 (0.6%)	0 (0.0%)
urogenital	2 (2.4%)	12 (3.4%)	12 (4.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
circulatory	1 (1.2%)	12 (3.4%)	9 (3.0%)	3 (5.0%)	0 (0.0%)	1 (0.5%)	1 (0.6%)	0 (0.0%)
general	72 (87.8%)	279 (78.4%)	237 (80.1%)	42 (70.0%)	46 (75.4%)	182 (85.5%)	141 (82.0%)	41 (100.0%)
integumental	2 (2.4%)	22 (6.2%)	3 (1.0%)	19 (31.7%)	0 (0.0%)	5 (2.4%)	3 (1.7%)	2 (4.9%)
neurological	9 (11.0%)	43 (12.1%)	38 (12.8%)	5 (8.3%)	2 (3.3%)	42 (19.7%)	24 (14.0%)	18 (43.9%)
respiratory	1 (1.2%)	4 (1.1%)	3 (1.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
musculoskeletal	17 (20.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
incidental finding	9 (11.0%)	47 (13.2%)	43 (14.5%)	4 (6.7%)	15 (24.6%)	32 (15.0%)	32 (18.6%)	0 (0.0%)
NA	0 (0.0%)	4 (1.1%)	3 (1.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Benchmarking Time-to-Treatment Initiation in Sarcoma Care Using Real-World-Time Data

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Simple Summary: Understanding the time it takes for sarcoma patients to start treatment after their diagnosis is essential, as a rapid onset of therapy could mean better survival chances. Sarcomas, which are rare and complex cancers, often require swift and specialized care. Our study delved into this time period, known as time-to-treatment initiation (TTI), across a variety of sarcoma cases using detailed, real-world-time data. We found that the length of TTI can differ significantly depending on the type of sarcoma and where the patients receive care. Notably, our comprehensive data collection process has shown that reported TTI using RWTD reflects a thorough account of the patient's experience from diagnosis to treatment start, which is crucial for developing a healthcare system that focuses on delivering value-based care. The insights from our analysis pinpoint where improvements are needed and how specialized sarcoma centers can better coordinate care to start treatment promptly, especially for those cases where early intervention is critical.

Abstract: Benchmarking is a fundamental tool for enhancing quality within a patient-centered healthcare framework. This study presents an analysis of time-to-treatment initiation (TTI) for sarcoma patients, utilizing a database encompassing 266 cases from the Swiss Sarcoma Network. Our findings indicate a median TTI of 30 days across the cohort, with bone sarcomas and deep soft tissue sarcomas demonstrating a shorter median TTI of 28 days, followed by superficial soft tissue sarcomas at 42 days. The data reveal that the use of real-world-time data (RWTD) may account for a longer TTI observed, as it offers more comprehensive capture of patient journeys, unlike conventional datasets. Notably, variability in TTI was observed between different treatment institutions, which underscores the need for standardized processes across centers. We advocate for a selective referral system to specialized centers to prevent capacity overload and ensure timely treatment initiation. Our analysis also identified significant delays in TTI for unplanned 'whoops'-resections, highlighting the importance of early specialist referral in optimizing treatment timelines. This study emphasizes the potential benefits of a streamlined, data-informed approach to sarcoma care. However, further research is required to establish the direct impact of integrated care models on TTI and patient outcomes in the context of sarcoma treatment.

Keywords: sarcoma; soft-tissue-sarcoma; time-to-treatment initiation (TTI); bone-sarcoma; integrated-practice units (IPUs); value-based healthcare system (VBHCS); multidisciplinary team/sarcoma board (MDT/SB); real-world-time data (RWTD)

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1. Introduction

Benchmarking plays a pivotal role in a patient-centered and quality-driven healthcare system [1–3]. It goes beyond identifying areas that need improvement, providing insights into various aspects like overall performance, treatment timelines, and efficiency [4]. To implement benchmarking in healthcare, the foundation of a value-based healthcare system (VBHCS) is a prerequisite [5–10]. This system is characterized by its emphasis on transparency, trust, and quality, based on real-world-time data (RWTD) assessment. Within the framework of VBHCS, sarcoma care can be assessed and systematically compared across diverse treatment facilities and multidisciplinary treatment teams (MDTs). Healthcare providers can make informed decisions based on data-driven insights, identify areas requiring improvement, and optimize resource allocation. The VBHCS forms the basis for developing strategies aimed at enhancing the overall quality of sarcoma care [11–13].

In sarcoma care, patient treatment has traditionally revolved around MDTs, which have been approved and accepted as an important quality indicator [11,13,14]. MDTs unite professionals from diverse disciplines to collectively elevate the standard of patient care. This is particularly important in sarcomas, a rare and highly heterogeneous group of mesenchymal tumors, where both diagnosis and treatment present significant challenges [15–18]. MDTs were proven to maintain treatment quality through their adherence to established guidelines [11]. This is particularly noteworthy when compared to treatments conducted in non-specialized sarcoma centers. Hence, it is imperative that, prior to the initiation of therapeutic interventions, a referral to an MDT be prioritized [11–13,19].

The Swiss Sarcoma Network (SSN) is dedicated to implementing a RWTD approach aligned with VBHCS principles to enhance benchmarking in sarcoma care [1,20,21]. This initiative includes the development of Sarconnector, a digital platform for RWTD assessment and automated analysis, enabling data-driven decisions to optimize resources and improve patient-centered outcomes [1,5,20,22]. Collaborating with an international consortium, the SSN has identified key quality indicators (QIs) for sarcoma management, with a particular focus on the 'time-to-treatment initiation' (TTI). TTI is pivotal for timing interventions effectively, ensuring optimal treatment processes, and facilitating continuous improvement through benchmarking [23,24]. This metric, measuring the interval from diagnosis to treatment start, is crucial in various tumor diseases and particularly significant in sarcoma care, where its definition is adapted to specific treatment contexts [25–27].

TTI is highly important for patient care and overall survival. Specifically, a delay has consistently been associated with lower overall survival rates [23]. In addition, an unclear or lengthy TTI creates psychological distress for patients, leading to increased anxiety and emotional strain. This emphasizes the importance of prompt care initiation [28–30]. TTI provides insight into treatment processes by revealing waiting times and promoting patient engagement in their care decisions. This involvement not only empowers patients but also enhances the relationship between healthcare teams and their patients. Additionally, TTI is essential for evaluating the efficiency of MDTs, which are responsible for treatment decisions, planning, and overseeing diagnostic and therapeutic processes [11,12,23,24].

Analysis of data from the US National Cancer Database (NCDB) between 2004 and 2013 indicates a median TTI of 22 days for both bone and soft tissue sarcomas, with a non-significant 30% increase over this period due to improvements in diagnostics and treatments [24]. A TTI exceeding 30 days correlates with poorer survival rates in high-grade soft tissue sarcomas, suggesting the importance of initiating treatment within this timeframe [23,28]. Challenges like unplanned resections and a lack of coordinated care, which contribute to prolonged TTI, highlight the need for management in specialized MDTs and emphasize the complex interplay of patient, socioeconomic, and healthcare system factors affecting TTI [31–35]. Notably, longer TTI can sometimes be beneficial, allowing for advanced diagnostics and referrals to specialized centers. This underscores the importance of benchmarking in identifying areas needing improvement and implementing a VBHCS [24,28,31–35].

The focus of this paper is, first, to assess and compare TTI in a real-world-time setting within multidisciplinary sarcoma centers and associated networks, consisting of two tertiary referral centers. Second, we want to compare our TTI to the literature, and third, we want to explore the potential of benchmarking TTI to identify potential areas for improvement.

2. Materials and Methods

2.1. Study Design and SSN

This study uses RWTD from patients registered within the SSN, established in 2018. The register functions as a national data platform connected to the weekly Multidisciplinary-Team/Sarcoma-Board (MDT/SB) meeting, facilitating knowledge exchange among sarcoma experts hailing from various institutions. This fosters transdisciplinary collaboration, promotes transparent practices in sarcoma therapy, and simultaneously yields valuable data for quality assessments. The process of data entry is a collaborative endeavor that engages physicians from diverse disciplines who are integrated into the MDT/SB meetings. These meetings serve as forums for reviewing patient information, treatment adjustments, and outcomes, thereby ensuring the integrity of the data. This study used a retrospective analysis of a prospectively collected dataset (based on a prospectively collected real-world-time data warehouse/lake; Sarconnector® (PH&BF, Zürich, Switzerland). Using predefined quality indicators (QI), as outlined by Heesen et al. [20]. Patients' written informed consent is a prerequisite for registry participation.

2.2. Subjects and Data Extraction

This study included patients affiliated with the SSN who were presented at the SSN MDT/SB between January 2018 and September 2022 and had received a suspected diagnosis of a bone or soft tissue tumor [36]. The diagnosis was established through histological assessment following the guidelines provided by the World Health Organization (WHO). It was distinguished between benign, intermediate, and malignant diseases. To gather more comprehensive data, the Adjumed platform (Adjumed Services AG, Zurich, Switzerland; accessed on 15 July 2023) was utilized subsequently. Patients presented at the SB could be transferred primarily for suspected lesions or secondarily when histological examination revealed sarcoma. Transfers occurred across primary, secondary, and tertiary care centers, ensuring a diverse dataset for analysis.

2.3. Definitions, Outcome Measurements and Clinical Characteristics

In both bone sarcoma and soft tissue sarcoma, TTI was defined as the time span in days between the receipt of the final pathological report and the earliest of the following: the first surgical procedure, the date of the first radiation, or the date of the first systemic therapy. In the context of an unplanned "whoops" resection, TTI was defined as the interval between the non-oncological surgical resection and the initiation of the first planned oncological excision procedure or initiation of either radiation or chemotherapy by the SSN after being presented to the MDT/SSN. To our knowledge, no universally accepted definition of TTI in unplanned resections currently exists.

Through our RWTD warehouse (Adjumed, Zürich, Switzerland), for each patient included, the following demographic and treatment-specific information was extracted and recorded: Age, sex, and treatment institution (A, B, and C, which represent three other institutions that were merged together due to the low number of patients). Furthermore, the tumor's pathological characteristics were documented, including its categorization as benign, intermediate, or malignant. Date of histological report or date of unplanned "whoops" resection, date of first treatment (chemotherapy, radiotherapy, or surgery), and the date of any subsequent treatment.

Sarcomas of the extremities—affecting both the upper and lower extremities—as well as of the abdomen, including retroperitoneal sarcomas, were incorporated into the study. Sarcomas were divided into different compartments (superficial soft tissues, deep soft tissues, or bone). The size was assessed in categories of 0–50 mm, 51–100 mm, 101–150 mm,

and >151 mm [32]. The location according to the fascia was distinguishing between epifascial and subfascial. The type of excision has also been recorded as either "unplanned whoops" or "planned" excision.

2.4. Statistical Analysis

Continuous variables are presented as the median (1st quartile, 3rd quartile), while categorical variables are presented as a number (percentage). The normal distribution of variables was assessed visually using histograms or QQ-plots. When continuous data were normally distributed, a *t*-test was performed, while a Mann–Whitney-U test was performed for non-normally distributed data. Differences between categorical variables were tested using a Chi-square test or Fisher's exact test (if the expected value was below 5). A p-value < 0.05 was considered statistically significant. All analyses were conducted using R (version 4.3.1).

3. Results

3.1. Study Patient Population

During the time period from January 2018 to September 2022, a total of 475 patients with bone or soft tissue tumors were presented to the MDT/SB. For the analysis, benign lesions were excluded since control of time to treatment is less meaningful in view of tumor prognosis and quality measurement, as well as patients with a metastatic disease or without therapy by the SSN, thereby yielding a final cohort of 266 patients with an intermediate or malignant sarcoma diagnosis (Figure 1).

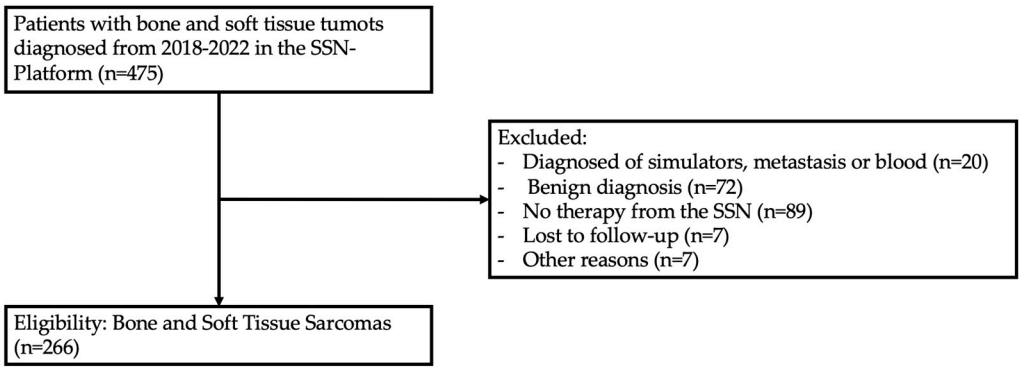


Figure 1. Decision tree on patient inclusion.

Of the 266 patients, 80.1% had a soft tissue sarcoma (STS), whereas bone sarcomas (BS) were seen in 19.9%. Superficial soft tissue sarcoma (S-STS) accounted for 22.5%, whereas deep soft tissue sarcomas (D-STS) were identified in 77.5% (Figure 2). Patients with a BS had a younger median age of 36 years compared to patients with a D-STS and an S-STS, each with a median age of 60 years. Females accounted for 44.7%, and the most common affected anatomical region was the lower extremity with 42.9%. Institution B accounted for the largest proportion with 53.4% (n = 142), followed by institution A with 30.1% (n = 80), and C made up 16.5% (n = 44) of the patients. Further details on baseline characteristics can be found in Table 1.

Table 1. Baseline characteristics of the SSN patients overall according to dignity and and specifically for bone sarcoma, deep and superficial soft tissue sarcoma according to dignity.

	Overall Sarcoma			**Bone Sarcoma**			**Deep Soft Tissue Sarcoma**			**Superficial Soft Tissue Sarcoma**		
	Overall	**Intermediate**	**Malignant**	**Overall**	**Intermediate**	**Malignant**	**Overall**	**Intermediate**	**Malignant**	**Overall**	**Intermediate**	**Malignant**
n, (%)	266 (100)	88 (33.1)	178 (66.9)	53 (19.9)	28 (52.8)	25 (47.2)	165 (62.0)	50 (30.3)	115 (69.7)	48 (18.1)	10 (20.8)	38 (79.2)
TTI, d (IQR)	30 (18–52)	49 (30–70)	25 (15–39)	28 (13–49)	42 (16–58)	20 (11–34)	28 (18–48)	56 (34–70)	22 (14–34)	42 (27–71)	43 (30–71)	42 (26–70)
Age, yrs *n* (IQR)	58 (42–70)	55 (33–66)	59 (47–72)	36 (20–56)	27 (17–46)	51 (22–66)	60 (49–72)	61 (48–71)	59 (49–73)	60 (46–71)	53 (34–65)	62 (53–73)
Female, *n* (%)	119 (44.7)	39 (44.3)	80 (44.9)	21 (39.6)	10 (35.7)	11 (44.0)	71 (43.0)	23 (46.0)	48 (41.7)	27 (56.3)	6 (60.0)	21 (55.3)
Whoops, *n* (%)	41 (15.4)	10 (11.4)	31 (17.4)	0 (0.0)	0 (0.0)	0 (0.0)	15 (9.1)	5 (10.0)	10 (8.7)	26 (54.2)	5 (50.0)	21 (55.3)
Institution, (%)												
A	80 (30.1)	37 (42.0)	43 (24.2)	23 (43.4)	18 (64.3)	5 (20.0)	48 (29.1)	17 (34.0)	31 (27.0)	9 (18.8)	2 (20.0)	7 (18.4)
B	142 (53.4)	40 (45.5)	102 (57.3)	23 (43.4)	8 (28.6)	15 (60.0)	90 (54.5)	25 (50.0)	65 (56.5)	29 (60.4)	7 (70.0)	22 (57.9)
C	44 (16.5)	11 (12.5)	33 (18.5)	7 (13.2)	2 (7.1)	5 (20.0)	27 (16.4)	8 (16.0)	19 (16.5)	10 (20.8)	1 (10.0)	9 (23.7)
Region, (%)												
Abdomen	36 (13.5)	6 (6.8)	30 (16.9)	0 (0.0)	0 (0.0)	0 (0.0)	34 (20.6)	5 (10.0)	29 (25.2)	2 (4.2)	1 (10.0)	1 (2.6)
Upper extremity	37 (13.9)	13 (14.8)	24 (13.5)	12 (22.6)	9 (32.1)	3 (12.0)	17 (10.3)	3 (6.0)	14 (12.2)	8 (16.7)	1 (10.0)	7 (18.4)
Axial	79 (29.7)	28 (31.8)	51 (28.6)	23 (43.4)	11 (39.3)	12 (48.0)	39 (23.6)	12 (24.0)	27 (23.5)	17 (35.4)	5 (50.0)	12 (31.6)
Lower extremity	114 (42.9)	41 (46.6)	73 (41.0)	18 (34.0)	8 (28.6)	10 (40.0)	75 (45.5)	30 (60.0)	45 (39.1)	21 (43.8)	3 (30.0)	18 (47.4)
Size, (%)												
0–50 mm	87 (32.7)	35 (39.8)	52 (29.2)	19 (35.8)	15 (53.6)	4 (16.0)	37 (22.4)	14 (28.0)	23 (20.0)	31 (64.5)	6 (60.0)	25 (65.8)
51–100, mm	91 (34.2)	22 (25.0)	69 (38.8)	25 (47.2)	12 (42.9)	13 (52.0)	51 (30.9)	8 (16.0)	43 (37.4)	15 (31.3)	2 (20.0)	13 (34.2)
101–150, mm	43 (16.2)	12 (13.6)	31 (17.4)	7 (13.2)	1 (3.6)	6 (24.0)	34 (20.6)	9 (18.0)	25 (21.7)	2 (4.2)	2 (20.0)	0 (0)
>150, mm	45 (16.9)	19 (21.6)	26 (14.6)	2 (3.8)	0 (0.0)	2 (8.0)	43 (26.1)	19 (38.0)	24 (20.9)	0 (0.0)	0 (0.0)	0 (0)

If not otherwise specified, data are numbers and percent values in brackets. Data for time-to-treatment initiation are median values with interquartile range in brackets in days. Baseline characteristics presented for patients included from the SSN with a visit between January 2018 and September 2022. Category "overall" includes both malignant and intermediate disease for the specific sarcoma type. "Intermediate" includes patients with an intermediate disease according to the WHO definition as declared in Section 2.2. "Malignant" includes patients with a malignant disease according to the WHO definition as declared in Section 2.2. Colors are used to illustrate the difference between intermediate and malignant dignities. Intermediate diseases are colored in blue; malignant diseases are colored in red. d, days; IQR, interquartile range; *n*, number; na, not applicable; TTI, time-to-treatment initiation; yrs, years.

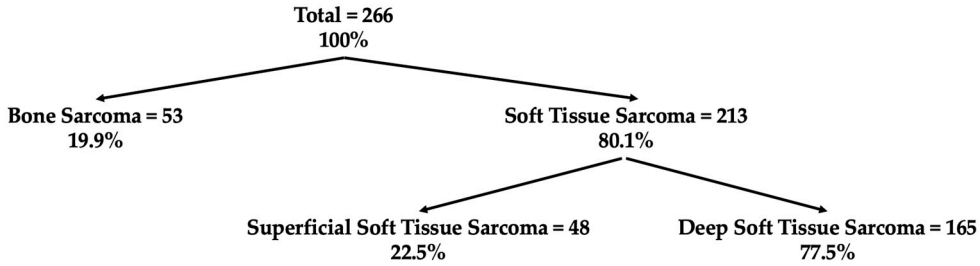


Figure 2. Partitioning of the patient cohort based on sarcoma type. Given in total number and percentage.

3.2. Overall TTI as Quality Assessment in Sarcoma Work-Up

The TTI for the entire cohort of 266 patients was 30 days. When stratified by sarcoma subtype, BS (including both malignant and intermediate) had the shortest TTI at 28 days, followed by D-STS (malignant and intermediate) with a TTI of 28 days, and S-STS (malignant and intermediate) with a TTI of 42 days (Table 1 and Figure 2).

3.2.1. TTI According to Sarcoma Type and Dignity

Significant statistical differences in TTI were identified among sarcoma types according to dignity. The TTI for malignant BS was 20 days, whereas intermediate BS had a TTI of 42 days ($p < 0.05$). TTI in malignant D-STS was 22 days and significantly faster compared to intermediate D-STS with a median TTI of 54 days ($p < 0.001$). No significant difference in TTI between malignant and intermediate sarcomas was seen in S-STS ($p > 0.05$). Malignant S-STS had a median TTI of 42 days, whereas intermediate S-STS had a median TTI of 43 days (Table 2).

Table 2. Time-to-treatment initiation of patients with a bone sarcoma, deep, or superficial soft tissue sarcoma according to dignity and treatment modality.

		Overall		Intermediate		Malignant		*p*-Value [a]
		n **(%)**	**TTI (IQR)**	***n*** **(%)**	**TTI (IQR)**	***n*** **(%)**	**TTI (IQR)**	
Bone sarcoma	Overall	53 (100)	28 (13–49)	28 (52.8)	42 (16–58)	25 (47.2)	20 (11–34)	0.025
	Surgery	37 (69.8)	37 (16–57)	27 (96.4)	41 (16–59)	10 (40.0)	29 (14–53)	0.62
	Chemotherapy	12 (22.6)	13 (8–17)	na	na	12 (48.0)	13 (8–17)	na
	Radiotherapy	4 (7.6)	35 (26–47)	1 (3.6)	51 (51–51)	3 (12.0)	27 (25–43)	0.29
Deep soft tissue Sarcomas	Overall	165 (100)	28 (18–48)	50 (100)	54 (30–70)	115 (100)	22 (14–34)	0.0001
	Surgery	64 (38.8)	41 (29–66)	46 (92.0)	56 (34–70)	18 (15.7)	30 (20–42)	0.007
	Chemotherapy	21 (12.7)	14 (8–18)	1 (2.0)	14 (14–14)	20 (17.4)	14 (8–18)	na
	Radiotherapy	80 (48.5)	25 (18–36)	3 (6.0)	49 (22–117)	77 (67.0)	24 (18–34)	0.11
Superficial soft tissue Sarcomas	Overall	48 (100)	42 (27–71)	10 (100)	43 (30–71)	38 (100)	42 (26–70)	0.63
	Surgery	27 (56.3)	50 (30–75)	10 (100)	43 (30–71)	17 (44.7)	54 (38–75)	0.73
	Chemotherapy	2 (4.2)	11 (10–12)	0 (0.0)	na	2 (5.2)	11 (10–12)	na
	Radiotherapy	19 (39.6)	39 (26–70)	0 (0.0)	na	19 (50.0)	39 (26–70)	na

Data presented in numbers (*n*) of patients for each category, with percent values in brackets. Data for time-to-treatment initiation are median values with interquartile range in brackets in days. Patients are categorized according to sarcoma type and dignity. Category "overall" includes both malignant and intermediate disease for the specific sarcoma type. Category "intermediate" includes patients with an intermediate disease according to the WHO definition as declared in Section 2.2. Category "malignant" includes patients with a malignant disease according to the WHO definition as declared in Section 2.2. Colors are used to illustrate the difference between intermediate and malignant dignities. Intermediate diseases are colored in blue; malignant diseases are colored in red. IQR, interquartile range; *n*, number; na, not applicable; TTI, time-to-treatment initiation; [a] *p*-value was calculated based on a Wilcoxon rank sum test for continuous variables with a continuity correction between intermediate and malignant sarcomas.

3.2.2. TTI According to Treatment Approach and Dignity

When assessing the treatment approaches for malignant sarcomas compared to intermediate sarcomas, the following findings emerged: In malignant BS, surgery and radiotherapy were faster compared to intermediate BS; however, both were statistically not significant ($p > 0.05$). It is important to note that none of the intermediate BS received chemotherapy. In D-STS, radiotherapy and surgery were performed faster in malignant disease; however, surgery was significantly faster in malignant D-STS (TTI of 30 days) compared to intermediate D-STS (TTI of 56 days) ($p < 0.01$). Chemotherapy had the same TTI in intermediate and malignant D-STS. Conversely, for S-STS, surgery was faster in intermediate cases compared to malignant cases, although this difference was not statistically significant ($p > 0.05$). No radiotherapy or chemotherapy was performed in intermediate S-STS. Further details on therapy modalities can be found in Table 2 and Figure 3.

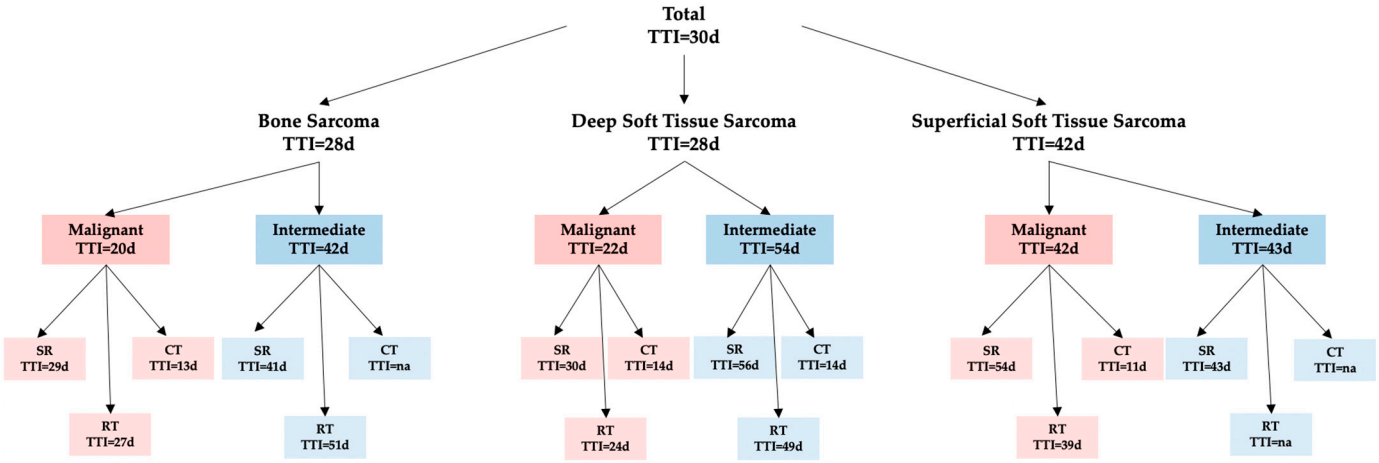


Figure 3. Overview of TTI according to sarcoma sub-type and dignity; SR, Surgery; RT, Radiotherapy; CT, Chemotherapy). Data for TTI are median values.

3.3. TTI in Malignant Sarcomas According to Institution and Therapy Modality

This sub-analysis specifically addresses malignant cases only.

3.3.1. Malignant Bone Sarcoma

In the context of BS, TTI was the shortest in Institution A, with 13 days, followed by Institution C at 14 days, and Institution B at 24 days. However, these differences did not reach statistical significance ($p > 0.05$). Regarding surgical interventions in malignant BS, Institution A had the shortest TTI at 10 days, followed by Institution C at 22 days, and Institution B at 37 days. Also not reaching statistical significance ($p > 0.05$). More details on therapy modalities in malignant BS can be found in Table 3.

Table 3. Analysis of only malignant sarcoma—showing time-to-treatment initiation depending on different institutions.

		Institution A		Institution B		Institution C	
		***n* (%)**	**TTI (IQR)**	***n* (%)**	**TTI (IQR)**	***n* (%)**	**TTI (IQR)**
Bone sarcoma	Overall	5 (100)	13 (10–25)	15 (100)	24 (12–43)	5 (100)	14 (6–30)
	Surgery	1 (20.0)	10 (10–10)	7 (46.7)	37 (24–85)	2 (40.0)	22 (14–30)
	Chemotherapy	3 (60.0)	13 (6–34)	6 (40.0)	13 (11–14)	3 (60.0)	6 (5–38)
	Radiotherapy	1 (20.0)	25 (25–25)	2 (13.3)	35 (27–43)	0 (0.0)	na
Deep soft tissue Sarcomas	Overall	31 (100)	25 (16–34)	65 (100)	21 (15–32)	19 (100)	21 (12–40)
	Surgery	4 (12.9)	13 (12–42)	7 (10.8)	29 (21–42)	7 (36.8)	33 (19–40)
	Chemotherapy	4 (12.9)	15 (12–17)	12 (18.5)	14 (8–21)	4 (21.1)	9 (1–18)
	Radiotherapy	23 (74.2)	29 (23–36)	46 (70.8)	21 (15–34)	8 (42.1)	21 (13–64)
Superficial soft tissue Sarcomas	Overall	7 (100)	38 (15–43)	22 (100)	52 (26–75)	9 (100)	42 (26–62)
	Surgery	2 (28.6)	41 (38–43)	12 (54.6)	55 (26–79)	3 (33.3)	62 (42–78)
	Chemotherapy	1 (14.3)	10 (10–10)	0 (0.0)	na	1 (11.1)	12 (12–12)
	Radiotherapy	4 (57.1)	40 (27–74)	10 (45.5)	44 (26–70)	5 (55.6)	32 (26–45)

Data presented in numbers (*n*) of patients for each categories, with percent values in brackets. Data for time-to-treatment initiation are median values with interquartile range in brackets in days. The analysis includes only patients with a malignant disease. Category "malignant" diseases were defined according to the WHO definition shown in Section 2.2. Data is presented for each different institution according to sarcoma type overall and according to the first treatment modality surgery, chemotherapy, or radiotherapy. IQR, interquartile range; *n*, number; na, not applicable; TTI, time-to-treatment initiation.

3.3.2. Malignant Deep Soft Tissue Sarcoma

In the group of malignant D-STS, Institution B and C had both an overall TTI of 21 days, which was not statistically faster than Institution A with a TTI of 25 days ($p > 0.05$). When considering only surgical interventions, there was a significant difference in time to surgery ($p < 0.01$). Institution A had a significantly shorter time to surgery of 13 days compared to Institutions B and C, which had 30 and 34 days, respectively. In terms of radiotherapy, Institution B had a statistically significant shorter TTI of 21 days compared to Institution A, where the time to radiotherapy was 29 days ($p < 0.01$). However, there were no significant differences in time to chemotherapy among the institutions in malignant D-STS. More details on therapy modalities for malignant D-STS can be found in Table 3.

3.3.3. Malignant Superficial Soft Tissue Sarcoma

In malignant S-STS, the fastest time to surgery was observed in Institution A, with a time of 41 days, compared to 55 days at Institution B and 62 days at Institution C. However, these differences were not significant ($p > 0.05$). Similarly, there were no significant differences in the time to radiotherapy ($p > 0.05$) between the institutions. More detailed information on TTI according to institution and therapy modalities in malignant S-STS can be found in Table 3.

3.4. TTI According to Resection Type

Out of the total of 266 patients (100%), 15.4% had an unplanned so-called whoops resection. The remaining 84.6% underwent planned resections. In whoops resections, 36.6% had a D-STS and 63.4% had a S-STS. In D-STS, 33.3% had an intermediate and 66.7% had a malignant diagnosis. In S-STS, 19.2% had an intermediate and 80.8% had a malignant disease. Notably, there were no occurrences of whoops resections in BS (Figure 4).

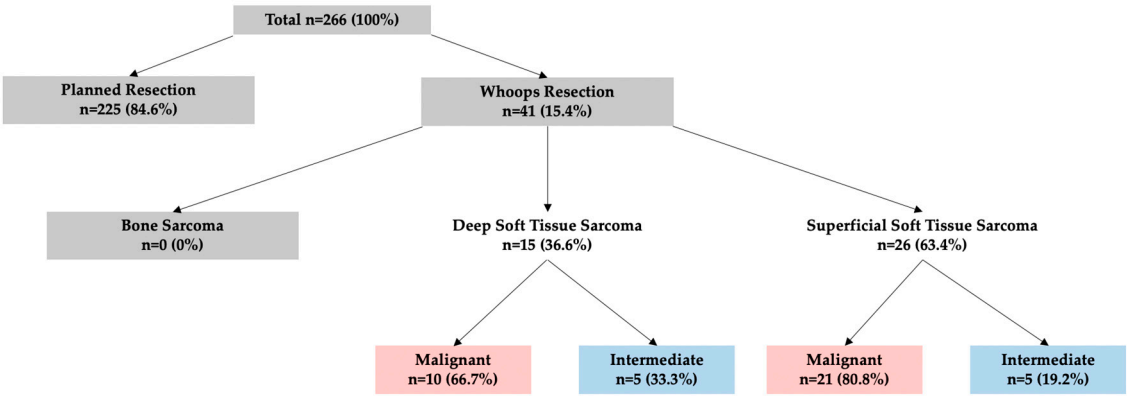


Figure 4. Distribution of whoops resections in total numbers and percentages.

In both malignant S-STS and D-STS, we observed a significant increase in TTI according to resection type. In malignant D-STS, planned resection had a significantly shorter overall TTI of 21 days compared to whoops resections with a TTI of 59 days ($p < 0.001$). The same significance was observed in malignant S-STS, where planned resections had a TTI of 27 days compared to whoops resections with a TTI of 62 days ($p < 0.01$). More detail on resection type in malignant sarcomas can be found in Table 4.

Table 4. Analysis of unplanned surgical resections ("whoops") for time-to-treatment initiation in deep and superficial soft tissue sarcoma compared to planned resections in malignant deep and superficial soft tissue sarcoma.

		Malignant Overall		Unplanned "Whoops"		Planned Malignant		*p*-Value [a]
		n (%)	TTI	*n* (%)	TTI	*n* (%)	TTI	
Deep soft tissue Sarcomas	Overall	115 (100)	22 (14–34)	10 (100)	59 (37–70)	105 (100)	21 (14–31)	0.001
	Surgery	18 (15.7)	30 (20–42)	2 (20.0)	38 (35–40)	16 (15.2)	29 (17–48)	0.44
	Chemotherap	20 (17.4)	14 (8–18)	1 (10.0)	18 (18–18)	19 (18.1)	13 (8–18)	0.49
	Radiotherapy	77 (66.9)	24 (18–34)	7 (70.0)	69 (51–79)	70 (66.9)	23 (15–32)	0.0001
Superficial soft tissue Sarcomas	Overall	38 (100)	43 (26–71)	21 (100)	62 (42–75)	17 (100)	27 (19–42)	0.003
	Surgery	17 (44.7)	54 (38–75)	11 (52.4)	62 (42–78)	6 (35.3)	36 (19–43)	0.09
	Chemotherap	2 (5.3)	11 (10–12)	1 (4.8)	12 (12–12)	1 (5.9)	10 (10–10)	na
	Radiotherapy	19 (50.0)	39 (26–70)	9 (42.9)	64 (45–75)	10 (58.8)	27 (25–39)	0.02

Data presented in numbers (*n*) of patients for each category, with percent values in brackets. Data for time-to-treatment initiation are median values with interquartile range in brackets in days. Analysis of time-to-treatment initiation of unplanned surgical resections ("whoops") compared to planned resections of only malignant sarcoma. Category "malignant overall" includes patients with a malignant disease defined according to the WHO definition shown in Section 2.2. Category "unplanned "whoops"" includes patients who underwent an unplanned surgical resection resulting in a malignant disease, followed by a definitive treatment by SSN. Definition of "whoops" resections is shown in Section 2.3. Category "planned malignant" includes patients diagnosed with a malignant sarcoma by biopsy and receiving a planned first treatment surgery, chemotherapy, or radiotherapy by SSN. IQR, interquartile range; *n*, number; na, not applicable; TTI, time-to-treatment initiation; [a] Comparing time-to-treatment initiation in patients with unplanned and planned resection using a Wilcoxon rank sum test for continuous variables.

Whoops resections are performed on patients not treated by MDT's. In assessing MDT quality, the results indicate that most patients with deep soft tissue sarcomas and all patients with bone sarcomas were aware of their conditions and were referred to an MDT/SB for further work-up and initiation of treatment. However, cases of S-STS were more often treated outside of an MDT/SB before being secondarily referred to it, resulting in whoops resections.

4. Discussion

This study provides RWTD with the aim of improving TTI treatment approaches through meta-level analysis. We conducted an analysis of the time it takes for sarcoma

patients to initiate their first treatment following the histological diagnosis. This approach seeks to optimize patient care, identify areas for improvement, establish standards, and enhance healthcare practices. The objective is to facilitate the attainment of optimal performance, with TTI serving as a quality indicator rather than judging respective units' or physicians' performance. This research contributes to the development of a VBHCS, aiming to shift the healthcare model from a service-driven, competition-based fee-for-service approach to an outcome-driven collaborating system, prioritizing the best possible patient care [37].

The study revealed a median TTI including all sarcoma sub-types with an intermediate or malignant dignity of 30 days. TTI varied based on factors such as the type of tumor, its malignancy, the treatment approach, and the healthcare institution. In a previous study by Curtis et al., conducted from 2004 to 2013, the median TTI for soft tissue sarcomas was 22 days, but it increased to 26 days by 2013 [28]. Similarly, Lawrenz et al. found a TTI of 22 days for primary bone sarcomas in data from the US national cancer database for the period of 2004 to 2013 [23]. However, it is important to note that careful consideration is needed when comparing these findings, as TTI definitions can vary, leading to differences in how diagnosis and treatment start are measured. Lawrenz et al. also studied the accuracy of TTI data from the database compared to manually calculated TTI. They found discrepancies, especially when TTI was recorded as 0 days, indicating potential issues with defining the start of therapy. Manual TTI calculations in one center of the national cancer database showed an average of 34 days with significant variability ($\pm$31.3 days) [38]. This observation underscores the complexity of TTI analysis and emphasizes the importance of standardizing and carefully interpreting data in comparative studies. In interpretation, our study's TTI values appear to be relatively longer when compared to international data. The prolonged TTI could be attributed to our more diverse RWTD dataset. Unlike the previous studies, we included both intermediate and malignant diagnoses and did not differentiate between curative and palliative cases. This approach was driven by our use of RWTD, which reflects the practical complexities of sarcoma care. RWTD offer a precise depiction of clinical practices by collecting observational data within real-life healthcare settings. Its comprehensive and dynamic nature facilitates an in-depth analysis of the medical decision-making process. RWTD provide valuable insights into adherence to clinical guidelines and variation in practices, which can be pivotal in addressing underuse or recommended treatments and standardizing care. By encompassing a broad spectrum of diseases, including rare conditions, RWTD enhance the applicability of research findings to wider patient populations, thereby advancing the quality and relevance of care. In this context, the TTI observed herein may appear somewhat extended when compared to other literature, which can be attributed to the utilization of RWTD. Unlike conventional datasets that might miss the nuances of patient care, RWTD provide a more complete and holistic view. This comprehensive data collection captures a wider range of patient experiences, leading to a more thorough understanding of treatment timelines. Consequently, RWTD's inclusivity and detail-oriented approach can result in a slightly higher TTI, reflecting a realistic scenario that incorporates all aspects of the patient's journey, from diagnosis to treatment initiation. This robust approach ensures a more accurate benchmark for sarcoma care and underscores the necessity for system-wide improvements based on RWTD practices [39–44].

TTI differed according to the therapy modality; we saw an extended time to surgery compared to chemotherapy and radiotherapy. The detailed reasons cannot be extracted from the study results. However, it could be suggested that the delay may be attributed to the complex nature of surgical procedures, which necessitate highly skilled teams from various surgical disciplines [45]. Specialized treatment teams are essential and require meticulous planning to ensure their availability for delivering the necessary care [11,13,14,46]. Despite advancements in diagnostic and therapeutic methods, the fundamental structure of healthcare systems has witnessed limited transformation. Within healthcare systems that emphasize fee-for-service models, patient care tends to remain fragmented and not

adequately centered on the patient's needs. Care is still predominantly confined within departmental boundaries, with some limited interdisciplinary collaboration, such as the introduction of sarcoma boards. However, there is a growing recognition that the existing healthcare model, characterized by departmental silos, may have inherent limitations. Shifting toward a more collaborative model, like a VBHCS with integrated practice units (IPU), could address some of these limitations. Porter et al. were the first to emphasize patient outcomes over sheer volume of services by introducing the VBHC model [6–8,10,37,47–50]. The shift from volume-based to value-based care augments the overall patient experience and satisfaction. The quality of care is gauged by objective indicators and benchmarks, encouraging healthcare providers to continually enhance their services to achieve better patient outcomes [1–3,12,29,51,52]. TTI also differed among the treatment centers, especially in the context of surgical interventions. However, the dataset does not provide clear reasons for these differences. It is worth noting that direct comparisons between the institutions are challenging, and larger patient numbers may help. Additionally, we have not delved into the details of the treatment contracts, which could explain why one center might handle more complex cases, leading to a greater need for diagnostics and complex treatments.

Significant disparities in TTI are evident across varying tumor types, with S-STS consistently exhibiting the lengthiest TTI when compared to BS and D-STS. While our dataset does not provide explicit reasons for the TTI delay associated with S-STS, an intriguing pattern emerges. Patients diagnosed with S-STS often commence their initial treatment outside the specialized environs of dedicated multidisciplinary sarcoma teams. Subsequently, once the diagnosis is definitively established, they are transferred to tertiary care facilities for ongoing management. A noteworthy observation within this context is the number of unplanned surgical excisions, so-called "whoops" resections, outside an MDT. These revelations underscore the immediate necessity for enhanced educational efforts aimed at improving the management of tumor masses and a heightened awareness of the potential repercussions stemming from the misinterpretation of a sarcoma diagnosis, particularly in treatment settings that operate outside sarcoma centers. However, this study serves as a poignant reminder that even superficially located tumor masses can potentially harbor malignancies, warranting greater diligence in the management of S-STS. Nevertheless, redirecting all tumor masses to dedicated sarcoma experts represents a logistical challenge. Striking the balance between timely diagnosis and the initiation of appropriate treatment necessitates a consideration of various factors, including the intricacies of diagnosis, TTI, and therapeutic management. To mitigate the risk of overburdening central sarcoma facilities and prolonging waiting times for patients, not all patients should be centralized; selective referral is essential. Sarcoma centers should facilitate easier access in accordance with the IPU model to prevent overwhelming their capacity. This entails expanding the network to incorporate all secondary surgeons and primary care physicians, allowing them to present their cases with a very low threshold, facilitating efficient and timely referral to a dedicated sarcoma center [22,53–58].

Despite efforts to reduce unplanned surgical excisions, a significant percentage of such incidents still occur. Our study observed a "whoops" resection rate of 15.4%, which is relatively lower compared to findings in existing literature. For example, a study conducted by Melis et al. from 2016 to 2019 reported a higher unplanned "whoops" resection rate of 18.2% in cases of STS. These unplanned "whoops" resections have significant implications for various aspects of sarcoma management, including overall survival, local recurrence rates, financial impacts on both the healthcare system and patients, and disease control. An in-depth examination of these implications is crucial for a comprehensive understanding of how unplanned "whoops" resections affect sarcoma care. This knowledge can guide clinical practices and treatment decisions and ultimately improve the overall management of sarcoma patients [50,59–64].

It is important to note that our dataset does not allow a conclusion about systemic control in patients with prolonged TTI. While our study provides insights into various aspects of sarcoma care, the specifics of systemic control, especially in cases with prolonged

TTI, are not addressed in our data. Factors like metastasis progression, the effectiveness of systemic therapies, and their impact on overall outcomes require more information than our dataset currently provides. These limitations underscore the necessity for more extensive data collection over a longer time period and future studies to explore the relationship between TTI and systemic control. The population of this study encompasses a wide range of sarcoma types, each with its own biology and impact on overall survival. This might as well be a reason for a variation in patient care. This diversity makes it challenging to draw broad conclusions and limits the statistical power of subgroup analyses due to the small sample sizes. TTI was analyzed exclusively for patients presented to the Sarcoma Board (SB), engendering an inherent selection bias as those not presented to the SB. TTI is part of an analysis of further quality metrics, all needed to explore aspects of the healthcare system and be able to improve patient quality care.

5. Conclusions

This study's analysis of time-to-treatment initiation (TTI) using real-world-time data (RWTD) elucidates the current landscape of sarcoma treatment initiation across various centers and sarcoma subtypes. Our findings indicate considerable variability in TTI, with notable delays, especially in cases of superficial soft tissue sarcoma and unplanned 'whoops' resections. The study highlights the imperative for strategic interventions aimed at standardizing care pathways and enhancing the referral process to specialized sarcoma centers. Importantly, while the data reflect a higher TTI relative to other studies, the comprehensive nature of RWTD captures a more accurate depiction of the patient journey, suggesting that previous reports may underrepresent actual TTI. Moving forward, it is crucial to balance the need for specialized care with the risk of central facility overload, advocating for a selective referral system that aligns with integrated practice units. Ultimately, this study serves as a catalyst for ongoing efforts to refine the sarcoma care model, emphasizing the need for a systemic shift towards a value-based healthcare framework that prioritizes patient outcomes and efficient resource utilization.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Article

Planned and Unplanned Sarcoma Resections: Comparative Analysis of Local Recurrence, Metastasis, and Mortality

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Simple Summary: Sarcomas are rare and diverse tumors that develop in various tissues like bone, muscle, and fat. This study examines the outcomes of two types of surgical removal of these tumors: planned resections (PEs), where the tumor is diagnosed a-priori and surgically removed with a plan, and unplanned resections (UEs), where the tumor is removed without prior diagnosis. We found that planned surgeries, while better at completely removing the tumor initially, are associated with more advanced tumors that have a higher chance of spreading and leading to cancer-related deaths. On the other hand, unplanned surgeries tend to have higher chances of the tumor coming back locally but do not significantly affect long-term survival. These findings highlight the importance of early detection and timely treatment at specialized centers to improve patient outcomes. Our research aims to help develop better tools for predicting and managing sarcomas to enhance patient care.

Abstract: Background: Sarcomas, a diverse group of malignant tumors arising from mesenchymal tissues, pose significant diagnostic and therapeutic challenges. This study compares the outcomes of planned resections (PEs) and unplanned resections (UEs) to inform better clinical practices. Methods: Data were analyzed from the Swiss Sarcoma Network (SSN), including patients with soft tissue and bone sarcomas treated at two major hospitals. This study utilized logistic regression and Cox regression models to examine the odds of UEs and their impact on local recurrence-free survival. Results: Among 429 patients registered by SSN members, 323 (75%) underwent PEs and 106 (25%) experienced UEs. PEs were associated with significantly larger tumors (94 mm vs. 47 mm, $p < 0.001$) and higher-grade tumors (Grade 3: 50.5% vs. 37.4%, $p = 0.03$). Despite achieving superior resection margins (R0: 78.8% vs. 12.6%, $p < 0.001$), PEs showed higher metastasis rates at follow-up (31.0% vs. 10.4%, $p < 0.001$) and greater cancer-specific mortality (16.7% vs. 6.6%, $p = 0.01$). UEs, while linked to higher local recurrence, did not significantly affect metastasis-free survival (MFS) or overall survival (OS). Conclusions: PEs achieve superior immediate surgical outcomes but are linked to higher metastasis and cancer-specific mortality due to the advanced stage of tumors. UEs, while associated with higher local recurrence rates, do not significantly impact MFS or OS. Early detection, comprehensive diagnostics, and timely referrals to specialized sarcoma hubs are essential to avoid UEs and reduce metastatic risk. Future research should focus on developing diagnostic tools using individual tumor and patient characteristics to improve sarcoma management.

Keywords: sarcoma; planned excision/resection; unplanned excision/whoops/resection; surgical outcomes; metastasis; cancer-specific mortality; tumor characteristics; early detection; predictive tools; sarcoma management

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1. Introduction

Sarcomas are a diverse group of malignant tumors arising from mesenchymal tissues, including bone, muscle, fat, and connective tissues [1]. Due to their rarity and heterogeneous nature, sarcomas present significant diagnostic and therapeutic challenges [2]. Surgical resection remains the cornerstone of sarcoma management, with the success of surgical outcomes heavily influenced by tumor characteristics such as size, grade, and anatomical location [3].

Unplanned resections (UEs) often occur when a sarcoma is not initially suspected, leading to suboptimal surgical outcomes [4–7]. These unplanned surgeries typically involve incomplete resections and higher rates of local recurrence [8]. Conversely, planned resections (PEs) are performed with a prior diagnosis of sarcoma, allowing for meticulous surgical planning and often achieving better immediate resection margins (R0 status). Our previous study highlighted that while unplanned resections are associated with higher local recurrence (LR) rates, there were no significant differences in metastasis-free survival (MFS) and overall survival (OS) between UE and PE groups [9]. This underscores the complexity of sarcoma management and the critical need for proper diagnosis and referral.

The early detection of sarcomas is crucial for optimal treatment planning. Proper diagnostic imaging and early referral to specialized sarcoma centers can significantly improve patient outcomes [10–13]. Early detection facilitates PEs, which are critical for achieving complete tumor removal and minimizing recurrence.

Several factors influence the probability of a sarcoma resection being planned or unplanned. Tumor size, grade, and anatomical location, as well as patient characteristics such as age and gender, play pivotal roles [14]. While composite predictive tools like Sarculator, which estimates survival rates, can aid clinicians in making informed decisions after a sarcoma is diagnosed, focusing on individual parameters provides more straightforward and actionable insights for early detection and intervention [15].

Despite the advantages of PEs in achieving complete tumor removal, the more advanced stage and aggressive nature of tumors requiring PEs may result in higher rates of metastasis and cancer-specific mortality [16–18]. This study aims to expand upon previous findings by further elucidating the differences in outcomes between PE and UE sarcoma resections, particularly addressing the ongoing debate in the literature about the impact of UEs on MFS and OS [19]. Understanding these differences is essential for improving early detection and optimizing referral practices, ultimately enhancing patient care and outcomes.

The objective of this study is to elucidate the differences in outcomes between PE and UE sarcoma resections and identify key predictive factors based on individual tumor and patient characteristics. By enhancing our understanding of these factors, this research aims to inform clinical practice and improve the management of sarcoma patients, ultimately leading to better survival rates and quality of life.

2. Materials and Methods

2.1. Data Source and Collection

Data from the Swiss Sarcoma Network (SSN) (https://www.swiss-sarcoma.net/ (accessed on 6 October 2024)) data warehouse were analyzed [20,21]. This network longitudinally collects data from patients with soft tissue and bone tumors, establishing a multicenter, prospective real-world/time data repository of high quality [22,23]. The current dataset is housed on Adjumed.ch (Adjumed Services AG, Zurich, Switzerland; www.adjumed.ch, accessed on 10 October 2023) and is expected to transition to the Sarconnector® (BF&PH, Zurich, Switzerland), a dynamic real-world/time data warehouse for automated analysis [20].

2.2. Study Population

As depicted in Figure 1, the SSN data warehouse hosts 2104 muskuloskeletal tumor cases registered by SSN members between 2018 and 2023. We included patients with a

sarcoma diagnosis treated either as PEs or UEs and treated at Institution A or Institution B (n = 477) [9]. The inclusion criteria for this study encompassed all patients referred to our sarcoma center. Patients were included if they had a histologically confirmed diagnosis of sarcoma and had undergone surgical resection. The follow-up starts at the first surgical resection and ends at the occurrence of the end point (local recurrence, metastasis, or death), administrative censoring, or 5 years of follow-up. The median follow-up time was 1.9 years (1st quartile (Q1), 3rd quartile (Q3); 0.8 years, 3.7 years). Anatomical sites were categorized separately, including extremities, head and neck, trunk, and retroperitoneal regions, to ensure that site-specific outcomes were captured in our comparison of planned versus unplanned resections. Low-grade lesions, such as atypical lipomatous tumors (ALTs), were not excluded but were listed separately in the results to account for their different biological behavior.

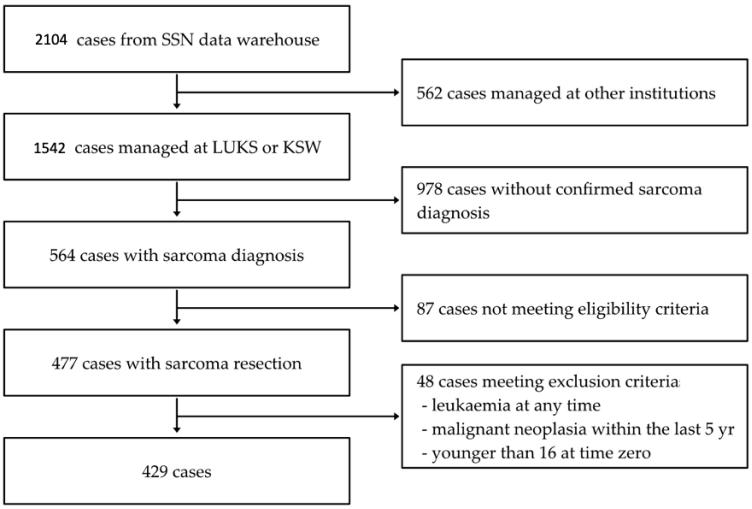


Figure 1. Flow chart.

Patients were excluded if they had a history of leukemia (n = 2), a malignant neoplasm within the last 5 years (n = 36), or were younger than 16 at time zero (n = 10). Additionally, the diagnosis of desmoid tumors was not included in this study population.

2.3. Study Design

The follow-up timeframe was defined from the initial surgical intervention (UE or PE) to predetermined outcomes (LR, metastasis, death) or to the date of the last patient contact. Logistic regression was used to ascertain the probability of UEs, with results represented by odds ratio (OR), 95% confidence interval (CI), and *p*-values. An OR above 1 indicated a higher likelihood of experiencing UEs, while an OR below 1 indicated a greater likelihood of PEs. A *p*-value below 0.05 was considered statistically significant. Variables included in the logistic regression analysis were sarcoma classification, anatomic region, size, grade, age, gender, Charlson comorbidity index (CCI), and diagnosis. Sensitivity analyses were conducted, encompassing additional statistical adjustments for additional variables such as various anatomic regions (head, neck, upper extremity, lower extremity, trunk, visceral, intraperitoneal, and retroperitoneal areas) and the five most common diagnoses (undifferentiated/unclassified sarcoma, atypical lipomatous tumor, myxoid liposarcoma, myxofibrosarcoma, and leiomyosarcoma) (see appendix). To account for the heterogeneity between soft tissue sarcomas and bone sarcomas, we stratified our analysis by sarcoma type. Separate statistical models were applied for each group, allowing for direct comparison while considering their distinct biological behaviors and treatment protocols. This approach provides a comprehensive yet focused analysis of the outcomes of planned versus unplanned resections for both sarcoma types. The management and characteristics of the UE group were characterized previously [9].

2.4. Statistical Analysis

The subset of UEs with LR was analyzed using both univariable and multivariable Cox regression models. The proportional hazards assumption for the Cox proportional hazards regression was examined using Schoenfeld residuals, and the linearity assumption for the covariates was assessed using Martingale residuals. In the multivariable Cox regression, Sarculator 5-year predictied survival was used to adjust for known prognostic factors due to the limited number of cases, necessitating a constraint on the number of variables [24]. Sarculator encompasses age, tumor size, FNCLCC grade, and histology, integrating multiple variables that would otherwise be analyzed separately. The 5-year Sarculator was chosen over the 10-year version based on the prevalence of five-year local recurrence-free survival rates reported in the existing literature. Myxoid liposarcoma was excluded from the Cox regression model due to its small sample size (only four patients in the UE group with one LR). We refrained from analyzing the subset of UEs with metastasis due to the limited sample size, rendering statistical analysis unfeasible (only nine patients with metastasis in the UE group).

2.5. Software and Ethical Considerations

Statistical analysis was conducted using the R statistical software (Version 4.3.2, Posit, PBC, Boston, MA, USA) [25]. This study was conducted in compliance with the Declaration of Helsinki and approved by the Ethics Committee of the Cantonal Ethics Committee Zurich, Switzerland (BASEC-Nr. 2019-01107/NCT04300257; 24 August 2021).

3. Results

We included 429 patients. Among them, 323 underwent PEs, while 106 experienced UEs. The baseline characteristics and outcomes of the study population, categorized into PE and UE treatment groups, are summarized in Table 1.

Table 1. Characteristics of the study population categorized by treatment groups.

	All	PEs	UEs	*p*-Value
n	429	323	106	-
Gender				
Male, n (%)	229 (53.4)	167 (51.7)	62 (58.5)	0.26
Female, n (%)	200 (46.6)	156 (48.3)	44 (41.5)	0.26
Age in years, median (Q1, Q3)	63 (51, 74)	63 (53, 74)	63.5 (47, 75)	0.45
Sarcoma classification				
SST, n (%)	69 (16.1)	31 (9.6)	38 (35.8)	<0.001
DST, n (%)	317 (73.9)	256 (79.3)	61 (57.5)	<0.001
Bone, n (%)	43 (10.0)	36 (11.1)	7 (6.6)	0.20
Diagnosis *				
Myxoid liposarcoma, n (%)	28 (6.5)	24 (7.4)	4 (3.8)	0.26
Dedifferentiated liposarcoma, n (%)	40 (9.3)	36 (11.1)	4 (3.8)	0.02
Leiomyosarcoma, n (%)	47 (11.0)	31 (9.6)	16 (15.1)	0.15
Atypical lipomatous tumor	63 (14.7)	51 (15.8)	12 (11.3)	0.34
Undifferentiated/unclassified sarcoma	64 (14.9)	52 (15.8)	12 (11.3)	0.27
Tumor size (largest diameter) in mm, median (Q1, Q3)	80 (50, 129)	94 (60, 143)	46.5 (27, 79)	<0.001
Anatomic region				
Upper extremity, n (%)	41 (9.6)	20 (6.2)	21 (19.8)	<0.001
Axial, n (%)	201 (46.9)	152 (47.1)	49 (46.2)	0.91
Lower extremity, n (%)	187 (43.6)	151 (46.7)	36 (34.0)	0.02
Resection grading (time zero)				
G1, n (%)	138 (34.5)	91 (30.2)	47 (47.5)	0.004
G2, n (%)	73 (18.3)	58 (19.3)	15 (15.2)	0.46
G3, n (%)	189 (47.3)	152 (50.5)	37 (37.4)	0.03
Resection status (time zero) †				
R0, n (%)	253 (63.1)	241 (78.8)	12 (12.6)	<0.001
R1/R2, n (%)	148 (36.9)	65 (21.2)	83 (87.4)	<0.001

Table 1. *Cont.*

	All	PEs	UEs	*p*-Value
CCI, median (Q1, Q3)	2 (0, 3)	2 (1, 3)	1 (0, 3)	0.15
Sarculator 5 years in %, median (Q1, Q3)	73 (54, 89)	68.5 (50, 83)	87 (73, 93)	<0.001
Local recurrence, n (%)	82 (19.1)	56 (17.3)	26 (24.5)	0.27
Metastasis at diagnosis, n (%)	23 (5.4)	20 (6.2)	3 (2.8)	0.22
Metastasis at follow-up, n (%)	111 (25.9)	100 (31.0)	11 (10.4)	<0.001
Death				
Overall, n (%)	71 (16.6)	61 (18.9)	10 (9.4)	0.25
Cancer specific, n (%)	61 (14.2)	54 (16.7)	7 (6.6)	0.01

The percentages correspond to the number of cases (n-values) listed in the first row of their respective columns. * The listing comprises only five common diagnoses within our study cohort. † Histological examination determines the R0 status. In contrast, a negative postoperative MRI finding characterizes R1 status, unlike R2. To distinguish between R1 and R2 statuses, the surgical report was also assessed.

The tumor size showed substantial differences between the groups, with PEs associated with larger tumors (median 94 mm) compared to UEs (median 47 mm) ($p < 0.001$). Tumors in the upper extremity were more frequent in the UE group (19.8%) than in the PE group (6.2%) ($p < 0.001$). In contrast, lower extremity tumors were more often represented in the PE group (46.7%) than in the UE group (34%) ($p = 0.02$).

Regarding resection grading, a greater number of Grade 1 tumors were observed in the UE group (47.5%) compared to the PE group (30.2%) ($p = 0.004$). Conversely, the PE group had a higher proportion of Grade 3 tumors (50.5% vs. 37.4% for UE, $p = 0.03$).

R0 resection was more common in the PE group (78.8%) compared to the UE group (12.6%) ($p < 0.001$). According to the Sarculator 5-year prognostic tool, the 5-year survival rate was significantly higher in the UE group (median 87%) than in the PE group (median 68.5%) ($p < 0.001$).

Notably, metastasis rates at follow-up were higher in the PE group (31%) compared to the UE group (10.4%) ($p < 0.001$). Similarly, cancer-specific mortality was higher in the PE group (16.7%) compared to the UE group (6.6%) ($p = 0.01$). Despite the superior resection status in the PE group, these patients exhibited worse outcomes regarding metastasis at follow-up and cancer-specific mortality.

3.1. Variables to Predict the Likelihood of an UE

As shown in Table 2, several variables are associated with the likelihood of UEs. Sensitivity analyses (Appendix A Tables A1–A11) confirmed that tumors situated in bone or deep soft tissue were less frequently associated with UEs, with an OR of 0.13 (95% CI: 0.04, 0.44; $p = 0.001$) for bone tumors and an OR of 0.33 (95% CI: 0.16; 0.66; $p = 0.002$) for deep soft tissue tumors, indicating a significant reduction in the association of these tumor types with UEs compared to superficial tumors. Tumor localization also played a critical role, with tumors in the upper extremity more likely to undergo UEs. Specifically, axial tumors had an OR of 0.32 (CI: 0.12, 0.84; $p = 0.02$) and lower extremity tumors had an OR of 0.33 (95% CI: 0.13, 0.83, $p = 0.02$), suggesting a strong association with UEs.

Tumor size significantly influenced the probability of UEs. Tumors measuring between 5 cm and 10 cm had an OR of 0.52 (95% CI: 0.27, 1.00; $p = 0.05$), while tumors larger than 10 cm had an OR of 0.16 (95 CI: 0.06, 0.41; $p < 0.001$), indicating that larger tumors are more often associated with PEs. Tumor grade similarly affected the likelihood of UEs, with Grade 2 tumors showing an OR of 0.13 (95% CI: 0.04, 0.36; $p < 0.001$) and Grade 3 tumors having an OR of 0.21 (95% CI: 0.09, 0.46; $p < 0.001$), suggesting that higher-grade tumors are more likely to be planned resections.

No age-related influence was observed (OR = 0.99; 95% CI: 0.96, 1.03; $p = 0.67$). However, gender was associated with a higher likelihood of UEs, with men having higher odds of UEs (OR = 2.11; 95% CI: 1.19, 3.84; $p = 0.01$). The Charlson comorbidity index (CCI) was not specifically linked to either UEs or PEs (OR = 1.06; 95% CI: 0.75, 1.48; $p = 0.75$).

Among the five most common diagnoses, myxoid liposarcoma was associated with PEs (OR = 0.20; 95% CI: 0.04, 0.81; p = 0.04), whereas leiomyosarcoma demonstrated a significant association with UEs (OR = 2.96; 95% CI: 1.14, 7.76; p = 0.03).

Table 2. Logistic regression analysis of predictor variables for UEs.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.13	0.04, 0.44	0.001
DST	0.33	0.16, 0.66	0.002
Anatomic region			
Upper extremity	—	—	
Axial	0.32	0.12, 0.84	0.02
Lower extremity	0.33	0.13, 0.83	0.02
Size			
<5 cm	—	—	
5–10 cm	0.52	0.27, 1.00	0.05
>10 cm	0.16	0.06, 0.41	<0.001
Grade			
1	—	—	
2	0.13	0.04, 0.36	<0.001
3	0.21	0.09, 0.46	<0.001
Age	0.99	0.96, 1.03	0.67
Gender			
Female	—	—	
Male	2.11	1.19, 3.84	0.01
CCI	1.06	0.75, 1.48	0.75
Diagnosis			
Rest	—	—	
Undifferentiated/unclassified sarcoma	1.12	0.42, 2.93	0.82
Atypical lipomatous tumor	0.48	0.15, 1.48	0.21
Myxoid liposarcoma	0.20	0.04, 0.81	0.04
Myxofibrosarcoma	1.99	0.63, 6.27	0.24
Leiomyosarcoma (excluding skin)	2.96	1.14, 7.76	0.03

The sensitivity analysis (see Appendix) showed no substantial impact on the results apart from the diagnosis of myxofibrosarcoma, which varies in its result depending on the tumor's location. Myxofibrosacoma reached statistical significance when used with the location of head and neck, lower extremity, trunk, retroperitoneal location, and visceral and intraperitoneal location. It does not display significant results when combined with the anatomical location of the upper extremity.

3.2. Independent Predictors of Local Recurrence-Free Survival in the UE Subset

The results, presented in Table 3, indicate that tumor sizes ranging between 5 cm and 10 cm (HR 2.89, 95% CI: 1.06, 7.87; p = 0.04), Grade 3 tumors (HR 2.97, 95% CI: 1.11, 7.94; p = 0.03), age (HR 1.04, 95% CI: 1.01, 1.07; p = 0.003), and CCI (HR 1.47, 95% CI: 1.13, 1.92; p = 0.004) were significantly associated with LR-free survival in the UE subset. Sensitivity analyses (Appendix A, Tables A1–A11) consistently supported these findings, highlighting the impact of these parameters across different tumor locations. As individual predictors, sarcoma classification, anatomical region, gender, and diagnosis do not influence local recurrence-free survival.

Table 3. Univariable Cox regression for local recurrence-free survival.

Characteristics	HR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	1.74	0.33, 9.14	0.51
DST	1.89	0.69, 5.17	0.22
Anatomic region			
Upper extremity	—	—	
Axial	1.58	0.56, 4.42	0.39
Lower extremity	0.61	0.18, 2.11	0.43
Size			
<5 cm	—	—	
5–10 cm	2.89	1.06, 7.87	0.04
>10 cm	2.86	0.78, 10.56	0.11
Grade			
1	—	—	
2	1.99	0.56, 7.12	0.29
3	2.97	1.11, 7.94	0.03
Age	1.04	1.01, 1.07	0.003
Gender			
Female	—	—	
Male	0.94	0.42, 2.11	0.89
CCI	1.47	1.13, 1.92	0.004
Diagnosis			
Rest	—	—	
Undifferentiated/unclassified sarcoma	1.75	0.47, 6.53	0.41
Atypical lipomatous tumor	1.12	0.37, 3.34	0.84
Myxofibrosarcoma	1.56	0.49, 4.94	0.45
Leiomyosarcoma (excluding skin)	0.67	0.15, 3.03	0.60

Table 4 shows that the Sarculator 5-year survival prediction remains a significant predictor of local recurrence-free survival in unplanned excisions (UEs). Used in this analysis were the variables sarcoma classification, anatomic region, size, grade, age, gender, cci, diagnosis, and Sarculator. Sarculator remains a significant variable, whereas the single variables showed no significance. This underscores Sarculator's utility as a reliable tool for predicting recurrence-free survival, even when individual variables show no significance.

Table 4. Multivariable Cox regression, Sarculator 5-year survival as reference.

Characteristics	HR	95% CI	*p*-Value	Sarculator 5y, HR	Sarculator 5y, 95% CI	Sarculator 5y, *p*-Value
Sarcoma classification				0.02	0.001, 0.24	0.003
SST	—	—				
Bone	1.50	0.26, 8.58	0.65			
DST	1.12	0.33, 3.82	0.86			
Anatomic region				0.02	0.002, 0.25	0.002
Upper extremity	—	—				
Axial	1.07	0.30, 3.80	0.92			
Lower extremity	0.72	0.17, 2.97	0.65			
Size				0.08	0.01, 1.30	0.08
<5 cm	—	—				
5–10 cm	2.50	0.69, 9.07	0.16			
>10 cm	5.60	0.62, 50.88	0.13			
Grade				0.03	0.002, 0.54	0.02
1	—	—				
2	1.09	0.18, 6.75	0.92			
3	1.51	0.32, 7.05	0.60			
Age	1.02	0.99, 1.05	0.21	0.02	0.002, 0.29	0.003

Table 4. *Cont.*

Characteristics	HR	95% CI	*p*-Value	Sarculator 5y, HR	Sarculator 5y, 95% CI	Sarculator 5y, *p*-Value
Gender				0.009	0.0007, 0.11	0.0003
Female	—	—				
Male	0.48	0.16, 1.44	0.19			
CCI	1.25	0.87, 1.78	0.23	0.02	0.00, 0.29	0.003
Diagnosis				0.02	0.00, 0.15	0.0003
Rest	—	—				
Undifferentiated/unclassified sarcoma	1.37	0.34, 5.45	0.66			
Atypical lipomatous tumor						
Myxofibrosarcoma	1.02	0.29, 3.57	0.97			
Leiomyosarcoma (excluding skin)	0.22	0.03, 1.82	0.16			

4. Discussion

Our study demonstrates that PEs are associated with larger, higher-grade tumors and better immediate surgical outcomes (R0 status) but also exhibit higher rates of metastasis and cancer-specific mortality compared to UEs. PEs typically involve tumors at a more advanced stage and with more aggressive characteristics, which contribute to poorer long-term outcomes. In contrast, UEs often involve smaller, less aggressive tumors detected earlier, leading to lower metastatic potential despite higher LR rates. These findings underscore the significant differences in tumor and patient characteristics, surgical outcomes, and prognosis between PEs and UEs.

In our previous paper, we reported that UEs were associated with higher LR rates but found no significant differences in MFS and OS between UEs and PEs [9]. This suggested that while UEs compromised local control due to suboptimal initial surgical margins, they did not necessarily impact the long-term risk of metastasis or OS. Our current study expands on these findings by demonstrating that PEs are associated with higher metastasis rates and cancer-specific mortality compared to UEs. This discrepancy can be attributed to the larger and more advanced nature of tumors typically encountered in PEs, which inherently increases the risk of distant spread and mortality despite achieving better local control with R0 resection margins. The existing literature on the relationship between UEs and metastatic risk is diverse and sometimes contradictory [26]. Several studies corroborate our initial findings, indicating that UEs primarily increase LR rates without significantly affecting MFS or OS [16,19,27,28]. Conversely, other studies suggest a potential link between UEs and increased metastatic risk, positing that inadequate initial surgery may facilitate metastatic progression [17,18,29]. Our current findings contribute to this debate by providing evidence that the advanced stage and larger size of tumors in the PE group are critical factors driving higher metastasis rates and cancer-specific mortality. These observations underscore the importance of early detection and timely referral to specialized sarcoma hubs to prevent the progression of sarcomas to advanced stages that necessitate PEs, thereby reducing the associated metastatic risk. In summary, while our predecessor paper and some studies suggest that UEs mainly compromise local control, our current findings emphasize that the characteristics of tumors requiring PEs, such as larger size and higher grade, are pivotal in determining metastatic potential and cancer-specific mortality, highlighting the need for strategies aimed at early detection and specialized intervention to improve patient outcomes [9].

The findings from our study have several important implications for clinical practice. The significant association between PEs and higher rates of metastasis and cancer-specific mortality underscores the necessity of early detection and timely intervention. However, early detection alone does not always guarantee a reduction in unplanned surgeries (whoops). Reducing the likelihood of UEs depends not only on diagnostic imaging but also on high clinical suspicion, standardized diagnostic protocols, and early referral to specialized sarcoma hubs. A multidisciplinary approach, involving experienced teams,

ensures more accurate diagnoses and improves surgical planning, ultimately minimizing the incidence of unplanned surgeries [11]. To reduce the incidence of UEs, clinicians should maintain a high index of suspicion for sarcomas, especially in patients presenting with suspicious soft tissue masses. Implementing standardized diagnostic protocols, including advanced imaging techniques and biopsy procedures, can aid in accurate diagnosis before any surgical intervention. Educational initiatives aimed at primary care physicians and general surgeons are essential to enhance early detection and appropriate referral practices. By increasing awareness and knowledge about sarcomas, these healthcare providers can better identify potential cases and refer patients to specialized sarcoma hubs sooner. Integrating AI-prediction tools into clinical workflows can help identify high-risk cases and facilitate personalized treatment planning. Moreover, there is a critical need for advanced diagnostic tools that can accurately differentiate between sarcomas and benign tumors. Developing and integrating such risk assessment tools would enable clinicians to better determine the likelihood of malignancy in suspicious cases, leading to more timely and appropriate interventions. These tools can analyze patient data to flag potential sarcoma cases for further investigation, ensuring that appropriate therapeutic measures are taken promptly. AI models can improve diagnostic accuracy, predict outcomes more effectively, and tailor interventions to individual patient profiles. Multidisciplinary tumor boards should review sarcoma cases to formulate comprehensive, individualized treatment plans that consider all relevant factors, including tumor size, grade, and anatomical location. This collaborative approach ensures that each patient receives a tailored treatment strategy designed to optimize outcomes. By focusing on early detection and appropriate surgical planning, we can reduce the incidence of UEs and improve long-term outcomes for patients with sarcomas. Early identification of sarcomas allows for PEs, which are associated with better immediate surgical outcomes and potentially lower rates of metastasis and cancer-specific mortality. Adopting these practices will significantly enhance patient care and survival rates.

Future research should focus on creating and validating these tools to predict high-risk cases accurately. By integrating individual tumor and patient characteristics, these models can enhance early detection, optimize treatment planning, and personalize therapeutic interventions. Additionally, studies exploring the implementation of standardized diagnostic protocols and their impact on reducing UEs could provide valuable insights. Investigating the long-term outcomes of patients with sarcomas managed with these advanced predictive tools and standardized protocols will help assess their effectiveness in real-world/time clinical settings. Research should also aim to better understand the genetic and molecular profiles of sarcomas, which can contribute to more targeted and effective treatment strategies. Longitudinal studies tracking the progression of sarcomas from diagnosis through treatment and follow-up could further elucidate the factors influencing metastasis and survival.

Our study has several limitations. Although the data were collected as real-world/time prospective data with retrospective review and control, potential biases such as selection bias and information bias may still be present. The accuracy of medical records can vary, potentially affecting the reliability of our findings. The study population, limited to patients treated at specialized sarcoma hubs, may not be representative of the broader population, affecting the generalizability of our findings to other settings with different patient demographics or healthcare resources. Variability in surgical techniques and postoperative care among different surgeons and institutions can influence outcomes, and although we attempted to control for these factors, residual confounding may still exist. Additionally, this study did not account for all possible variables influencing outcomes, such as genetic factors, detailed patient comorbidities beyond the Charlson Comorbidity Index, and specific treatment regimens, which may affect sarcoma prognosis. The follow-up period may not be sufficient to capture all long-term outcomes, particularly late metastasis and OS, necessitating longer follow-up studies to confirm the durability of observed outcomes and provide a comprehensive understanding of the long-term implications of PEs versus

UEs. While our study highlights key factors influencing sarcoma outcomes and suggests the potential benefits of AI prediction tools, further research is needed to develop and validate these tools in diverse clinical settings. Prospective studies with larger, more diverse populations and standardized protocols are necessary to confirm our findings and enhance the applicability of AI models in clinical practice. Despite these limitations, our study provides valuable insights into the differences between PEs and UEs and underscores the importance of early detection and appropriate referral to specialized sarcoma hubs. Future research should aim to address these limitations and further explore the potential of advanced predictive tools in improving sarcoma management.

5. Conclusions

Our study demonstrates that PEs achieve superior immediate surgical outcomes (R0 resection) but are linked to higher metastasis and cancer-specific mortality due to the advanced stage of tumors. Conversely, UEs, while associated with higher LR rates, do not significantly affect MFS or OS. These findings, building on our predecessor study, highlight the critical role of tumor characteristics in long-term outcomes. Early detection, comprehensive diagnostics, and timely referrals to specialized sarcoma hubs are essential to avoid UEs and reduce metastatic risk. This study addresses the ongoing literature debate on UEs' impact, emphasizing that advanced tumor features primarily drive poor prognosis. Variations in study populations, treatment modalities, and parameter distributions can explain contradictory findings in the literature. Future research should focus on developing predictive tools using individual tumor and patient characteristics to improve sarcoma management. This includes the creation and validation of AI-based models to accurately predict cases with a high risk of sarcoma diagnosis, which can facilitate early detection and personalized surgical planning, ultimately improving patient outcomes.

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Informed Consent Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Table A1. Sensitivity analysis, head and neck—logistic regression.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.18	0.05, 0.56	0.004
DST	0.36	0.18, 0.72	0.004
Anatomic region			
Head and neck	—	—	
Rest	0.86	0.22, 3.40	0.82
Size			
<5 cm	—	—	
5–10 cm	0.52	0.27, 1.00	0.05
>10 cm	0.15	0.06, 0.37	<0.001
Grade			
1	—	—	
2	0.14	0.05, 0.38	<0.001
3	0.21	0.09, 0.47	<0.001
Age	0.99	0.96, 1.02	0.56
Gender			
Female	—	—	
Male	1.95	1.11, 3.49	0.02
CCI	1.05	0.75, 1.46	0.76
Diagnosis			
Rest	—	—	
Undifferentiated/unclassified sarcoma	1.38	0.54, 3.45	0.50
Atypical lipomatous tumor	0.51	0.16, 1.52	0.23
Myxoid liposarcoma	0.20	0.04, 0.77	0.03
Myxofibrosarcoma	3.41	1.22, 9.69	0.02
Leiomyosarcoma (excluding skin)	3.01	1.17, 7.81	0.02

Table A2. Sensitivity analysis, upper extremity—logistic regression.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.13	0.04, 0.43	0.001
DST	0.33	0.16, 0.66	0.002
Anatomic region			
Rest	—	—	
Upper extremity	3.08	1.27, 7.54	0.01
Size			
<5 cm	—	—	
5–10 cm	0.51	0.27, 0.99	0.05
>10 cm	0.16	0.06, 0.41	<0.001
Grade			
1	—	—	
2	0.13	0.04, 0.36	<0.001
3	0.21	0.09, 0.47	<0.001
Age	0.99	0.96, 1.03	0.67
Gender			
Female	—	—	
Male	2.11	1.19, 3.81	0.01
CCI	1.06	0.75, 1.48	0.75
Diagnosis			
Rest	—	—	
Undifferentiated/unclassified sarcoma	1.13	0.44, 2.87	0.80
Atypical lipomatous tumor	0.48	0.16, 1.47	0.20
Myxoid liposarcoma	0.20	0.04, 0.77	0.03
Myxofibrosarcoma	2.02	0.67, 6.11	0.21
Leiomyosarcoma (excluding skin)	2.96	1.14, 7.75	0.03

Table A3. Sensitivity analysis, lower extremity—logistic regression.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.19	0.06, 0.61	0.006
DST	0.36	0.18, 0.71	0.004
Anatomic region			
Lower extremity	—	—	
Rest	1.31	0.72, 2.41	0.38
Size			
<5 cm	—	—	
5–10 cm	0.50	0.26, 0.96	0.04
>10 cm	0.15	0.06, 0.37	<0.001
Grade			
1	—	—	
2	0.15	0.05, 0.40	<0.001
3	0.21	0.09, 0.47	<0.001
Age	0.99	0.96, 1.02	0.53
Gender			
Female	—	—	
Male	1.93	1.10, 3.46	0.02
CCI	1.05	0.75, 1.46	0.76
Diagnosis			
Rest	—	—	
Undifferentiated/unclassified sarcoma	1.47	0.57, 3.74	0.42
Atypical lipomatous tumor	0.55	0.18, 1.69	0.30
Myxoid liposarcoma	0.23	0.04, 0.96	0.06
Myxofibrosarcoma	3.53	1.27, 10.0	0.02
Leiomyosarcoma (excluding skin)	2.97	1.16, 7.66	0.02

Table A4. Sensitivity analysis, trunk—logistic regression.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.17	0.05, 0.55	0.004
DST	0.34	0.17, 0.70	0.003
Anatomic region			
Rest	—	—	
Trunk	0.90	0.42, 1.87	0.79
Size			
<5 cm	—	—	
5–10 cm	0.52	0.27, 1.01	0.05
>10 cm	0.15	0.06, 0.37	<0.001
Grade			
1	—	—	
2	0.14	0.05, 0.38	<0.001
3	0.21	0.09, 0.46	<0.001
Age	0.99	0.96, 1.02	0.60
Gender			
Female	—	—	
Male	1.97	1.13, 3.52	0.02
CCI	1.05	0.74, 1.45	0.79
Diagnosis			
Rest	—	—	
Undifferentiated/unclassified sarcoma	1.35	0.53, 3.36	0.52
Atypical lipomatous tumor	0.50	0.16, 1.50	0.22
Myxoid liposarcoma	0.19	0.04, 0.76	0.03
Myxofibrosarcoma	3.29	1.18, 9.33	0.02
Leiomyosarcoma (excluding skin)	2.93	1.14, 7.66	0.03

Table A5. Sensitivity analysis, retroperitoneal—logistic regression.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.17	0.05, 0.54	0.003
DST	0.38	0.19, 0.75	0.006
Anatomic region			
Rest	—	—	
Retroperitoneal	0.44	0.12, 1.30	0.17
Size			
<5 cm	—	—	
5–10 cm	0.53	0.28, 1.02	0.06
>10 cm	0.16	0.06, 0.39	<0.001
Grade			
1	—	—	
2	0.15	0.05, 0.41	<0.001
3	0.22	0.10, 0.49	<0.001
Age	0.99	0.96, 1.02	0.58
Gender			
Female	—	—	
Male	1.99	1.13, 3.56	0.02
CCI	1.07	0.76, 1.48	0.71
Diagnosis			
Rest	—	—	
Undifferentiated/unclassified sarcoma	1.20	0.47, 3.02	0.70
Atypical lipomatous tumor	0.48	0.15, 1.45	0.20
Myxoid liposarcoma	0.19	0.04, 0.72	0.03
Myxofibrosarcoma	3.02	1.09, 8.56	0.04
Leiomyosarcoma (excluding skin)	3.15	1.21, 8.30	0.02

Table A6. Sensitivity analysis, visceral and intraperitoneal—logistic regression.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.18	0.05, 0.55	0.004
DST	0.35	0.17, 0.70	0.003
Anatomic region			
Rest	—	—	
Visceral and intraperitoneal	1.05	0.38, 2.65	0.92
Size			
<5 cm	—	—	
5–10 cm	0.52	0.27, 0.99	0.05
>10 cm	0.15	0.06, 0.37	<0.001
Grade			
1	—	—	
2	0.14	0.05, 0.38	<0.001
3	0.21	0.09, 0.47	<0.001
Age	0.99	0.96, 1.02	0.58
Gender			
Female	—	—	
Male	1.96	1.12, 3.51	0.02
CCI	1.05	0.75, 1.46	0.77
Diagnosis			
Rest	—	—	
Undifferentiated/unclassified sarcoma	1.36	0.54, 3.40	0.51
Atypical lipomatous tumor	0.50	0.16, 1.51	0.22
Myxoid liposarcoma	0.20	0.04, 0.77	0.03
Myxofibrosarcoma	3.37	1.21, 9.60	0.02
Leiomyosarcoma (excluding skin)	2.95	1.13, 7.87	0.03

Table A7. Sensitivity analysis, undifferentiated/unclassified sarcoma—logistic regression.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.15	0.05, 0.45	<0.001
DST	0.34	0.17, 0.66	0.001
Anatomic region			
Upper extremity	—	—	
Axial	0.30	0.13, 0.70	0.006
Lower extremity	0.26	0.11, 0.61	0.002
Size			
<5 cm	—	—	
5–10 cm	0.40	0.21, 0.73	0.003
>10 cm	0.11	0.05, 0.26	<0.001
Grade			
1	—	—	
2	0.30	0.13, 0.67	0.004
3	0.37	0.19, 0.73	0.004
Age	1.00	0.97, 1.03	0.90
Gender			
Female	—	—	
Male	1.84	1.06, 3.23	0.03
CCI	1.01	0.72, 1.41	0.94
Diagnosis			
Undifferentiated/unclassified sarcoma	—	—	
Rest	1.18	0.51, 2.84	0.71

Table A8. Sensitivity analysis, atypical lipomatous tumor—logistic regression.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.14	0.04, 0.43	<0.001
DST	0.35	0.18, 0.67	0.002
Anatomic region			
Upper extremity	—	—	
Axial	0.30	0.13, 0.71	0.006
Lower extremity	0.26	0.11, 0.62	0.002
Size			
<5 cm	—	—	
5–10 cm	0.41	0.22, 0.76	0.005
>10 cm	0.13	0.05, 0.31	<0.001
Grade			
1	—	—	
2	0.26	0.11, 0.61	0.003
3	0.31	0.15, 0.63	0.001
Age	1.00	0.97, 1.04	0.82
Gender			
Female	—	—	
Male	1.87	1.08, 3.31	0.03
CCI	1.01	0.72, 1.40	0.97
Diagnosis			
Atypical lipomatous tumor	—	—	
Rest	1.58	0.57, 4.54	0.38

Table A9. Sensitivity analysis, myxoid liposarcoma—logistic regression.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.14	0.04, 0.40	<0.001
DST	0.34	0.17, 0.66	0.002
Anatomic region			
Upper extremity	—	—	
Axial	0.29	0.12, 0.68	0.004
Lower extremity	0.28	0.12, 0.68	0.005
Size			
<5 cm	—	—	
5–10 cm	0.45	0.24, 0.84	0.01
>10 cm	0.11	0.05, 0.26	<0.001
Grade			
1	—	—	
2	0.27	0.11, 0.60	0.002
3	0.31	0.16, 0.59	<0.001
Age	1.00	0.97, 1.03	0.83
Gender			
Female	—	—	
Male	1.92	1.10, 3.39	0.02
CCI	1.03	0.73, 1.43	0.85
Diagnosis			
Myxoid liposarcoma	—	—	
Rest	4.01	1.08, 20.0	0.06

Table A10. Sensitivity analysis, myxofibrosarcoma—logistic regression.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.17	0.05, 0.51	0.002
DST	0.35	0.18, 0.69	0.002
Anatomic region			
Upper extremity	—	—	
Axial	0.37	0.15, 0.93	0.03
Lower extremity	0.29	0.12, 0.73	0.01
Size			
<5 cm	—	—	
5–10 cm	0.39	0.21, 0.73	0.003
>10 cm	0.12	0.05, 0.27	<0.001
Grade			
1	—	—	
2	0.30	0.13, 0.67	0.004
3	0.35	0.18, 0.65	0.001
Age	1.00	0.97, 1.03	0.98
Gender			
Female	—	—	
Male	1.80	1.04, 3.17	0.04
CCI	1.01	0.72, 1.40	0.94
Diagnosis			
Myxofibrosarcoma	—	—	
Rest	0.56	0.20, 1.54	0.26

Table A11. Sensitivity analysis, leiomyosarcoma—logistic regression.

Characteristics	OR	95% CI	*p*-Value
Sarcoma classification			
SST	—	—	
Bone	0.16	0.05, 0.46	0.001
DST	0.32	0.16, 0.62	<0.001
Anatomic region			
Upper extremity	—	—	
Axial	0.27	0.11, 0.64	0.003
Lower extremity	0.25	0.10, 0.59	0.002
Size			
<5 cm	—	—	
5–10 cm	0.42	0.22, 0.78	0.01
>10 cm	0.12	0.05, 0.28	<0.001
Grade			
1	—	—	
2	0.20	0.07, 0.49	<0.001
3	0.34	0.18, 0.64	<0.001
Age	1.00	0.97, 1.03	0.98
Gender			
Female	—	—	
Male	1.96	1.12, 3.48	0.02
CCI	1.03	0.73, 1.44	0.85
Diagnosis			
Leiomyosarcoma (excluding skin)	—	—	
Rest	0.37	0.15, 0.90	0.03

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Article

Enhancing Patient Experience in Sarcoma Core Biopsies: The Role of Communication, Anxiety Management, and Pain Control

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Simple Summary: This study emphasizes the crucial role of effective communication to improve patients' understanding and satisfaction during biopsy procedures. It highlights the importance of managing patient anxiety and fear, which can directly impact pain experiences. The study also identifies areas where real-time pain management can be enhanced and underscores the need for clear and accurate patient education to address concerns after the procedure.

Abstract: Background/Objectives: This study evaluates the effectiveness of communication strategies and pain management protocols to enhance patients' experiences during sarcoma core biopsies. Recognizing the complexity and anxiety associated with sarcoma diagnoses, this research aims to assess the utility of the Invasive Procedure Assessment (IPA) tool, focusing on its ability to identify areas for improvement through Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs). **Methods:** Conducted at two Integrated Practice Units (IPUs) within the Swiss Sarcoma Network, this study involved 282 consecutive patients who underwent core biopsies. One week post-procedure, patients completed the IPA questionnaire, which included PROMs and PREMs. Statistical analyses explored correlations between physician communication, patient understanding, anxiety, pain, and overall satisfaction. **Results:** The IPA tool effectively captured patient perspectives on sarcoma core biopsies. A significant positive correlation (rho = 0.619, $p < 0.0001$) was found between effective physician communication and patient understanding, which was associated with reduced anxiety and pain. Higher anxiety levels strongly correlated with increased pain perception (rho = 0.653, $p < 0.0001$), emphasizing the need for anxiety management. Patients with malignant tumors reported lower overall satisfaction compared to those with benign tumors ($p = 0.0003$), highlighting the need for tailored communication and pain management strategies. The data also suggested that clear communication might mitigate overly negative subjective impressions, such as concerns about wound complications. **Conclusions:** Effective communication and anxiety management are essential for improving patient satisfaction during sarcoma core biopsies. The study emphasizes the need for personalized care strategies tailored to tumor characteristics and patient demographics. Future research should validate these findings in diverse healthcare settings and explore the broader application of the IPA tool across different cultural and demographic contexts.

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Keywords: sarcoma; core biopsy; patient-reported outcomes; anxiety management; pain control; communication strategies; healthcare quality; PROMs; PREMs; invasive procedures; Invasive Procedure Assessment (IPA)

1. Introduction

The diagnosis of sarcomas poses significant challenges due to their heterogeneity and overlap of clinical features with other benign and malignant conditions [1]. Accurate diagnosis is crucial for effective treatment planning and improving patient outcomes. Core needle biopsies are essential in confirming the diagnosis of sarcoma, as they provide sufficient tissue samples for histopathological evaluation while minimizing procedural risks [2]. Studies have shown that core needle biopsies have high diagnostic accuracy and are critical for differentiating between malignant and benign lesions, ensuring that appropriate management strategies are implemented [1,3,4].

The importance of Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs) in healthcare is increasingly recognized [5]. These tools capture patients' perspectives on their health and care, thereby informing patient-centered care and improving healthcare quality by addressing both clinical outcomes and patient experiences [5]. PROMs and PREMs help clinicians understand the impact of illness and treatment from the patient's point of view, which is essential for tailoring treatment. Notably, the development of disease-specific instruments, such as sarcoma-specific PROMs described by Mosku et al., emphasizes the need for tools that reflect the unique challenges faced by sarcoma patients, including heterogeneity of the disease and complexity of its treatment [6]. Incorporating such tailored PROMs and PREMs into clinical practice has been shown to be associated with better clinical outcomes, improved patient satisfaction, and enhanced communication between patients and healthcare providers [5,7–9]. The sarcoma-specific instrument, in particular, underscores the potential of PROMs to provide comprehensive longitudinal assessments, thus facilitating shared decision-making and enhancing quality of care throughout the entire care cycle [6].

Patients undergoing biopsy procedures often face challenges such as fear, pain, and post-procedural concerns. Anxiety about the procedure is common, as patients fear the unknown and potential pain associated with the biopsy [10–12]. This anticipatory anxiety can amplify pain perception, a phenomenon known as the nocebo effect, where negative expectations lead to worse outcomes [13,14]. Despite the use of local anesthesia, many patients report significant pain during procedures like bone marrow and prostate biopsies [15,16]. Effective pain management strategies are crucial to minimize discomfort and improve the patient's tolerance of the procedure [11]. Post-procedural concerns, such as complications related to bleeding, infection, and wound healing, can further increase anxiety and decrease satisfaction [17].

Thorough pre- and post-procedural education helps to mitigate these concerns by setting appropriate expectations, significantly reducing patient anxiety and overall stress [18–20].

Inadequate pain management and poor communication can heighten anxiety and create a negative perception of the procedure. Conversely, comprehensive information and effective pain relief are associated with higher satisfaction and better experiences. This communication is vital for improving patient's comfort and satisfaction [11,18,21–24].

The rationale for this study is to address significant gaps in understanding and managing patient experiences during sarcoma core biopsies. While PROMs and PREMs have been widely used in cancer care, their application in sarcoma care and biopsies specifically remains under-examined. This study aims to evaluate the effectiveness of current communication strategies during sarcoma core biopsies, focusing on their impact on the reduction in patient anxiety and improving the overall perception of the procedure. Additionally, it seeks to assess the adequacy of pain management protocols in minimizing patient discomfort and enhancing satisfaction. Identifying specific areas for improvement in communication

and pain management to optimize patient experiences and outcomes is also a key objective. Addressing these objectives will provide evidence-based recommendations, enhancing patient care and leading to better outcomes within the healthcare system.

2. Materials and Methods

This study was conducted between June 2021 and March 2024 at two Integrated Practice Units of the Swiss Sarcoma Network in Switzerland (IPU-A; IPU-B). A total of 305 consecutive participants were recruited. Inclusion criteria encompassed all patients with a suspicion of sarcoma who were undergoing an invasive core biopsy procedure under local anesthesia, with no restrictions on demographics. Due to incomplete data sets, 23 patients were excluded, leaving a final cohort of 282 participants.

Demographics, the anatomical region, and the biological behavior of the tumors are summarized in Table 1. Tumors were classified using a Comprehensive Sarcoma Classification (CSC) system that operates on two key dimensions [25]:

1. **Anatomical Regions**:
   - **Axial Regions**: Includes the head and neck, trunk, and visceral regions (further divided into intraperitoneal and retroperitoneal).
   - **Appendicular Regions**: Encompasses the upper extremities and lower extremities.
2. **Tissue of Origin**:
   - **Superficial Soft Tissue (SST)**: Tumors originating in tissues close to the skin or epifascial.
   - **Deep Soft Tissue (DST)**: Tumors originating in deeper tissues, such as muscles or below the superficial fascia.
   - **Bone**: Tumors originating from or within bone structures.

Table 1. Age, gender, IPU, and sarcoma classification and biological behavior of the tumor among all participants (n = 282).

Parameter	Values
Age (years)	55.6 ± 17.6 *
Male/Female (n (%))	147 (52)/135 (48)
Integrated Practice Units (IPUs) (n (%)) [1]	
IPU-A	146 (52)
IPU-B	136 (48)
Anatomic region (n (%)) [2]	
Trunk	85 (30)
Head/Neck	7 (2)
Visceral retroperitoneal	7 (2)
Visceral intraperitoneal	3 (1)
Upper extremity	39 (14)
Lower extremity	141 (50)
Origin of lesion (n (%))	
DST [3]	192 (68)
SST [4]	48 (17)
Bone	43 (15)
Benign/malignant (n (%)) [5]	181 (64)/101 (36)

* Mean ± SD. [1] Defines in which IPU the study was conducted. [2] Anatomic region. [3] Deep soft tissue. [4] Superficial soft tissue. [5] Defines the biological behaviors of the tumors.

To provide a visual representation of the types of tumors observed in this study, Figure 1 illustrates the distribution of tumor diagnoses among the participants.

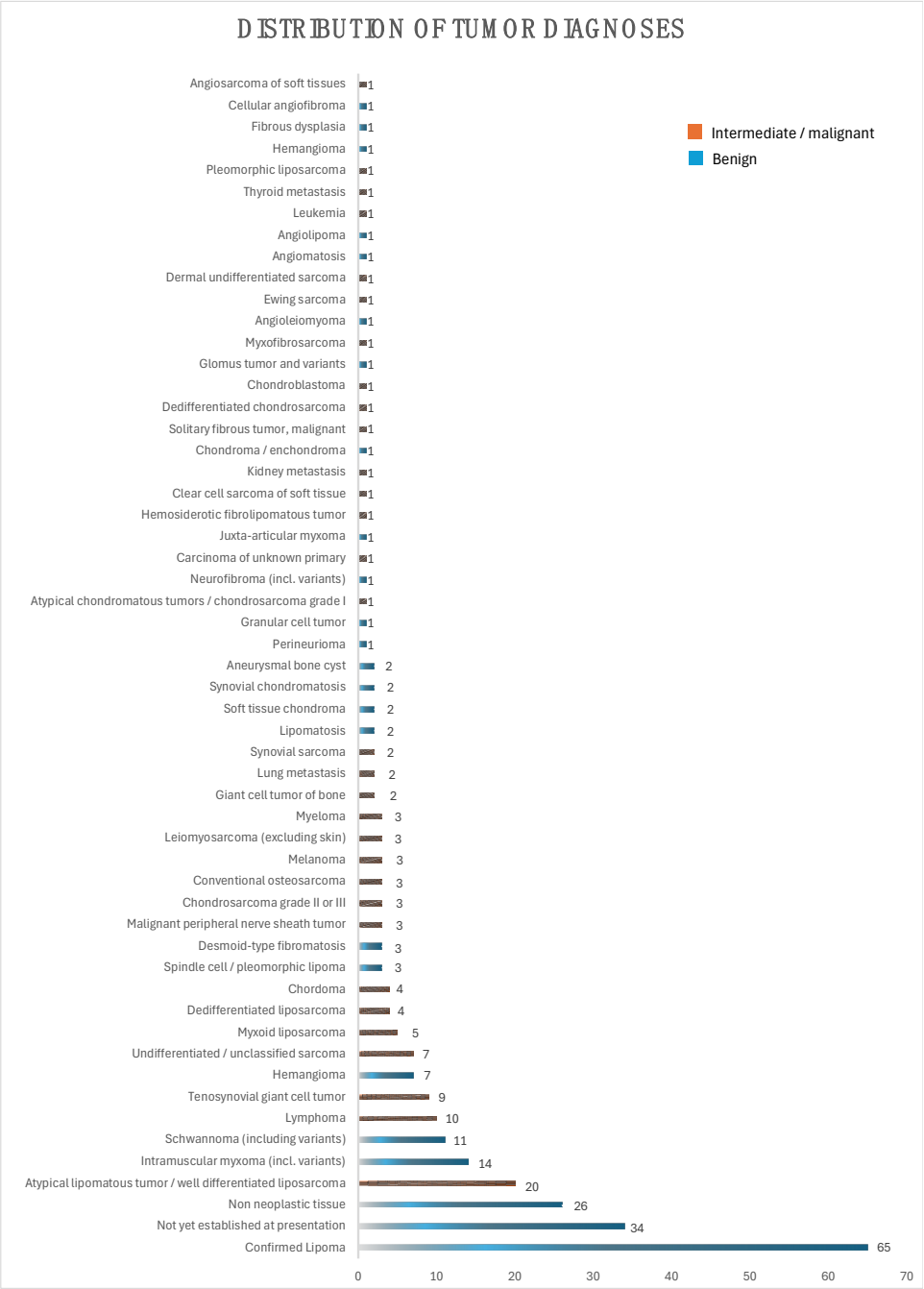


Figure 1. Distribution of diagnoses according to the results of biopsy at the time of presentation (n).

2.1. Creating the IPA Questionnaire for Detailed PREM and PROM Evaluation

Our Invasive Procedure Assessment (IPA) Questionnaire was developed to capture patient-reported experiences and outcomes related to invasive core biopsy procedures (Table 2). The aim was to create a comprehensive and balanced tool that would assess both positive and negative aspects of the patient's experiences and outcomes during the biopsy process. The following four categories were evaluated: procedure perception, overall experience and comfort, pain and medication analysis, and post-procedural outcomes.

The final questionnaire consisted of 13 questions and the EQ VAS scale, which is a vertical visual analog scale ranging from 0 to 100, with endpoints labeled 'The worst health you can imagine' and 'The best health you can imagine'. This scale allows for a standardized measurement of the patient's overall health perception [26]. Additionally, Patient-Reported Experience and Outcome Measures (PREMs and PROMs) were assessed

using a standardized section of the questionnaire, with questions rated on a scale from 1 to 10. This part of the questionnaire was completed by patients one week after the biopsy, immediately before their diagnosis was explained.

Table 2. Categorization of PROMs and PREMs in the IPA questionnaire.

PREMs		**PROMs**	
Procedure Perception	Overall Experience and Comfort	*Pain and Medication Analysis*	Post-Procedural Outcomes
Necessity (Q1) **Explanation (Q2)** **Understanding (Q3)** **Fear (Q4)**	**Team/Room (Q5)** **Organization (Q6)**	**Pain perception (Q7)** **Pain expectation (Q8)** **Medication (Q9)** **Pain Control (Q10)**	**Observation (Q11)** **Bleeding (Q12)** **Wound complications (Q13)**

By carefully selecting the aspects integrated into our questionnaire, we aimed to develop a comprehensive and practical tool suitable not only for assessing biopsy procedures but also other invasive procedures in an outpatient setting. The initial application of the questionnaire at multiple IPUs within the Swiss Sarcoma Network serves as a first step in a formal validation process [27], ensuring that it effectively captures relevant data to improve patient care and communication strategies.

Questions composing the questionnaire:
Q1: Did you understand the reason and necessity for the procedure?
1 (not at all understood)—10 (fully understood)
Q2: Was the procedure well explained by the physician who performed it?
1 (not at all explained)—10 (very well explained)
Q3: How well did you understand what was done during the procedure?
1 (not at all understood)—10 (perfectly understood)
Q4: How strong was your fear from the procedure?
1 (strongest fear ever experienced)—10 (no fear)
Q5: Consider the entire procedure, did you feel comfortable with the team and the room set-up?
1 (not at all comfortable)—10 (very comfortable)
Q6: How would you rate the entire organization process of the procedure?
1 (not at all good)—10 (very good)
Q7: How badly did you feel the pain during the procedure?
1 (strongest pain ever experienced)—10 (no pain)
Q8: Did the pain experienced during the procedure match your expectation?
1 (not at all matched)—10 (perfectly matched)
Q9: How satisfied were you with the medication you received during the procedure?
1 (not at all satisfied)—10 (very satisfied)
Q10: Was the pain well controlled during the first 24–48 h after the procedure?
1 (not at all controlled)—10 (very well controlled)
Q11: Was the observation period after the procedure long enough until dismissal?
1 (it was not long enough, I felt stressed)—10 (it was long enough, I did not feel stressed at all)
Q12: Was there any bleeding after the procedure?
1 (heavy bleeding)—10 (no bleeding)
Q13: Did you experience other local problems after the procedure (hematoma, redness, infection, swelling, other)?
1 (many other problems)—10 (no problems)

2.2. Data Analyses

The variable "overall satisfaction" (OS) was defined as the mean of all scores from the respective IPA questions:

$$OS = \frac{Q1 + Q2 + Q3 + Q4 + Q5 + Q6 + Q7 + Q8 + Q9 + Q10 + Q11 + Q12 + Q13}{13}$$

Data were analyzed using the R statistical software version R 4.0.2. Descriptive statistics were computed for all variables, including means and standard deviations (SDs) for normally distributed data, and medians with interquartile ranges (IQRs) for non-normally distributed data. Normality was assessed through a visual inspection of histograms and the Shapiro–Wilk W test. For normally distributed data, parametric tests were applied, while non-normally distributed data were analyzed using non-parametric methods. Variables significantly deviating from normality were transformed to correct skewness before further analysis. Differences in PROMs by gender, anatomic region, and tumor localization were examined using the Wilcoxon rank-sum test or Kruskal–Wallis test, depending on the number of groups compared. In cases where the Kruskal–Wallis test indicated significant differences, post hoc pairwise comparisons were conducted using the Dunn test with Bonferroni correction to control for multiple testing. Spearman's rank correlation was also computed. Significance was set at $p < 0.05$.

3. Results

3.1. Differences Depending on Gender, Anatomic Region of the Tumor, Origin of Lesion, and Biological Behavior of the Tumor

Analysis by gender, different anatomic regions, or tissue of origin revealed no statistically significant differences in most PROMs, including necessity (Q1), explanation (Q2), understanding (Q3), fear (Q4), team room (Q5), organization (Q6), pain perception (Q7), pain expectation (Q8), medication (Q9), pain control (Q10), observation (Q11), bleeding (Q11), wound complication (Q13), EQ VAS, and overall satisfaction. However, a notable exception was found in the PROM "understanding" (Q3), where patients with retroperitoneal tumors reported significantly lower scores compared to those with tumors in the head and neck ($p = 0.032$), lower extremity ($p = 0.024$), and trunk regions ($p = 0.013$). This may reflect the added complexity or less visible nature of these tumors.

Furthermore, the PROM "fear" (Q4) also showed significant variation by anatomic region ($p = 0.015$), with patients having trunk tumors reporting higher fear (lower scores in Q4) compared to those with upper extremity tumors ($p = 0.006$). This increased fear in patients with trunk tumors may be associated with the proximity of vital organs in these cases.

Statistically significant differences were observed in the PROM "observation" (Q11) depending on the anatomic region of the tumor ($p = 0.023$). Specifically, patients with tumors in the trunk reported higher observation time scores compared to those with tumors in the upper extremity ($p = 0.009$), which may reflect greater caution or concern in clinical observation for these tumors.

Additionally, a significant difference was noted in the EQ VAS score depending on the biology of the tumor, with patients diagnosed with malignant tumors reporting lower overall health scores compared to those with benign tumors ($p = 0.0003$). This underscores the profound impact of malignant pathology on patients' health status and perception, highlighting the potential need for additional supportive care measures for these patients.

3.2. Overall Analyses of IPA PROMs and PREMs

Table 3 provides a detailed overview of the Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs) for all participants (n = 282), showing the total number of participants who reported each score and the corresponding percentage. This table allows for a granular understanding of the distribution of responses across different domains, including pain, satisfaction with medication, observation period,

bleeding, local problems, pain control, understanding of the biopsy necessity, fear, explanation by the physician, understanding of the procedure, comfort with the team and room setup, and the overall organization process. See Figure 2 for a visual representation of these measures across all participants.

Table 3. Summary of PROMs and PREMs for all participants (n = 282), showing scores and percentages.

PROM Domain	Median (IQR)	0 (n(%))	1 (n(%))	2 (n(%))	3 (n(%))	4 (n(%))	5 (n(%))	6 (n(%))	7 (n(%))	8 (n(%))	9 (n(%))	10 (n(%))
Q1 necessity	10 (10–10)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	3 (1.1)	1 (0.4)	5 (1.8)	12 (4.3)	16 (5.7)	244 (86.5)
Q2 explanation	10 (10–10)	0 (0)	2 (0.7)	0 (0)	0 (0)	1 (0.4)	7 (2.5)	0 (0)	10 (3.5)	17 (6.0)	25 (8.9)	220 (78.0)
Q3 understanding	10 (9–10)	0 (0)	5 (1.8)	1 (0.4)	2 (0.7)	0 (0)	13 (4.6)	4 (1.4)	8 (2.8)	22 (7.8)	31 (11.0)	196 (69.5)
Q4 fear	5 (1–9)	0 (0)	89 (31.6)	26 (9.2)	11 (3.9)	5 (1.8)	29 (10.3)	6 (2.1)	15 (5.3)	12 (4.3)	25 (8.9)	64 (22.7)
Q5 team/room	10 (10–10)	0 (0)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0)	7 (2.5)	3 (1.1)	4 (1.4)	16 (5.7)	29 (10.3)	220 (78.0)
Q6 organization	10 (10–10)	0 (0)	0 (0)	0 (0)	2 (0.7)	1 (0.4)	12 (4.3)	1 (0.4)	8 (2.8)	18 (6.4)	24 (8.5)	216 (76.6)
Q7 pain perception	6 (1–9)	0 (0)	87 (30.8)	16 (5.7)	7 (2.5)	8 (2.8)	18 (6.4)	6 (2.1)	12 (4.3)	27 (9.6)	34 (12.1)	67 (23.8)
Q8 pain expectation	9 (5–10)	0 (0)	21 (7.4)	9 (3.2)	12 (4.3)	4 (1.4)	31 (11.0)	9 (3.2)	14 (5.0)	24 (8.5)	28 (9.9)	130 (46.1)
Q9 medication	10 (8–10)	0 (0)	10 (3.5)	2 (0.7)	1 (0.4)	2 (0.7)	43 (15.2)	1 (0.4)	6 (2.1)	16 (5.7)	15 (5.3)	186 (66.0)
Q10 pain control	10 (5–10)	0 (0)	30 (10.6)	9 (3.2)	4 (1.4)	3 (1.1)	50 (17.7)	2 (0.7)	10 (3.5)	14 (5.0)	18 (6.4)	142 (50.4)
Q11 observation	10 (10–10)	0 (0)	6 (2.1)	3 (1.1)	2 (0.7)	1 (0.4)	15 (5.3)	2 (0.7)	4 (1.4)	8 (2.8)	29 (10.3)	212 (75.2)
Q12 Bleeding	8 (1–10)	0 (0)	76 (27.0)	9 (3.2)	6 (2.1)	6 (2.1)	21 (7.4)	3 (1.1)	12 (4.3)	32 (11.3)	41 (14.5)	76 (27.0)
Q13 wound complications	8 (1–10)	0 (0)	91 (32.3)	4 (1.4)	9 (3.2)	3 (1.1)	11 (3.9)	4 (1.4)	4 (1.4)	23 (8.2)	24 (8.5)	109 (38.7)
Q14 overall satisfaction	8 (7–9)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.7)	7 (2.5)	16 (5.3)	100 (35.5)	54 (19.1)	80 (28.4)	23 (8.2)

3.3. Results According to IPA Categories

3.3.1. Procedure Perception

The results indicated generally positive perceptions regarding the procedure, with high scores for understanding the necessity (median score 10, IQR 10–10), explanation (median score 10, IQR 10–10), and procedural understanding (median score 10, IQR 9–10); a significant level of fear was reported, with 31.6% of patients expressing the highest level of fear (score 1 on a scale of 1–10). This fear could stem from concerns about the procedure itself or the potential consequences, such as being diagnosed with a malignant lesion, as indicated by the distribution of lower scores in the "fear" domain (median score 5, IQR 1–9). The distinction between these sources of fear is essential for developing targeted strategies to alleviate anxiety.

3.3.2. Overall Experience and Comfort

The overall experience and comfort of patients were rated highly, with the median scores for satisfaction with the team and room setup at 10 (IQR 10–10) and 78% of patients rating their experience as the highest possible score (score 10) (Table 4, Q5). The organization of the procedure also received positive feedback, with a median score of 10 (IQR 10–10), and 76.6% of patients rated the organization as excellent (score 10) (Table 3, Q6). These

high ratings indicate that the environment and professionalism of the medical staff greatly contributed to patient comfort. There were no immediate areas identified for improvement in this category, suggesting that the current practices are effective in ensuring a supportive procedural environment.

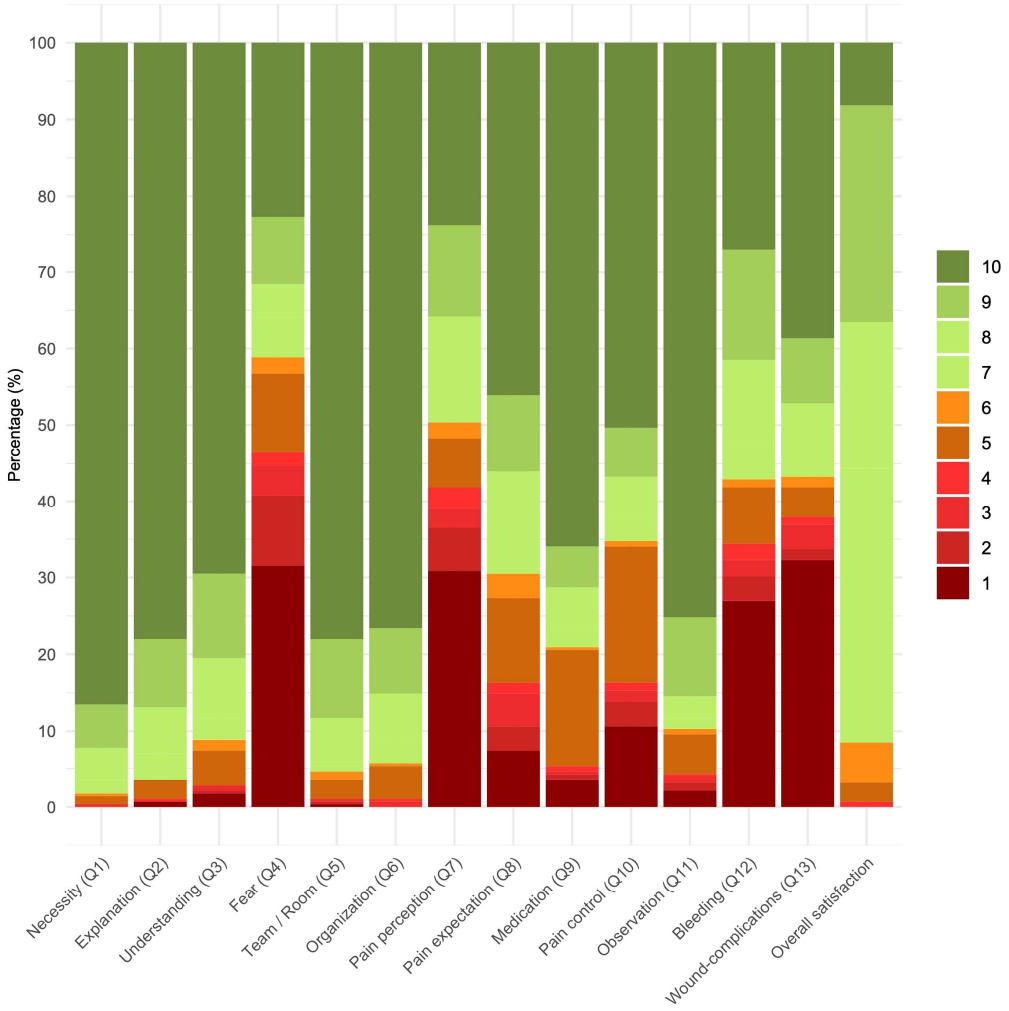


Figure 2. Patient reported outcome/experience measures of all participants (n = 282).

Table 4. Analysis of PROM/PREM differences between IPU-A (n = 146) and IPU-B (n = 136).

IPA Domain	IPU-A	IPU-B	*p*-Value
Q4 fear	4.5 ± 3.7 * 3 (1–8.8) **	5.8 ± 3.7 6 (2–10)	0.002
Q7 pain perception	4.8 ± 3.7 4 (1–9)	6.4 ± 3.7 8 (1–10)	<0.001
Q5 team/room	9.4 ± 1.3 10 (9–10)	9.6 ± 1.3 10 (10–10)	0.047
Q9 overall satisfaction	7.7 ± 1.2 7 (7–9)	8.1 ± 1.3 8 (7–9)	0.003

* mean ± SD, all such values
** median (IQR), all such values

3.3.3. Pain and Medication Analysis

Pain management emerged as a crucial area with room for improvement. Patients reported experiencing high levels of pain during the procedure, with a median score of 6

(IQR 1–9), where 30.8% of patients rated their pain at the highest level (score 1) (Table 3, Q7). This pain often matched their expectations, with a median score of 9 (IQR 5–10) for pain expectation alignment (Table 3, Q8), suggesting a potential "self-fulfilling prophecy" effect. While medication was generally considered sufficient, with a median score of 10 (IQR 8–10) and 66% of patients rating their satisfaction with medication at the highest level (score 10) (Table 3, Q9), pain control during the procedure itself showed room for improvement. Pain control post-procedure was relatively well-rated, with a median score of 10 (IQR 5–10), and 50.4% of patients felt that their pain was very well controlled within the first 24–48 h after the procedure (Table 3, Q10). These data indicate that although post-procedural pain control was effective for most patients, enhancing intra-procedural pain management could further improve patient experiences.

3.3.4. Post-Procedural Outcomes

Post-procedural outcomes were largely positive, with high satisfaction regarding the observation period after the procedure, as indicated by a median score of 10 (IQR 10–10) and 75.2% of patients rating the observation period at the highest level (score 10) (Table 3, Q11). Despite this, 27% of patients expressed concerns about post-procedural bleeding, with scores reflecting the presence of bleeding rated at a median of 8 (IQR 1–10) (Table 3, Q12). Additionally, concerns about wound complications were noted, with a median score of 8 (IQR 1–10) and 32.3% of patients reporting high levels of worry about wound-related issues (score 1) (Table 3, Q13). Importantly, no cases required surgical revisions or therapeutic interventions, suggesting that these concerns were likely due to misaligned expectations. Enhancing patient education on what to expect post-procedure could help to mitigate these concerns and further improve overall satisfaction.

3.4. Correlations Between PROMs

3.4.1. Correlation Between Physician Explanation and Various PROMs

A significant positive correlation was observed between the PROM related to the physician's explanation and the PROM related to understanding the procedure (rho = 0.619, $p < 0.000$), indicating that clear and comprehensive explanations from physicians strongly enhance patient comprehension, which is crucial for reducing anxiety and improving overall patient experience. Additionally, a significant positive correlation was found between the explanation and the understanding of the necessity of the biopsy (rho = 0.288, $p < 0.000$), further emphasizing the importance of clear communication in ensuring that patients understand the rationale behind the procedure.

While the correlation between physician's explanation and fear of biopsy was negative, it did not reach statistical significance (rho = −0.117, $p = 0.052$), suggesting that although better explanations may help reduce fear, this effect might be limited or require more targeted interventions to achieve significant anxiety reduction. Furthermore, significant positive correlations were observed between the explanation provided by the physician and satisfaction with the setup (rho = 0.573, $p < 0.000$), satisfaction with the organization (rho = 0.389, $p < 0.000$), and overall satisfaction (rho = 0.241, $p < 0.000$), highlighting that effective communication not only improves understanding but also enhances overall procedural satisfaction and the perception of care quality.

3.4.2. Correlations Between Fear of the Biopsy and Pain

There was a significant positive correlation between fear of the biopsy and experienced pain during the biopsy (rho = 0.653, $p < 0.001$). Additionally, there was a significant negative correlation between fear of biopsy and pain control after biopsy (rho = −0.287, $p < 0.001$) (Table 5).

3.4.3. Correlations Between Expected Pain, Experienced Pain, and Pain Control

There was no significant correlation between the expected pain and the experienced pain during the biopsy. However, there was a significant weak negative correlation between

experienced pain during biopsy and pain control for 24 h post-procedure (rho = −0.257, $p < 0.001$) (Table 5).

Table 5. Positive and negative correlations between PROMs and PREMs. This table presents the significant positive and negative correlations between various Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs).

Positive Correlations		Negative Correlations	
PREMs/PROMs	**rho-/*p*-Value**	**PREMs/PROMs**	**rho-/*p*-Value**
explanation and understanding	0.619/<0.0001	explanation and fear	−0.117/0.052
explanation and necessity	0.288/<0.0001	fear and pain control	−0.287/<0.0001
fear and pain	0.653/<0.0001	pain perception and control	−0.257/<0.0001

3.5. Comparison of Patient-Reported Outcome Measures Between IPU-A and IPU-B

Upon comparing the two Integrated Practice Units (IPUs), IPU-A and IPU-B, there were no significant demographic differences found between patient populations, including age, gender, and sarcoma classification. Despite statistically significant differences in several areas, the actual mean and median values between IPU-A and IPU-B were quite similar, indicating that these differences may have limited practical impact (Table 5). For instance, patients at IPU-B reported lower levels of fear and pain during the biopsy, as well as higher overall satisfaction, compared to those at IPU-A. On the other hand, IPU-A scored slightly better in the procedural setup and patients' overall health perception as measured by the EQ VAS scale. These findings indicate that both institutions provide a high standard of care, with only minor differences in specific aspects of patient experience (Table 4; Supplementary Figures S1 and S2).

4. Discussion

This study evaluated the use of Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs) in assessing sarcoma biopsy procedures, with a focus on identifying areas for improvement [5,8,9,28–30]. Given the unique challenges in sarcoma care, the development and application of sarcoma-specific instruments, as highlighted by Mosku et al., are crucial for accurately capturing patient experiences and outcomes, especially when dealing with such a heterogeneous and complex disease [4,6]. Data from 282 patients undergoing core biopsies with the suspicion of sarcoma at two Integrated Practice Units (IPUs) of the Swiss Sarcoma Network (SSN) highlighted generally high patient satisfaction, but also identified critical areas needing enhancement, particularly in managing anxiety, pain, and post-procedural concerns such as bleeding or wound complications.

Our findings demonstrate a significant positive correlation between detailed explanations provided by physicians and patients' understanding of the procedure and the necessity of the biopsy. This correlation highlights the critical role of effective communication in reducing anxiety and pain during the procedure, suggesting that clear and compassionate communication may directly influence patients' physiological responses, potentially through mechanisms such as the modulation of stress and pain pathways. This is consistent with the broader literature on the impact of communication in medical settings [10,11,18,19,31]. These findings underscore the importance of clear and compassionate communication in improving patient outcomes, as has been observed in studies on breast and lung biopsies [10,11,31]. It appears that this positive effect of communication extends to the sarcoma patient population as well.

Despite these positive correlations, this study also revealed areas where patient experiences could be improved, particularly in managing intra-procedural pain. The significant correlation between fear and pain perception suggests that anxiety management is not

only important for emotional well-being but may also have a direct impact on physical pain experiences during the procedure. While post-procedural pain management was generally effective, controlling pain during the biopsy remains a significant challenge. This aligns with previous research on the persistent pain experienced during procedures such as bone marrow and prostate biopsies, despite the use of local anesthesia [15,16,32]. The "self-fulfilling prophecy" nocebo effect, where patients' expectations of pain may lead to heightened pain perception, further complicates this issue [14]. This relationship underscores the importance of addressing psychological factors, such as fear and anxiety, as part of a comprehensive pain management strategy. Implementing advanced pain relief methods, such as music therapy or virtual reality, particularly for patients experiencing high levels of anxiety, may be considered to improve patient comfort during these procedures [33,34].

The comparison between the two IPUs, while revealing some statistically significant differences in fear, pain, and overall satisfaction, suggest that these differences are nuanced rather than indicative of major disparities in care quality. This finding is intriguing, especially given the similar demographic and cultural contexts of the two sites. Future research could explore whether these subtle differences might be more pronounced in more culturally or demographically diverse settings, which could provide valuable insights into how various factors influence Patient-Reported Outcome Measures.

Additionally, this study found that fear of the biopsy was a significant predictor of pain perception, a relationship well documented in clinical settings involving both acute and chronic pain [35–39]. This finding suggests that fear may amplify the sensory experience of pain, possibly through heightened activation of the central nervous system's pain pathways, and indicates that psychological factors can significantly influence the physical experience of pain. This correlation highlights the need for targeted interventions to manage patient anxiety before and during the procedure. Strategies that incorporate cognitive-behavioral approaches, mindfulness, or other anxiety reduction techniques could be effective in mitigating this fear–pain relationship. Improving patient education about post-procedural outcomes, particularly regarding common but minor complications like hematomas, could also enhance overall satisfaction. Many patients expressed concern about bleeding and wound complications, likely due to misaligned expectations. Educating patients on what to expect after the procedure could alleviate these concerns and reduce anxiety [10,17,18].

While the sample size of this prospective study was adequate for the purposes of the analysis, larger studies could provide more robust data and help confirm the findings. However, the reliance on self-reported data introduces potential biases, such as recall bias or social desirability bias, which may affect the accuracy and reliability of the findings. Moreover, this study's focus on a specific demographic group in Switzerland limits the generalizability of the results to other populations or healthcare systems. The healthcare context in Switzerland, characterized by specific organizational and cultural factors, may not be directly comparable to other settings, which could limit the applicability of the findings. Future research should include more diverse populations and healthcare settings to explore how these findings translate across different contexts. Additionally, addressing potential selection bias by ensuring a more representative sample of patients, including those from varied socioeconomic and cultural backgrounds, would enhance the validity of future studies [40,41].

To fully understand the potential of the Invasive Procedure Assessment (IPA) tool, future studies should explore its application in a variety of settings and contexts. Testing the IPA across different healthcare environments—such as diverse geographic locations, cultural backgrounds, and medical specialties—would help validate its effectiveness and reveal its versatility. This broader application could uncover specific insights about patient experiences in different scenarios, demonstrating how the IPA can be an effective tool for assessing and improving medical procedures in various settings. This approach would highlight the IPA's capacity to enhance patient-centered care on a larger scale.

5. Conclusions

This study underscores the critical importance of effective communication and personalized pain management in enhancing patient experience during sarcoma core biopsies. Integrating PROMs and PREMs into routine practice facilitates a deeper understanding of patient needs and highlights areas for improvement. By addressing both psychological and physical aspects of care, we can significantly improve patient-centered outcomes. Future research should validate these findings in diverse settings and explore the broader application of the IPA tool to further optimize patient care.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers16233901/s1, Figure S1. Patient reported outcome/experience measures at IPU-A (n = 147). Figure S2. Patient reported outcome/experience measures at IPU-B (n = 136).

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Biopsy Ratio of Suspected to Confirmed Sarcoma Diagnosis

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Simple Summary: Determining the biology of mesenchymal tumor, imaging alone is usually not enough, and the final diagnosis is established through tissue analysis If the indication to perform a biopsy is not established frequently enough, an undesired unplanned resection of a sarcoma may result, and conversely, a patient's discomfort as well as costs may increase. In here, using a real-world data registry of quality, we included the absolute number of a consecutive series of patients, to determine the prevalence of biopsies and its related diagnosis, to establish a reference, which may allow for the definition of a quality indicator for the work-up within a multidisciplinary team.

Abstract: The ratio of malignancy in suspicious soft tissue and bone neoplasms (RMST) has not been often addressed in the literature. However, this value is important to understand whether biopsies are performed too often, or not often enough, and may therefore serve as a quality indicator of work-up for a multidisciplinary team (MDT). A prerequisite for the RMST of an MDT is the assessment of absolute real-world data to avoid bias and to allow comparison among other MDTs. Analyzing 950 consecutive biopsies for sarcoma-suspected lesions over a 3.2-year period, 55% sarcomas were confirmed; 28% turned out to be benign mesenchymal tumors, and 17% non-mesenchymal tumors, respectively. Of these, 3.5% were metastases from other solid malignancies, 1.5% hematologic tumors and 13% sarcoma simulators, which most often were degenerative or inflammatory processes. The RMST for biopsied lipomatous lesions was 39%. The ratio of unplanned resections was 10% in this series. Reorganizing sarcoma work-up into integrating practice units (IPU) allows the assessment of real-world data with absolute values over the geography, thereby enabling the definition of quality indicators and addressing cost efficiency aspects of sarcoma care.

Keywords: sarcoma; biopsy; suspicion; confirmation; ratio

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1. Introduction

Sarcomas are malignant tumors of mesenchymal origin [1]. They account for 1% of all human cancers [2]. Sarcomas have an incidence of between 1 and 5 per 1,000,000 people [1], and are therefore considered a rare disease. Their diagnosis usually requires a high level of suspicion from the beginning of the correct and efficient work-up [3–5]. Once the diagnosis is established, not all suspicious lesions turn out to be malignant. According to Rowbotham et al. [6], who assessed all referrals to the sarcoma service in the UK, out of 49 patients who underwent biopsy with the suspicion of sarcoma, only 17 patients (35%) resulted with a malignant diagnosis, of which 13 (27%) were primary soft tissue sarcomas, 4 (8%) were soft tissue metastases (breast cancer, squamous cell carcinoma, colon carcinoma) and 32 (65%) were benign lesions (lipoma n = 19, posttraumatic lesions n = 5, vascular malformations n = 5, fibrous lesions n = 2 and nerve sheath tumor n = 1). In another study, Buvarp-Dyrop et al. [7] assessed the routes to diagnoses for suspected sarcoma in Denmark. Out of 545 patients, 102 (18.7%) were diagnosed as sarcoma and 68 (12.5%) as

other malignancies, of these the most frequent being: metastasis (n = 30), lymphoma (n = 23) and myeloma (n = 6). The remaining 375 (68.8%) were benign lesions, the most frequent being: lipoma (n = 60), reactive tissue changes (n = 46), and schwannoma/neurofibroma (n =23). In another study made in the Rhone-Alpes region in France (Lurkin et al. 2010) [8], to evaluate the concordance between initial diagnosis and central pathology review for sarcoma cases, out of 366 patients diagnosed with sarcoma over a period of 1 year, 199 (54%) had full concordance between primary diagnosis (first pathologist) and second opinion (expert center pathologist), 97 (27%) had partial concordance (identical diagnosis of conjunctive tumor, but different grade or subtype), and 70 (19%) had complete discordance (different histological type or invalidation of the diagnosis of sarcoma). Another study (Gassert, F.G et al.) [9] analyzed retrospectively the histopathologic findings of 1753 patients presenting with a soft tissue lesion $\leq$5 cm. They found that 22.4% of these lesions were malignant.

The information about the relation between clinical suspicion of malignancy and the definitive histopathologic confirmation of sarcoma is important, because not all suspected sarcoma will ultimately be confirmed as such, but nevertheless absorb logistical and manpower capacities within the sarcoma work-up, besides causing inconveniences to the patients [10–12]. As long as the absolute number of biopsies for sarcoma suspicion as well as RMST are not defined, it will be impossible to determine whether too many or too few biopsies within an MDT actually are performed, and what for [13,14]. This may be particularly important in order to possibly understand the often frustratingly high rate of unplanned resections and potentially redefine the process of work-up of patients with mesenchymal tumors.

For these reasons, we are specifically asking the following questions:

(1). How many consecutive biopsies were performed with the suspicion of sarcoma over a 3.2-year period (January 2018–March 2021) in our network?
(2). How often was the suspicion of sarcoma confirmed as sarcoma?
(3). What types of non-sarcoma lesions, so-called sarcoma simulators, were diagnosed?

2. Materials and Methods

Reorganizing the MDT into an integrated practice unit over the geography (IPU) [15], the Swiss Sarcoma Network (www.swiss-sarcoma.net, accessed on 23 February 2022, has established a prospective, real-world shared data sarcoma registry of quality, including the full longitudinal care cycle of patients over time. This registry focuses on the longitudinal assessment of the quality indicators of sarcoma care, with the aim of exchanging transdisciplinary and transparently sarcoma therapy relevant absolute data and of defining quality scores for sarcoma treatment [16].

All prospectively collected data from 1 January 2018 to March 2021 were included in this study for analysis. The data are stored with Adjumed and analyzed with the Adjumed Analyze tool (Adjumed Services AG, Zurich, Switzerland; www.adjumed.ch, accessed on 10 March 2022), which can be used for basic/descriptive statistics (such as combinations of parameters, and the extraction of data), as well as R statistical program (version 4.1.0). In this study, we have used the descriptive summary statistics and the two-sample differences tests.

All consecutive patients who have undergone a biopsy of any type to work up a suspicious mesenchymal mass during the indicated time period, independent of its anatomic location, and presented to the multidisciplinary team meeting/sarcoma board, were included in this study (https://swiss-sarcoma.net/pdf/GCP_1_minimal_workup_requirements.pdf, accessed on 17 January 2022).

Core biopsy is considered standard in this series; ultrasound-guided biopsy was applied for soft tissue tumors, and CT-guided biopsy was usually used with bone tumors. Excisional biopsies were performed when the non-lipomatous lesions were small (>2 cm) and epifascially located. Incisional biopsies were only indicated in exceptions. The diagnostic yield of the biopsies was >93%; for this analysis, only the first diagnostic biopsy per patient was included. In a study done in 2019 [3] to evaluate the diagnostic yield of the

core biopsy in soft tissue lesions of the extremities, Qi, D. et al. [3] found a diagnostic yield of 96%.

All tissue specimens were assessed by a sarcoma reference pathologist according to the World Health Organization (WHO) classification of mesenchymal tumors and defined as benign, intermediate and malignant mesenchymal tumors, hematologic malignancy, metastasis and sarcoma simulators [11].

3. Results

3.1. Biopsies of Mesenchymal Tumors Performed over a 3.2-Year Period

Overall, 950 biopsies with the suspicion of sarcoma were performed during the study period. The biopsy specimens were collected from 950 different patients during the abovementioned time period. The type of biopsy was categorized into ultrasound (musculosceletic and visceral lesions), fluoroscopic (bone lesions) or CT-guided (thoracic, abdominal, pelvic lesions) core biopsy, fine needle aspiration, incisional and excisional biopsies [17,18], each separated into with or without (so-called whoops surgeries) suspicion of sarcoma (Table 1). In our study, sarcoma was confirmed in 62% of excisional biopsies, 57% in core biopsies, 53% in incisional biopsies and 48% in fine needle aspirations. The total amount of unplanned resections, i.e., so-called "whoops" surgeries, was 10% (21 incisional and 75 excisional biopsies without sarcoma suspicion) (Table 2).

Table 1. Classification of mesenchymal biopsies.

Suspicion of Sarcoma	Confirmed Sarcoma	Malignant
		Intermediate
	Benign Mesenchymal Tumors	
	Lesions other than Mesenchymal Tumor	Metastasis
		Hematologic Tumors
		Sarcoma Simulators

Table 2. Types of biopsies performed; n = 950.

	Types of Biopsies	No./% of Cases	No./% of Confirmed Sarcoma
1	Core Biopsy	409/43%	542/57%
2	Fine Needle Aspiration	130/14%	456/48%
3	Incisional Biopsy with suspicion of sarcoma	110/11%	504/53%
4	Excisional Biopsy with suspicion of sarcoma	90/10%	589/62%
5	Incisional Biopsy without suspicion of sarcoma	136/14%	Not Applicable
6	Excisional Biopsy without suspicion of sarcoma	75/8%	Not Applicable

The study found also similar RMST according to anatomic body regions. This ratio was 63% in the head and neck region, 61% in the trunk, 49% in the lower extremity and 47% in the upper extremity (Table 3).

Table 1 describes the 3 groups that resulted from the 950 biopsies and the subgroups for each of them.

Table 2 describes the types of biopsies performed and their respective percentages.

Table 3 describes differences in the RMST according to anatomic body regions.

Table 3. RMST according to anatomic region.

Anatomic Regions Sarcoma Diagnosed	No./RMST
Head and Neck	598/63%
Trunk	579/61%
Upper Extremity	447/47%
Lower Extremity	466/49%

3.2. Types of Tumors Identified through Biopsy

Overall, 55% (n = 522) of tumors were confirmed as sarcomas and, consequently, 45% (n = 428) of all biopsies turned out not to be sarcoma. Of the latter, 28% (n = 259) were benign lesions, and 17% (n = 169) were sarcoma simulators. Hence, the RMST was 0.55. Specifically, the final diagnoses included malignant (358; 38%) and intermediate mesenchymal tumors (164; 17%), benign mesenchymal tumors (259; 28%), metastasis (34; 3.5%), hematologic tumors (14; 1.5%) and sarcoma simulators (121; 13%) (Figures 1–3).

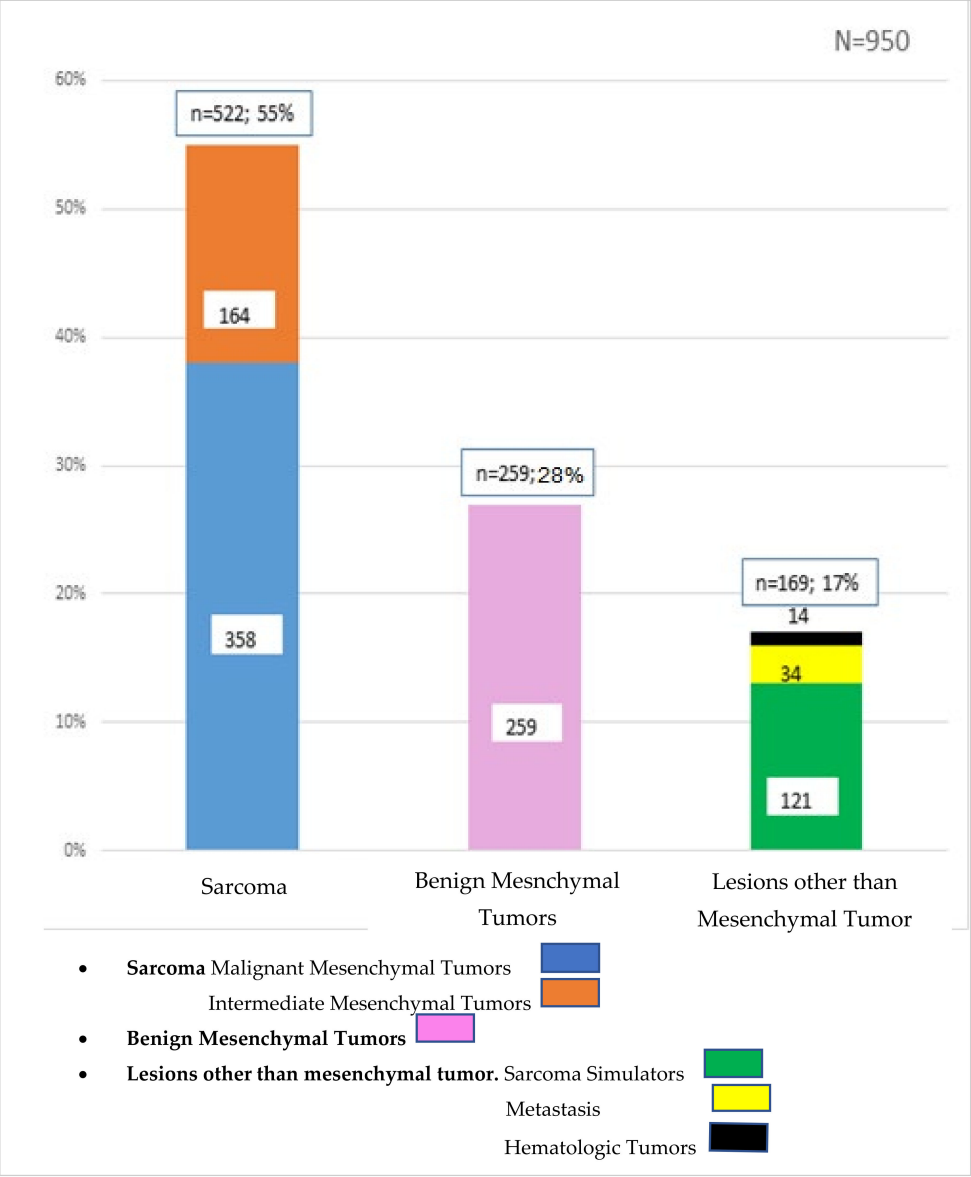


Figure 1. Types of lesions after biopsy.



Figure 2. List of benign mesenchymal tumors.

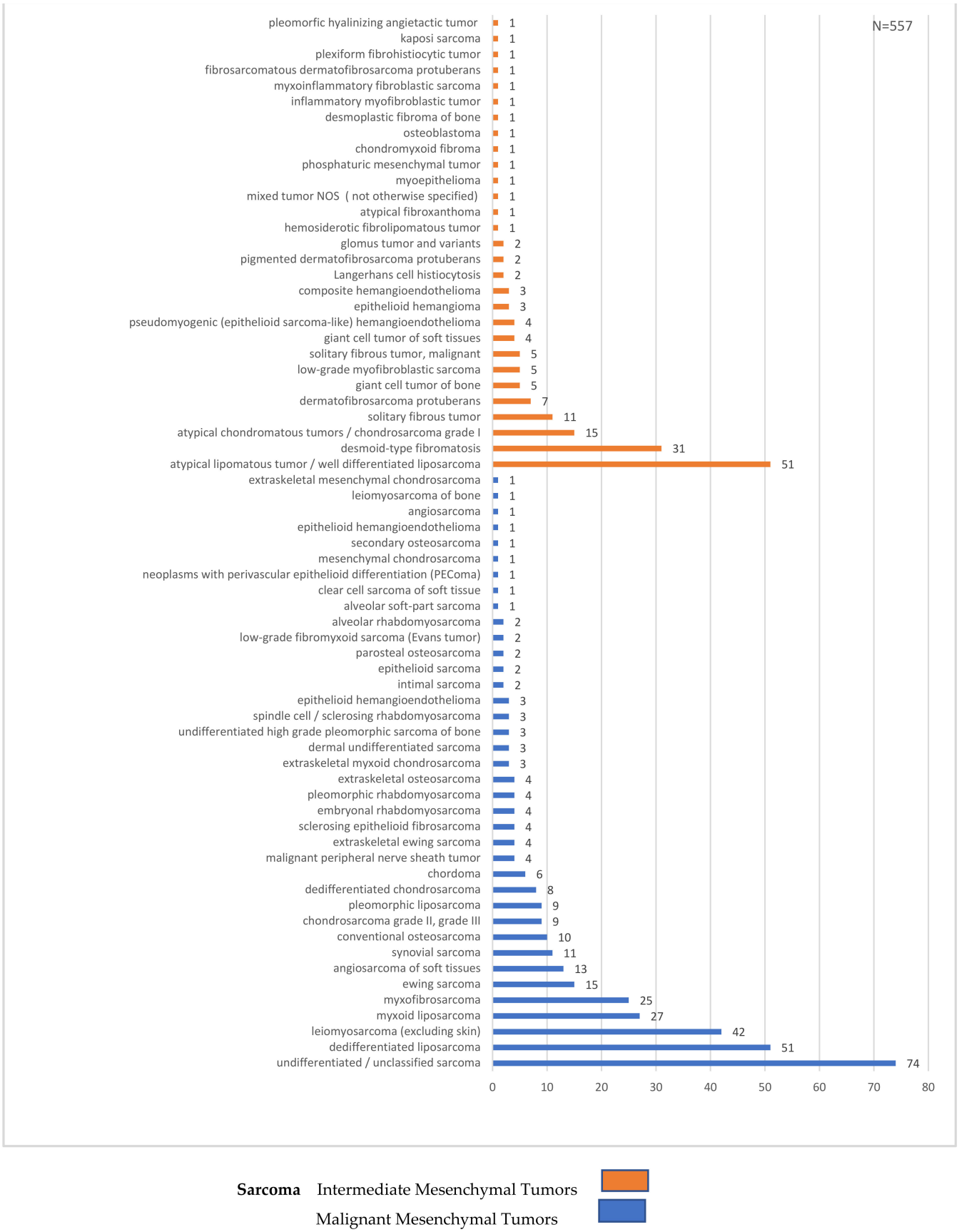


Figure 3. Histological types of sarcoma diagnoses.

3.3. Types of Sarcoma Simulators

Among the diagnoses other than mesenchymal tumors, 20% (n = 34) were metastasis, 8% (n = 14) were hematologic cancers, and 72% (n = 121) were sarcoma simulators.

Sarcoma simulators included 22 different types of lesions, the most common being inflammatory processes of soft tissues (15; 9%), degenerative processes of bones (14; 8%), granulomatous processes of soft tissues (11; 7%), pathologic fractures (9; 5%), hyperplastic granulation tissue (9; 5%), rheumatoid knots (9; 5%), epidermoid cysts (8; 5%), bone infarct (8; 5%) and periprosthetic inflammations (6; 4%) (Figure 4).

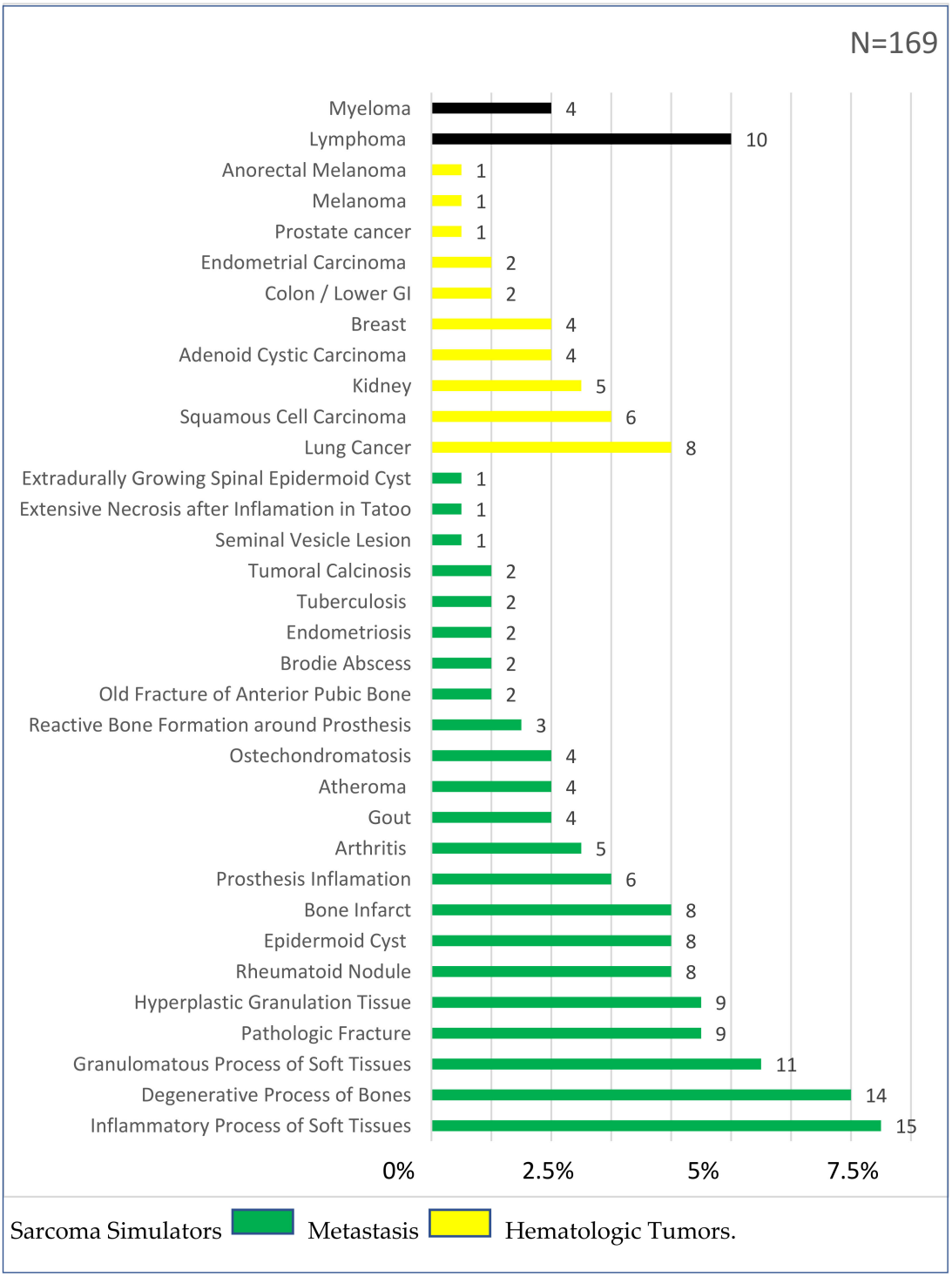


Figure 4. Types of lesions other than mesenchymal tumors.

4. Discussion

This study analyzed 950 consecutive biopsies which were performed for sarcoma suspicion over a 3.2-year period. Of these, 10% were unplanned "whoops" resections. Of all biopsies, 83% were mesenchymal tumors and only 55% ultimately proved to be sarcomas. Of the non-mesenchymal tumors, 4% were other malignancies and 13% were sarcoma simulators with a wide variety of pathologies. Overall, the RMST in this series was 0.55.

There is only sparse information in the literature to include the analysis of a consecutive series of biopsies for mesenchymal tumor suspicions, and there is no analysis of sarcoma simulators specifically reported [19]. The largest study on the analysis of biopsies included 545 patients from Denmark and reported a rate of confirmed sarcoma diagnosis of only 19% (RMST 0.19), which is in contrast to the 55% (RMST 0.55) in this series [7]. The other study made in the Rhone-Alpes region in France, with 366 patients, reported a rate of 54% concordance between primary diagnosis and expert center definitive diagnosis [8]. One reason for this discrepancy may be explained by the lack of accepted defined categories to analyze and compare biopsy results. In addition, RMST depends on a multitude of other parameters. Such discrepancy in establishing the sarcoma diagnosis, however, evidences an unmet need in the work-up of sarcoma patients [9]. It may be helpful to agree on a common definition as to how to analyze biopsies to allow the comparison among multidisciplinary teams (MDTs). We believe that separating mesenchymal tumors (to define intermediate and malignant versus benign lesions) from non-mesenchymal tumors may be helpful [3] (Table 1). The latter category includes hematologic tumors as well as metastases from carcinomas, leaving a group with so-called sarcoma simulators [4]. In our MDT, for example, all subfascially located lipomatous lesions are biopsied, resulting in 114 mdm2-negative tumors and 51 atypical lipomatous tumors in our series, rendering an RMST for lipomatous lesions of 0.39 (39%). A comparison of RMST among various MDTs will be important to define a minimal percentage of conducted biopsies of lipomatous lesions for quality purposes [20]. In this context, it can also be speculated that there may be a minimal amount of sarcoma diagnosis established per diagnostic unit overall. This may reveal, for a respective MDT, whether patients undergo biopsies too frequently, or in contrast, not frequently enough, which conversely is indicated by the number of unplanned ("whoops") resections [5]. Assessing the RMST of an MDT may serve as a quality indicator and ultimately also help to lower the unsatisfactory rate of unplanned resections [21].

The rate of unplanned resections has remained unchanged over decades [16,22], and the introduction of MDT per se may not have influenced this number either. There is currently no obvious strategy to address this issue. According to Abellan, J.F. et al. (2009) [19], in the 1990s, between 19% and 53% of the new patients seen in sarcoma centers were referred after an inadequate initial excision or whoops procedure. Another study (Pretell-Mazzini, J.) [14] pointed out that unplanned excisions of sarcoma occur in up to 50% of all patients with soft-tissue sarcoma. According to Zaidi, M.Y. et al. [16], considering the rarity of soft tissue sarcoma (STS) on the one hand, and the prevalence of benign soft tissue masses on the other hand, up to 50% of patients with STS will undergo a non-oncologic, unplanned excision for a mass initially presumed to be benign.

In this current report, the rate of unplanned resections was 10%, which is lower compared to the reports in the literature, and also lower compared to the rate of our own series before our prospective real-world shared data registry on quality was introduced. Obviously, the lower number in this report is explained by the inclusion of the total number of all biopsies, i.e., including all benign lesions (extrapolated on malignant tumors only, the rate of whoops surgeries was similar to international observations of 20%). On the other hand, based on a value-based geography model (VBGM) of care [23], the MDT herein represents multiple institutions and is therefore responsible for an entire region and not only for a single institution, thereby reaching all frontline care providers over a large geographic area.

When a biopsy for a tumor of the connective tissues is considered, the intention is to either confirm or exclude a sarcoma [24]. To the best of the authors' knowledge, there is no detailed analysis of lesions which turned out to be non-mesenchymal tumors, which in this series totaled 17%. The majority of these were so-called sarcoma simulators, defined as benign lesions mimicking sarcomas clinically or on imaging. They comprise 13% of all biopsies performed and include mainly degenerative and inflammatory diagnoses, as illustrated in Figure 1. Whereas it is important to avoid unnecessary biopsies (to lower costs and potential complications) [25], the risk to not detect all sarcoma diagnoses has to be kept as low as possible. Assessing the sarcoma simulators of other MDTs will be instrumental to define a minimal RMST threshold, as a quality indicator of an MDT. Such information is also valuable to establish integrated practice units (IPU), to include the supra-regional work-up of potential sarcoma patients in the context of VBGM. For example, in dedicating resources, the hospital management must understand that of all lesions being worked up, only half of all patients ultimately need sarcoma care. On the other hand, such supra-regional IPU work-up units are considered the entry gate, allowing the assessment of the absolute number of patients, which is the base for real-world data. The VBGM of care creates new incentives and is associated with a transformation of healthcare delivery, to create a novel ecosystem. A prerequisite for such transformation of healthcare delivery, however, is the assessment of absolute patient numbers and respective interventions [26]. We therefore speculate that such novel ecosystem of care delivery, together with measuring the outcome using RMST, may reduce the rate of unplanned whoops resections.

There are some limitations of this study to be considered. Although the total number of biopsies is sizable, it remains unclear whether a larger cohort of patients may affect the results differently. It has to be taken into account that such analysis may vary from institution to institution, and from one healthcare system to another of respective countries [27]. The numbers for one single MDT presented herein, therefore, cannot be directly compared with other MDTs unless they are consecutive and represent absolute or real-world data (RWD) values. In order to define the ratio of suspected/confirmed sarcoma as a quality indicator, several MDTs would need to assess their own ratio for comparison and define a standard. Based on the absolute numbers, our study revealed some variations in RMST, both with respect for type of biopsy performed and anatomic regions. However, because of the sample bias, a superiority of one method over the other cannot be concluded in order to choose a type of biopsy, and may therefore not alter current practice of using core biopsy as standard of care [28].

To the best of the authors' knowledge, this is the first study which focuses specifically on the ratio between sarcoma suspicion and ultimate sarcoma confirmation, with detailed analysis of sarcoma simulators. Assessing the absolute number of patients as RWD helps to define RMST, which may serve as a potential quality indicator of sarcoma work-up [29]. It may reduce the "scotoma" for unplanned "whoops" resections, which is considered an indicator of underestimation of the true number of sarcoma patients. On the other hand, infrastructure and personnel need to be dedicated to establish supra-regional sarcoma work-up units/IPUs to address and include absolute real-world data, thereby creating a novel ecosystem with a refined work-up approach [30]. This will ultimately allow sharing the experience between sarcoma networks independent of the geography.

5. Conclusions

The ratio of sarcoma suspicion to sarcoma confirmation is an important concept in the management of sarcoma patients. It is a quality indicator of the sarcoma work-up and may be a predictor for the cost efficiency of the care given to these patients. This ratio can be applied to all sarcoma MDTs, to increase the detection of sarcoma without increasing the number of unnecessary biopsies.

6. Patents

The results of this work and the new quality indicators that it has established are possessions of the Swiss Sarcoma Network.

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Research Article

Time and Accuracy to Establish the Diagnosis of Soft Tissue Tumors: A Comparative Analysis from the Swiss Sarcoma Network

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Soft tissue tumors are rare tumors, and their histological examination remains a challenge. The establishment of the correct initial histopathologic diagnosis is critical. However, due to the rarity of soft tissue and bone tumors and the inherent difficulty of their classification and diagnostics, discrepancies may occur in up to one third of cases. For these reasons, several studies recommend the involvement of experienced pathologists frequently performing sarcoma diagnostics. Until now, there is only scarce information about how long it takes to establish a correct sarcoma diagnosis. We thus analyzed all consecutive patients presented to the Swiss Sarcoma Network Tumor Board (SSN-MDT/SB) with a primary diagnosis of a soft tissue tumor over a 2-year period (01/2019 to 12/2020) based on a tumor biopsy. We then compared the final histopathological diagnosis of two comparable institutions with similar case load, but different workflows: (i) institution A, with an initial diagnosis performed by a local pathologist, and reviewed by a reference pathologist, and (ii) institution B, with the final diagnosis performed directly by a reference pathologist. In addition, we analyzed the time from biopsy to establishment of the diagnosis. A total of 347 cases were analyzed, 196 from institution A, and 149 from institution B. In 77.6% of the cases, the diagnosis from the local pathologist was concordant with the expert review. Minor discrepancies were found in 10.2% of the cases without any consecutive changes in treatment strategy. In the remaining 12.2% of the cases, there were major discrepancies which influenced the treatment strategy directly. Establishing the final report took significantly longer in institution A (4.7 working days) than in institution B (3.3 working days; $p < 0.01$). Our results confirm the importance of a pathological second review by a reference pathologist. We recommend direct analysis by experts, as diagnoses can be made more accurately and quickly. Within the SSN, establishing the sarcoma diagnosis is overall accurate and quick but still can be improved.

1. Introduction

Soft tissue tumors are rare tumors and histological examination remains a challenge [1]. The recently published WHO Classification of Soft Tissue and Bone Tumors [2] lists over 100 tumor entities including variants, often characterized by specific genetic aberrations, which can be detected by molecular diagnostic studies. Establishing the precise tissue diagnosis of a soft tissue or bone tumor is of utmost importance with respect to the choice of a correct treatment strategy for the patient. An incorrect histopathological diagnosis may lead to the initiation of an incorrect therapy with potentially severe or even lethal consequences for the patient [3–8].

Yet, due to the rarity of soft tissue and bone tumors and the inherent difficulty for a correct classification and diagnostic, discrepancies may occur in up to one third of cases [3–8]. For these reasons, several studies recommend the involvement of experienced pathologists who are involved in sarcoma diagnostics on a daily basis and who have access to auxiliary studies [3, 4, 9].

Various studies [4, 5, 7, 8] have shown that establishing the correct diagnosis for the treatment of soft tissue tumors is indeed a challenge, with 14% [10] to 43% [4] of all patients receiving an incorrect diagnosis, which could lead to incorrect treatment. Therefore, any multidisciplinary team (MDT) must assess these numbers constantly to compare with the reference benchmark for quality purposes.

Further, there is only scarce information on how long it takes to establish an expert review. Besides the correct diagnosis, the time from biopsy to establishing the diagnosis is an important quality indicator for the work-up of sarcoma patients. To the best of our knowledge, this factor has not yet been considered in published literature.

The patients treated in the Swiss Sarcoma Network (SSN) are either [1] referred directly to the member institutions prior to biopsy or [2] following a diagnosis of a mesenchymal tumor in an earlier outside biopsy. The current study concentrates on the first group in order to study the condition to optimize the diagnostic paths within the network. As the expansion of the network progresses in the future, there is hope that the percentage of the tissue studies outside the network (including "whoops" unintended resections) will diminish. Herein, we report first on the quality of accuracy in establishing the sarcoma diagnosis within the Swiss Sarcoma Network, and second, assess how long it takes to establish the diagnosis including expert review analysis.

2. Materials and Methods

All consecutive patients presented at the Swiss Sarcoma Network Board with a primary diagnosis of a soft tissue tumor from January 1, 2019, to December 31, 2020, were included in this study. Patients with incomplete records were excluded. A record was marked as incomplete when, for example, a case from institution A was missing an expert review, or when a case from institution B was initially diagnosed locally. The diagnoses were classified according to the WHO into benign, intermediate and malignant [11].

The biopsies of the two institutions were analyzed and compared. The samples of institution A were initially analyzed by the local pathology institute. This is a general pathology institute without specific subspecialization. Afterwards, the samples being reviewed and assessed by a reference institute pathologist specialized in soft tissue tumors. Conversely, institution B cases were assessed directly by the reference institute pathologist. These workflows are illustrated in Figure 1.

To determine the time from biopsy to the establishment of the diagnosis, the days between the arrival of the tissue specimen at the pathology institute until the date of the final report were calculated. Weekend days or holidays were not counted, unless the report was issued on one of these days. In the analysis of the current study only cases which can be diagnosed by conventional histopathologic staining, immunohistochemistry, and FISH were included, as these studies have a short turn-around-time of one to two days. The cases requiring PCR or NGS based analyses were excluded as they methodically require several days independently of the performance of the pathologist.

The accuracy of the diagnoses of the local histopathology institute A and the expert analysis was examined in a second step. Here, the diagnoses of institute A were compared with the expert opinion and divided into 3 groups according to the classification of Thway et al. [6]:

(i) Cases without diagnostic discrepancy between local and reference institutions were classified into category A

(ii) Category B includes cases with minor discrepancy in diagnosis but without therapeutic consequences

(iii) Category C contains all cases where the diagnosis from the reference pathologist changed the treatment

In addition, all cases where the final report from institution A did not establish a diagnosis were consequently classified under category C [6].

The data were collected using the Adjumed ® -Database (www.adjumed.ch; Zurich, Switzerland) and analyzed with the statistical package "stats" of the open source software "R" [12].

The cantonal ethic commission has approved the application of the Swiss Sarcoma Network under the agreement number BASEC-NR 2019-01107. The study is also registered on https://climincaltrials.gov with the number NCT04300257 [13].

3. Results

3.1. Patient and Tumor Characteristics. A total of 347 cases were analyzed, 196 from Institution A and 149 from Institution B. 179 patients were female and 168 were male, and the median age was 55 (range 12–90) years. 163 cases were classified as benign (46.9%), 114 cases were malignant (32.8%), 66 cases were intermediate (19%), and 4 cases were unclassifiable (see Table 1).

The most common benign diagnosis was lipoma (69 cases, 42.3% of all benign tumors), followed by Schwannoma (11 cases, 6.7%). Regarding the malignant diagnosis, undifferentiated/unclassified sarcoma was the most common diagnosis (19 cases, 16.6% of all malignant tumors) followed by the dedifferentiated liposarcoma (14 cases, 12.2%, see Table 2).

3.2. Accuracy. Of the 196 tumors specimens from institution A (which underwent initial diagnosis by a local pathologist followed by specimen being reviewed by a reference pathologist, see Figure 1), 152 tumors (77.6%) were diagnostically concordant according to category A. Of the latter 152 tumors, 46.7% were benign, 18.4% were intermediate, 33.5% were malignant, and 1.4% unclassifiable. There were 20 cases (10.2%) with minor discrepancies, according to category B (Table 3). Of these, 70% were malignant, 15% intermediate, and 15% benign diagnoses. There were 24 tumors (12.2%) with major diagnostic discrepancies (Table 3) according to category C. 50% of these were malignant cases. From these major discrepancies, 12 cases were classified in this category because of a missing diagnosis in the

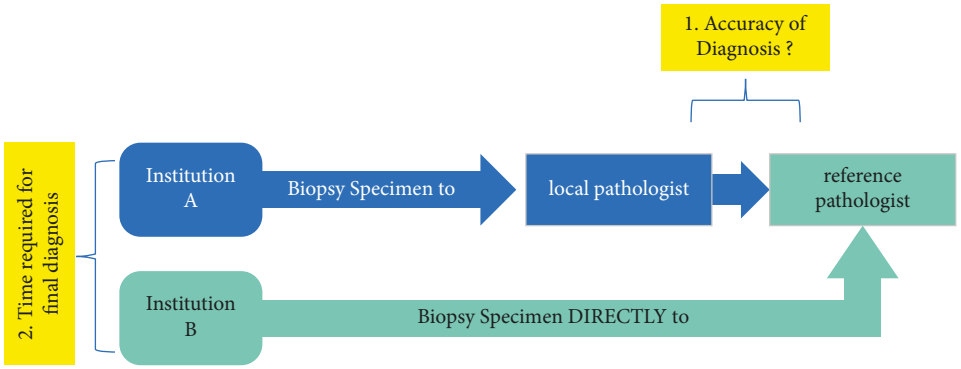


Figure 1: Workflow of the study.

Table 1: Patient and tumor characteristics.

Total	347
Institution A	198 (57%)
Institution B	149 (43%)
Male	168 (48.5%)
Female	179 (51.5%)
Median age	55 (range 12–90) years
Benign diagnosis	163 (46.9%)
Intermediate diagnosis	66 (19%)
Malignant diagnosis	114 (32.8%)
Unclassified diagnosis	4 (1.2%)

Table 2: Most common diagnoses.

Benign	Intermediate	Malignant
Lipoma (69 cases)	Atypical lipomatous tumor/well differentiated liposarcoma (17 cases)	Unclassified/undifferentiated sarcoma (19 cases)
Schwannoma (11 cases)	Aneurysmal bone cyst (11 cases)	Dedifferentiated liposarcoma (14 cases)
Intramuscular myxoma (8 cases)	Desmoid-type fibromatosis (9 cases)	Leiomyosarcoma (11 cases)

final report from institution A. In one case, there was a reclassification from benign to malignant and one case was reclassified from malignant to benign. A summary of all original diagnoses, which were discordant from the expert review is shown in Table 3.

3.3. Analysis of Time to Diagnosis. Establishing the final report took on average 4.7 working days for institution A, which is significantly longer than the 3.3 days required by institution B (Figure 2). 10 cases were excluded from the analysis (7 from institution A and 3 from institution B) due to the necessity of NGS for the final diagnosis. We analyzed the data with a two-sided Wilcoxon t-test and found a p value of $p < 0.01$.

If only malignant diagnoses were considered for analysis, establishing the diagnosis averaged 5.2 days in institution A, and 3.4 days, respectively, for institution B ($p < 0.01$, see Figure 2).

According to the most commonly diagnosed lesion of all, the diagnosis of a lipoma averaged 4.6 days at institution A and 3.2 days, respectively, at institution B ($p < 0.01$). Accordingly, and with respect to undifferentiated/unclassified sarcoma, institution A required 5.2 days, and institution B 3.0 days ($p < 0.01$).

4. Discussion

To the best of our knowledge, this is the first analysis comparing the duration of a histological review to establish a sarcoma diagnosis. Our results confirm the importance of a second pathological review by a reference pathologist. With an overall concordance of 77%, the results are comparable to the already published literature.

In 1986, Presant et al. [7] first reported on a histopathologic peer review of specimens from 216 consecutive patients with soft-tissue or bone sarcomas by a panel of three pathologists. Subtype of sarcoma, degree of confidence in diagnosis, and grade were compared with agreement or disagreement in pathologic opinion from the primary member institution versus the pathology review panel. There was a complete agreement between the primary pathologist

Table 3: Minor/major discrepancies.

	Minor discrepancies	
	Benign	
	Institution A	*Institution B*
L107	Fibroblastic/myofibroblastic proliferates in predominantly tight connective tissue with partly regressive changes.	Collagen-rich myofibroblastic proliferation
L108	Chondrogenic neoplasm, highly differentiated	Enchondroma
L198	Fibrin and blood, intercalated with some lamellar bone tissue and connective tissue	Intraosseous ganglion
	Intermediate	
	Institution A	*Institution B*
L31	Spindle-cell, partly multinucleated giant-cell tumor with osteoid formation	Aneurysmal bone cyst
L34	Giant cell tumor of the soft tissue	Plexiform fibrohistiocytic tumour
L112	Chondroid neoplasia with cancellous bone	Epiphyseal atypic chondrogenic tumor
	Malignant	
	Institution A	*Institution B*
L4	Spindle-cell high-grade sarcoma	Spindle and pleomorphic high-grade malignant unclassified sarcoma G3
L11	Spindle-cell pleomorphic sarcoma, high grade, with evidence of myogenic differentiation	Leiomyosarcoma
L19	Epithelioid sarcoma (proximal type)	Epithelioid angiosarcoma
L29	Lymph node metastasis of a solid tumor (differential diagnosis: clear cell sarcoma or malignant melanoma)	Lymph node metastasis of malignant melanoma
L35	Pleomorphic undifferentiated sarcoma with necrosis zones	Pleomorphic liposarcoma (G3)
L60	Spindle-cell pleomorphic neoplasia with striated muscles	Sclerosing epithelioid fibrosarcoma
L63	Sarcoma, spinel and partly pleomorphic cells	Spindle and pleomorphic cell soft tissue sarcoma at least G2 with FNCLCC score of 4
L64	Highly differentiated liposarcoma	Dedifferentiated liposarcoma with low-grade dedifferentiated portion, malignancy grade at least G2
L84	Myxofibrosarcoma	Undifferentiated spindle cell sarcoma
L110	Myxofibrosarcoma (high grade)	High-grade, unclassifiable spindle cell sarcoma (G2)
L140	Undifferenciated pleomorphic sarcoma	High-grade, unclassifiable spindle cell sarcoma (G2)
L157	Myxofibrosarcoma, high grade	High-grade, unclassifiable spindle cell sarcoma (G2)
L188	Pleomorphic highly proliferative tumor	Giant cell-rich leiomyosarcoma at least G2
L201	Myxofibrosarcoma (high grade)	Spindle cell sarcoma at least G2
	Major discrepancies	
	Benign	
	Institution A	Institution B
L2	Fat necrosis	PHAT (pleomorphic hyalinizing angiectatic tumor of soft parts)
L37	Fibrin-rich connective tissue with low chronic inflammation and regressive changes	Nodular fasciitis
L52	Mature teratoma/dermoid	Spinal dermoid cyst
L57	Spindle-cell mesenchymal myofibroblastic proliferation with low MIB-1 proliferation rate along with skeletal muscles	Intramuscular myxoma
L66	Parts of a spindle-cell myxoid-chondroid impinging neoplasia	Benign portion of a peripheral nerve sheath tumor
L109	Slightly atypical spindle cell tumor with myxoid background and increased proliferation (Ki67) of approx. 30%.	Myofibroblastic proliferation of the nodular fasciitis type
L113	Low-grade fibromyxoid sarcoma	Intramuscular myxoma
L145	Smooth-muscular proliferation with scaly calcifications as well as circumscribed ossification without necrosis or evidence of mitoses	Leiomyoma of the deep somatic soft tissues
L195	Intramuscular lipoma	Intramuscular haemangioma
	Intermediate	
	Institution A	*Institution B*
L100	Spindle cell mast cell-rich proliferation with low proliferation rate and immunohistochemically S-100 positive with negativity for SOX-10	Solitary fibrous tumor (SFT)
L101	Plump spindle-cell tumour with multiple multinucleated giant cells	Periosteal aneurysmal bone cyst (ABC)
L117	Cell-rich neoplasia of oval, plump spindle mononuclear cells intermixed with giant cells and haemorrhage residues in connective tissue.	Tenosynovial giant cell tumor of the diffuse type
	Malignant	
	Institution A	*Institution B*
L1	Epithelioid sarcoma	Angiosarcoma
L6	Osteosarcoma	Chondrosarcoma
L7	Highly differentiated/dedifferentiated or a myxoid liposarcoma	Dedifferentiated liposarcoma (low grade)
L51	Myxoid chondrosarcoma	Myxoid liposarcoma (G1)
L70	Chondroid and focal spindle cell neoplasia	Mesenchymal chondrosarcoma
L76	Slightly hypercellular chondrogenic tissue, connective tissue and skeletal muscle	Conventional chondrosarcoma
L94	Pleomorphic liposarcoma	Round cell liposarcoma G3
L150	Small blue round cell tumor with low proliferation (Ki67) of approx. 10-15%.	Granulosa cell tumor
L164	Atypical lipomatous tumor/well-differentiated liposarcoma	Dedifferentiated liposarcoma, at least G2
L171	Neoplasia, predominantly spindle cell in cancellous bone with focal evidence of irregular osteoid.	Osteosarcoma, high grade
L191	Infiltrates of small, round and blue cell neoplasia	Poorly differentiated neuroendocrine carcinoma (Merkel cell carcinoma)
L204	Spindle and pleomorphic cell neoplasm with myxoid background of partial expression of MDM2	High-grade myxofibrosarcoma (G2-3)

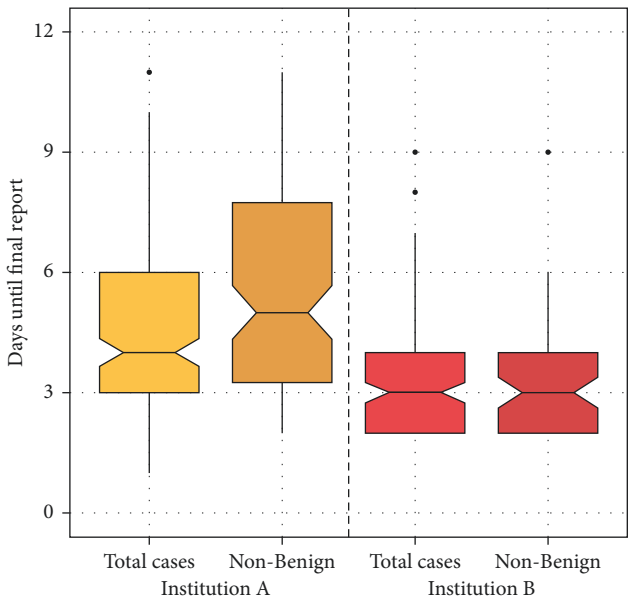


Figure 2: Days until final report.

and reviewer in 66% of cases. However, after the review, 12 cases (6%) were considered not to be sarcoma. In 27% of cases, the subtype of sarcoma was felt to be incorrect by reviewers.

In 2008, Lehnhardt et al. [5] reviewed 603 patients who were operated with the diagnosis of soft tissue sarcoma. They found a concordance in primary diagnostics of 28.3% for pathologists in private clinics, 29.6% for hospital affiliated pathologists, 36.8% for academic medical centers, and 70.5% for the department of pathology at their institution.

In 2010, Lurkin et al. [8] analyzed all histological data of all patients diagnosed with sarcoma in the Rhone-Alpes region between March 2005 and February 2006. Primary diagnoses were systematically compared with second opinions from regional and national experts. They included 366 patients; of these, 199 (54%) had full concordance between primary diagnosis and second opinion, 97 (27%) had partial concordance (identical diagnosis), and 70 (19%) had complete discordance.

Ray-Coquard et al. [4] reviewed the histological data of patients diagnosed with sarcoma in Rhone-Alpes (France), Veneto (Italy) and Aquitaine (France) over a 2-year period. Initial diagnoses were systematically compared with the second opinions from members of the group of pathologists of the GSF-GETO (French Unicancer Sarcoma Group). 1463 cases matched the inclusion criteria and were analyzed. Full concordance between primary and second diagnosis was observed in 824 (56%) cases, partial concordance in 518 (35%) cases and complete discordance in 121 (8%) cases.

A summary of the studies can be found in Table 4.

Interestingly, and specifically contrasting the analysis between benign and malignant lesions, the uncertainty to establish the correct diagnosis was greater in malignant lesions. Considering the analysis of minor discrepancies in the diagnosis comparing first line with expert review, the expert review delivers more diagnostic details or a supplement in the classification without obvious consequences regarding the treatment modality, specifically also for malignant diagnoses.

Our study has several limitations: The number of biopsies analyzed is still relatively small, and many diagnoses are benign, thereby not allowing further subgroup analysis. Also, considering the rarity of the disease and the 68 sarcoma entities included therein, further subtype analysis is not possible. The definition of diagnostic discordances is not always obvious and may skew the results. Arbitrarily, descriptive pathology reports without specification of dignity were classified as major discrepancies because adequate treatment can only be initiated when the final diagnosis is made.

Although there is a significant difference in the time to diagnosis, one may critically question to what extent this value has an influence on the time to diagnosis and further therapy. The time it takes to establish the histological examination is only one step on this path. It would therefore be interesting if a further study examines not only the duration of the biopsy, but the entire process from the suspected diagnosis to the initiation of the correct therapy. But from the point of view of the patient who must wait for a diagnosis, every day that is gained with a faster diagnosis is worth a lot. In addition, a rapid histological diagnosis is essential for a timely discussion at the multidisciplinary sarcoma board.

Any additional examination, especially if not done in the same institution, will lead to delays in the diagnostic process.

Several studies confirmed that a centralized pathological review improved the quality of the diagnosis. Lurkin et al. [8] support the direct analysis by an expert pathologist because of the multitude and complexity of sarcoma tumors. Also, the access to molecular biology analysis can be provided. Compared to the recommendation of the ECCO Essential Requirements for Quality Cancer Care, the pathway of Institution B is to be favored [14].

In a small country like Switzerland, and with sarcoma being a rare disease, establishing the correct pathological diagnosis is very challenging. The main reason is the small amount of cases per individual hospital. Compared with the volume of international sarcoma reference centers, the data of the entire country needs to be pooled and shared to reach high enough numbers for expert experience and teaching purposes. With the recently established Swiss Sarcoma Network, allowing real-world outcome analytics, there is the possibility to improve the precision, timeliness, and accuracy of sarcoma diagnosis in Switzerland in the near future. As of now, 7 central referral institutions joined the Swiss Sarcoma Network so far and benefit from a second opinion by an expert pathologist.

There is no clear definition in the literature on how a sarcoma expert is defined. As for the pathologists, the sarcoma experts within the Swiss Sarcoma Network are defined by their specific training, their specific sarcoma interest, defined by dedication of >30–50% of their duty time spent on treating sarcoma patients, their yearly scientific contributions, their number of cases reviewed and/or treated per year, and their participation of the weekly

Table 4: Overview of literature.

Author (year)	Interval	No. of cases	% concordance	% minor deviations	% major deviations
Peasant (1986)	May 1974 to May 1982	216	66% (137)		
Lehnhardt (2008)	1995 to 2001	603	28.3–70.5%		
Lurkin (2010)	March 2005 to February 2006	366	54%(199)	27% (97)	19% (70)
Ray-Coquard (2012)	March 2005 to February 2007 resp. January 2007 to December 2008	2016	56% (824)	35% (518)	8% (121)
Our study	January 2019 to December 2020	196	77.6% (152)	10.2% (20)	12.2% (24)

multidisciplinary tumor board including the number of discussed cases and strategic decisions.

5. Conclusions

The diagnosis of sarcoma remains challenging. According to our study and the current literature, an expert review by an experienced pathologist within a network such as the Swiss Sarcoma Network proves to be highly useful and beneficial for the patient both regarding accuracy and timeliness to establish the diagnosis. Establishing the sarcoma diagnosis as early as possible after biopsy is a critical quality indicator for a multidisciplinary team. Considering the rapidly rising health care costs, the potential increase in cost efficiency of such a process needs to be determined next.

Data Availability

The data used to support the findings of this study may be released from the Adjumed®-Database upon request to the Swiss Sarcoma Network (office@sarcoma.surgery).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Swiss Sarcoma Network

Wie entwickelt sich die Sarkomchirurgie?

Die Chirurgie erzielt von allen Therapiemodalitäten bei Sarkomen die höchste Lokalkontrollrate. Das primäre Ziel der Sarkomchirurgie besteht darin, den Tumor mikroskopisch komplett zu entfernen. Grundsätzlich kann davon ausgegangen werden, dass, je weiter reseziert wird, desto potenziell besser dieses Ziel erreichbar ist bzw. umso höher die lokale Tumorkontrollrate ist, aber umso potenziell schlechter die resultierende Funktion.

KEYPOINTS

- *Transdisziplinäre Sarkomchirurgie-Kompetenzteams bilden, um die R0-Resektionsrate zu verbessern bzw. die Rate der «Whoops»-Resektionen zu senken*
- *Sarkombehandlung vom in sich abgeschlossenen Disziplinen-Denken zum offenen Netzwerkverhalten entwickeln*
- *«Real world data»-Register führen, welche das Management vom Sarkomboard mit dem Register koppeln*
- *Qualitätsindikatoren definieren und analysieren, die Arzt- und Patienten-basiert sind*

Im Gegensatz zu Karzinomen, die nur im Verbund wachsen, können peritumorale Sarkom-Satellitenzellen als Einzelzelle wieder zu einem Rezidiv heranwachsen. Eine Nachresektion macht deswegen – im Gegensatz zu Karzinomen – nur Sinn, wenn das komplette Tumorbett miteinbezogen wird. Zudem wird eine adäquate Resektion, nebst der Komponente des individuellen Chirurgen, auch durch das biologische Wachstumsmuster der einzelnen Sarkomentität sowie von der lokalen Anatomie beeinflusst («anatomische Grenzen»). Die R0-Resektion ist deswegen in der Sarkomchirurgie ein zentraler, hochkomplexer Parameter – keine andere Therapiemodalität kann für eine inadäquate Resektion kompensieren. «Worst case scenario» chirurgischerseits ist die ungeplante Operation mit Überraschungsresultat «Sarkom» (sog. «whoops lesion»).

Wo liegen die grössten Herausforderungen?

Die wichtigsten Parameter betreffend lokale Tumorkontrolle sind der erzielte chirurgische Resektionsrand bzw. ungeplante Operationen («whoops»); diese sind wichtiger als Grading, Grösse und Lage des Tumors.[1] Obwohl die R0-Resektion einen zentralen Parameter in der Sarkombehandlung darstellt, ist kaum bekannt, wie häufig eine solche erreicht wird. Eine der Erklärungen liegt darin, dass keine einheitliche Definition für «R0» besteht:

- Rein metrisch, oder in Abhängigkeit von biologischen Strukturen und anatomischen Barrieren?
- Mitberücksichtigung neoadjuvanter Therapien?
- Angabe definiert vom Chirurgen, vom Pathologen oder aber aus der Synthese der beiden nach interdisziplinärer Diskussion?
- Zudem undefiniert: Wie wird sichergestellt, dass nicht die postoperative Aufarbeitung des Resektates durch den Pathologen selbst zu einem iatrogenen Resektionsrand führt?

Ungeplante Resektionen («Whoops»-Operationen) nach dem Motto «Schneiden wir den Tumor raus, um zu sehen, was es ist», stellen ein internationales Problem dar und führen häufig zu inadäquaten Resektionen mit potenziellem lokalem Kontrollverlust des Tumors.[2] Rund 20 % aller Sarkome werden auch heute noch auf diese Weise diagnostiziert/operiert, was eine sehr grosse Herausforderung für das allfällig weiterbehandelnde Sarkomteam («best case») darstellt. «Whoops»-Operationen bedeuten für betroffene Patienten eine verzögerte korrekte Behandlung, oft zusätzliche Eingriffe, nicht selten letztlich eine dadurch ab initio schlechtere Prognose. Um diese vielfältigen Herausforderungen meistern zu können, ist ein prätherapeutischer transdisziplinärer Austausch mittels einer gemeinsamen Plattform (Multidisziplinäres Tumorboard, MTB) unabdingbar, zur Definition einerseits des Resektionsrandes und andererseits der weiteren interdisziplinären Abläufe zur

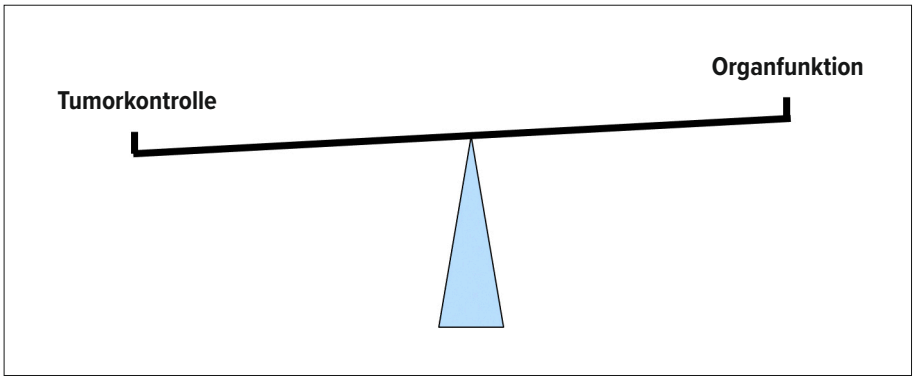
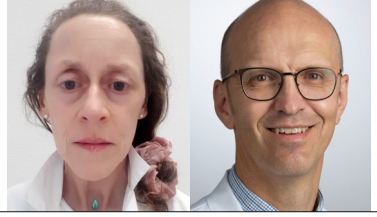


Abb. 1: Das Sarkombehandlungsteam muss zu Beginn mit dem Patienten festlegen, welches Ausmass eine Tumorresektion einnimmt, welche funktionellen Konsequenzen eine solche nach sich zieht und inwieweit dies direkt mit der Tumorkontrolle assoziiert ist



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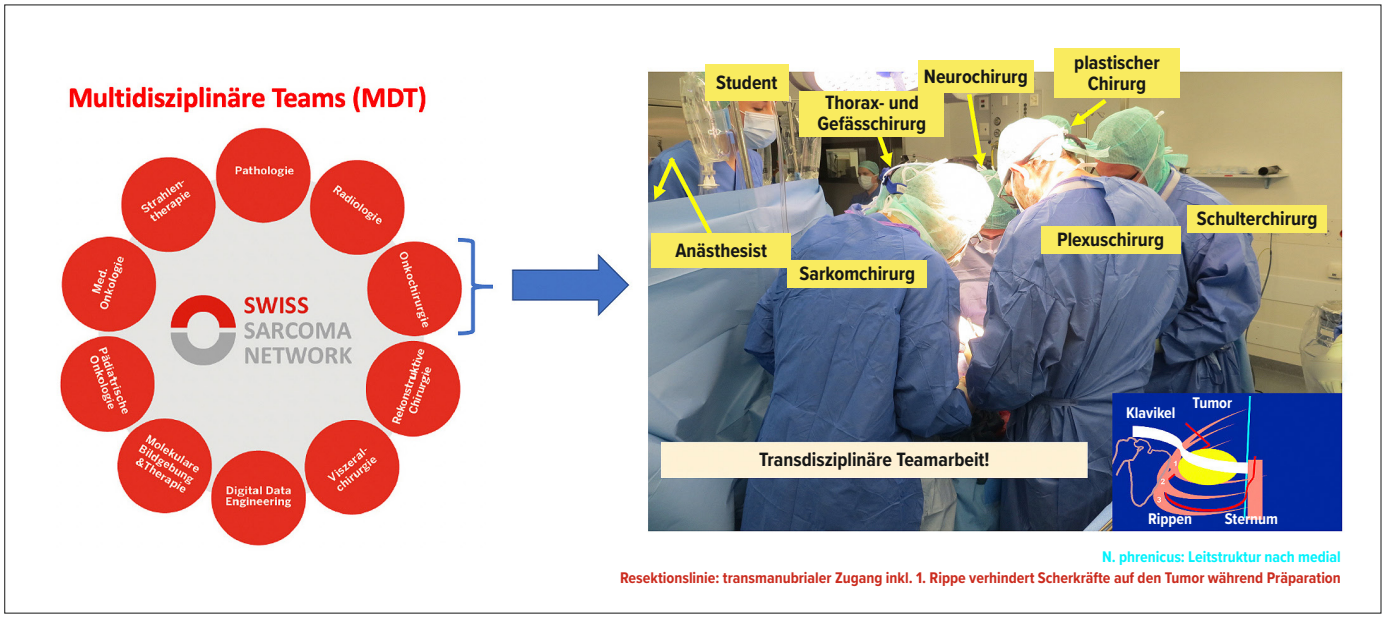


Abb. 2: Die Organisation einer Sarkomeinheit in multidisziplinären Teams – in Analogie zum chirurgischen multidisziplinären Kompetenzteam – ist entscheidend für die optimale Behandlung der Sarkompatienten. Eine solche Einheit verwendet optimalerweise eine gemeinsame digitale Plattform zum nationalen und internationalen Austausch und zur Definition und Erfassung der Qualität

Abklärung bzw. Behandlung von Patienten mit Sarkomverdacht.

Was ist Sarkomchirurgie?

Die Sarkomchirurgie stellt keine eigentliche Disziplin dar, sie setzt sich vielmehr aus verschiedenen Disziplinen zusammen, in Abhängigkeit von der anatomischen Lage des Sarkoms. Sarkomchirurgie ist deshalb nicht Disziplin-fokussiert, sondern vielmehr Problem-orientiert. Da die Chirurgie je nach anatomischer Region technisch hochspezialisiert ist, können prinzipiell nicht alle Operationen von einer Person auf technisch höchstem Niveau durchgeführt werden.

Wie wird ein Sarkomchirurg definiert?[3] Er hat eine entsprechende vertiefte zusätzliche onkologische Ausbildung auszuweisen, eine > 10-jährige Berufserfahrung auf dem Fachgebiet und ist mit den Prinzipien der Sarkomchirurgie vertraut. Darüber hinaus muss er fähig/willig sein, in einer entsprechenden Struktur und Kultur ein Team von technisch versierten Chirurgen-Kollegen einbeziehen zu können, um die anatomischen Erfordernisse ausreichend adressieren zu können (intraprofessionelle Kooperation). Dies gilt sowohl für die Resektion eines Tumors als auch für die anschliessende Rekonstruktion. Dabei geht es immer um die Balance zwischen Tumorkontrolle und resultierender Funktion; diese muss eng abgesprochen werden mit dem Patienten und im Behandlungsteam (Abb. 1). Einen solch engen Austausch hat ein Sarkomchirurg mit dem Pathologen und dem Facharzt für interventionelle Radiologie zu etablieren, um die Abklärung von Patienten mit mesenchymalen Tumoren als Abklärungseinheit möglichst zielgerichtet umzusetzen, damit die Rate der ungeplanten Resektionen gesenkt werden kann; dasselbe gilt für die gemeinsame weitere Therapieplanung im Hinblick auf adjuvante Therapien (interprofessionelle Kooperation).

Diese Überlegungen führen als Konsequenz zur Bildung eines Sarkom-Kompetenzteams, in dem alle erforderlichen Ansprüche transdisziplinär auf den Patienten massgeschneidert unter der Koordination des Sarkomchirurgen orchestriert werden. Es wird dabei inskünftig zentral sein, dass die Leistung eines solchen transdisziplinären Sarkom-Kompetenzteams nicht mehr isoliert wie bisher, sondern Outcome-basiert als Einheitsleistung erfasst und ausgewiesen wird, mittels eines Registers, das die Daten und Qualitätsparameter aller Disziplinen miteinschliesst (Abb. 2).

«The power of data bases»

Wieso ist ein transdisziplinäres Register notwendig? Die «French sarcoma group» bildete 2010 ein Sarkomregister; mittlerweile sind bereits mehr als 55 000 Patienten eingeschlossen, das Register stellt damit die derzeit grösste existierende Sarkom-Informationsquelle dar.[4] Die Franzosen konnten damit zeigen, dass zum Beispiel die Fallbesprechung an einem interdisziplinären Tumorboard assoziiert ist mit besserem rezidivfreiem (sowohl lokal wie systemisch) Überleben, weniger Reoperationen und einem besseren Umsetzen der «clinical practice guidelines».[5] Sie zeigten auch die Wichtigkeit eines Zweit-Reviews der Diagnose durch

einen weiteren Fachpathologen: In einem Kollektiv von 1017 Patienten musste bei 27 % eine Revision der Diagnose vorgenommen werden, die eine relevante Änderung der Therapie nach sich zog.[6] Sie zeigten zudem, dass, wenn die Operation innerhalb des Netzwerks stattfand, die R0-Resektionsrate deutlich höher war (R0-Resektionsrate innerhalb des Netzwerkes bei 52 %, ausserhalb nur gerade 26 %) und dies assoziiert war mit besserem Lokalrezidiv-freiem, ereignisfreiem sowie Gesamtüberleben.[7] Diese Daten erlauben grundlegende Rückschlüsse mit sehr grosser Bedeutung für unseren klinischen Alltag, so wie wir sie bisher nicht kannten.

Was sind die Ansprüche an ein Register?

Ein Register ist ein zentraler Pfeiler, um die Qualität der Patientenbehandlung zu erfassen bzw. die Teamkompetenz zu verbessern. Aufgrund obiger Ausführungen ist evident, dass ein Sarkomregister alle Disziplinen gleichzeitig einzuschliessen hat (Endresultat definiert durch schwächstes Glied in der Kette). Mittlerweile ist die Wichtigkeit von «real world data» erkannt und etabliert. Das Sarkomboard ist der einzige Moment in der Prozesskette, in dem sich alle Disziplinen zur Diskussion der Faktenlage und der weiteren Strategien der Behandlung der Sarkompatienten treffen – dieser Schlüsselmoment muss in einem «Real world data»-Register entsprechend abgebildet werden. Es ist deshalb notwendig, das gesamte Sarkomboard-Management mit dem Register zu koppeln. Ein Sarkomregister muss erlauben, alle aktuellen WHO(«World Health Organization»)-Diagnosen und anatomischen Lokalisationen zu erfassen, idealerweise auch alle Arten von chirurgischen Resektionen und Rekonstruktionen.

Das Register erlaubt die Analyse eines jeden einzelnen Parameters und jegliche Kombination derselben sowie Standard- und spezifische Auswertungen (wie zum Beispiel Qualitätsindikatoren) pro gewählte Zeiteinheit. Da die «patient-reported outcome measures» (PROM) auch in Europa zunehmend wichtiger werden, sollte ein solches System ebenfalls erlauben, entsprechende Rückmeldungen seitens der Patienten im Follow-up zu ergänzen. Ein solches Tool erlaubt nicht nur den erleichterten transdisziplinären Austausch im Alltag, sondern wird auch die Basis darstellen, um die Qualität der Sarkombehandlung zu definieren und zu messen («outcome measurement») – letztlich der einzig rechtfertigende Parameter für die Anerkennung eines solchen MDT bzw. die einzige Möglichkeit für den Vergleich der Analysen mit anderen Zentren.

Definition und Erfassung von Qualitätsindikatoren

In der Schweiz, wie auch in anderen Ländern, wird es ab April 2021 eine gesetzliche Grundlage und damit Verpflichtung zur Qualitätserfassung geben. Der Ausweis von Qualität in der Sarkombehandlung bezieht sich aber nicht nur auf die Sarkomchirurgie, sondern auf die gesamte Organisationseinheit (s. oben). Die Analyse diverser Parameter bei Patienten mit Bindegewebstumoren (z. B.: Wie lange dauert das Erstellen einer Diagnose? Wird eine Biopsie vor Behandlungsbeginn durchgeführt? Wartezeiten auf einzelne Aktionsschritte?) ist ein Qualitätsausweis – bislang kaum beachtet und entsprechend kaum erfasst. Ebenso sollte Sarkomchirurgie hinsichtlich ihrer Komplexität und Qualität analysierbar werden, genauso die Chemotherapie und Radiotherapie. PROM müssen hier ebenfalls als Ergänzung eingebracht werden. Idealerweise soll ein «Real world data»-Register alle diese Herausforderungen abdecken.

Erwartungen und Ausblick

Die Sarkomchirurgie wird sich vom monodisziplinären Denken lösen und sich zunehmend transdisziplinär organisieren müssen. Nur so können wir jeder spezifischen initialen Präsentation eines einzelnen Patienten onkochirurgisch sowie anatomisch-technisch gerecht werden. Durch die Organisation im Sinne eines Sarkom-Kompetenzteams wird erwarteterweise[7] die R0-Resektionsrate verbessert und die Rate ungeplanter Resektionen gesenkt. Dieses transdisziplinäre Denken ist seitens aller beteiligten Disziplinen erforderlich.

Es zeichnet sich damit ab, dass eine solche Kompetenzeinheit nicht an einer einzelnen Institution angesiedelt sein kann, sondern überregional/national in einem Netzwerk organisiert sein muss, um das Wissen der Experten und die Behandlung der Patienten unabhängig von der geografischen Lokalisation zu maximieren. ■

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cancers

MDPI

Article

How Is the Spectrum of Sarcoma Surgery Assessed?

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Simple Summary: Sarcoma surgery is the cornerstone of sarcoma therapy, which is organized highly multidisciplinarily. The critical determinant of tumor control depends on the experience of the multidisciplinary team (MDT), in which sarcoma surgery plays a pivotal part. In this study, an interoperable digital platform on sarcoma surgery was established to assess its spectrum based on a single sarcoma surgeon over one decade as a pilot. Being used at large scale, this platform may become an indispensable instrument to assess the contributions of sarcoma surgery within an MDT to tailor personalized patient quality care in the future.

Abstract: Purpose: To meet the challenges of the precision medicine era, quality assessment of shared sarcoma care becomes pivotal. The MDT approach is the most important parameter for a successful outcome. Of all MDT disciplines, surgery is the key step to rendering sarcoma patients disease free; therefore, defining its spectrum is critical. To the best of the authors' knowledge, a comprehensive interoperable digital platform to assess the scope of sarcoma surgery in its full complexity is lacking. Methods: An interoperable digital platform on sarcoma surgery has been created to assess the clinical exposure, tumor characteristics, and surgical settings and techniques applied for both resections and reconstructions of sarcomas. Results: The surgical exposure of an individual surgeon over time served as a pilot. Over the study period of 10 years, there were 723 sarcoma board/MDT meetings discussing 3130 patients. A total of 1094 patients underwent 1250 surgical interventions on mesenchymal tumors by one single sarcoma surgeon. These included 615 deep soft tissue tumors (197 benign, 102 intermediate, 281 malignant, 27 simulator, 7 metastasis, 1 blood); 116 superficial soft tissue tumors (45 benign, 12 intermediate, 40 malignant, 18 simulator, 1 blood); and 519 bone tumors (129 benign, 112 intermediate, 182 malignant, 18 simulator, 46 metastasis, 14 blood, and 18 sequelae of first treatment). Detailed types of resections and reconstructions were analyzed. Conclusions: An interoperable digital data platform on sarcoma surgery with transparent real-time descriptive analytics is feasible and enables large-scale definition of the spectrum of sarcoma surgery to meet the challenges of sarcoma precision care in the future.

Keywords: sarcoma; multidisciplinary team/MDT; sarcoma surgery; orthopedic oncology; real-world data; interoperable digital platform; exposure; experience

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1. Introduction

Sarcoma treatment includes various disciplines and is carried out by so-called multidisciplinary teams (MDTs). MDTs represent the cornerstone for the quality of sarcoma care [1–5]. Recently, quality indicators of global sarcoma care were reported [6]. Quality of sarcoma care is greatly dependent on various disciplines collaborating under one roof and its associated infrastructure and processes, as well as an adequate surgery and the surgical margins achieved thereby [7]. The latter, in turn, depends on the experience of the surgeon and his team and the complexity of the procedure. Of all the involved disciplines, surgery is the most important pillar to render a patient disease free and, hence, a surgeon's

experience plays a pivotal role; for this reason, the quality of surgery deserves particular attention [8]. Counting the number of surgeries alone serves at best as a surrogate but does not reflect per se the quality of surgery or the surgeon's experience. For example, the surgical procedure of an Ewing sarcoma of the great toe differs greatly from that on the pelvis, as does the biology of the wide array of sarcoma entities representing different diseases. A sarcoma surgeon, therefore, is not only technically skilled but also understands the biology and various treatment aspects of the disease, including the process of performing longitudinal follow-up of the patients over time [9,10]. Most importantly, the sarcoma surgeon is capable of assembling a multidisciplinary team for sarcoma care, specifically for the wide and complex spectrum of surgical resections and reconstructions [9]. However, before the complexity or indicators of quality for sarcoma surgery are defined specifically, the surgical spectrum needs to be described by outlining the role of a sarcoma surgeon. Sarcomas may arise in any part of the entire body, thereby requiring an entire spectrum of surgical techniques, which one single surgeon in present times is unable to cover. Sarcoma surgery may include not only the resection of the tumor alone, but also subsequent reconstructions, adding another level of surgical complexity. Although sarcoma resection is driven by the biology of the lesion, which is most often independent of the anatomic location, reconstruction is highly site dependent because surgical techniques vary greatly depending on the anatomical locations. For these reasons, sarcoma surgery needs to be organized in a highly transdisciplinary fashion by personalizing each sarcoma surgery specifically to each patient's situation, which does need to be taken into account when defining the complexity or also the quality of sarcoma surgery.

Health care cost explosion and the emerging skills shortage require the development of a novel ecosystem, moving away from a legacy system to a value-based system, in which the patient's value is defined by the quality and outcome divided by the total costs over the full care cycle [4,11–14]. Moreover, from this economic perspective, the definition of quality of sarcoma care is indispensable. Sarcoma surgery shows a great level of complexity, which, in turn, is intimately related to the experience of the respective surgeon [15,16]. Defining the spectrum of sarcoma surgery is paramount to then defining the complexity of a procedure, but also for personalized teaching of the next generation of sarcoma surgeons and for continuous education purposes, as well as ultimately ascertaining the quality in every day practice and patients' safety within an MDT. Defining the spectrum of sarcoma surgery may also assist in addressing the geography model of care by the regionalization of our patients, depending on patient- and disease-based parameters of sarcoma and the establishment of integrated practice units. Above all, it may make it possible to revisit the current reimbursement system in many countries without the capacity to mirror the specific scope of sarcoma surgery adequately using commonly available clinical information systems [4,11–14]. Therefore, challenges include the assessment of the various types and the technical aspects of surgical procedures using structured data on a respective interoperable digital platform [17].

To the best of the authors' knowledge, there are no reports on how to assess and report on the spectrum of sarcoma surgery within an MDT. Because most of the clinical information systems in hospitals are not designed for the detailed search of sarcoma-surgery-specific aspects, we designed a novel web-based interactive real-world-time (RWDT) interoperable digital platform on sarcoma surgery to assess, identify, and analyze the spectrum of sarcoma surgery to meet the challenges of the precision medicine era.

2. Materials and Methods

A set of parameters including all single steps of all types of sarcoma surgeries was assembled [18]. As a prototype, this list was then applied on all surgeries of mesenchymal tumors performed by one single surgeon over a 10-year period. Registration was performed using the AdjumedCollect "Interoperable digital platform on Sarcoma Surgery" (Adjumed Services, AG, Zurich, Switzerland, http://www.adjumed.com/ (accessed on 30 November 2022)). The AdjumedAnalyze tool (Adjumed Services AG, Zurich, Switzerland) can be used

for basic statistics, such as combinations of parameters, and allows for the extraction of data. The individual scores were calculated later in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

The parameters to describe the sarcoma surgery spectrum include four main categories: clinical patient exposure, tumor characteristics, surgical settings, and techniques (Figure 1).

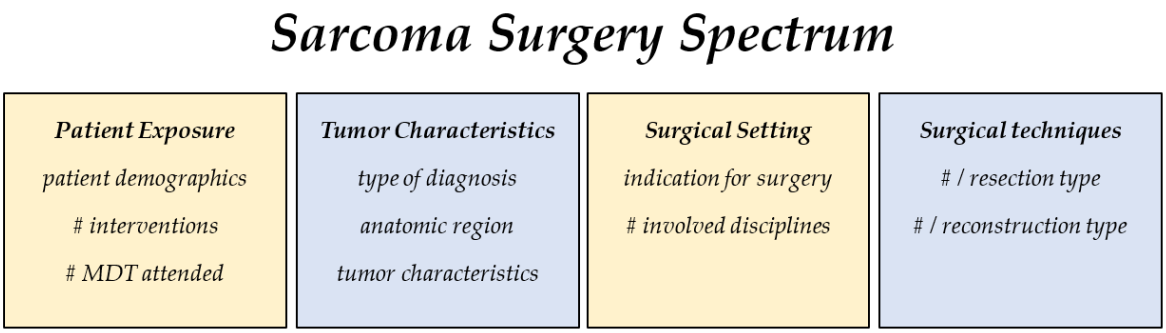


Figure 1. The exposure to sarcoma surgery is assessed in the following 4 categories: patient exposure, tumor characteristics, surgical setting, and surgical techniques applied. # number of.

3. Results

3.1. Patient Exposure

Over a 10-year period of time, there were 723 MDT or sarcoma board meetings, in which 3130 patients were discussed, and 5930 sarcoma board decisions were made (Figure 2). This averages a total of 313 patients and 593 sarcoma board decisions per year.

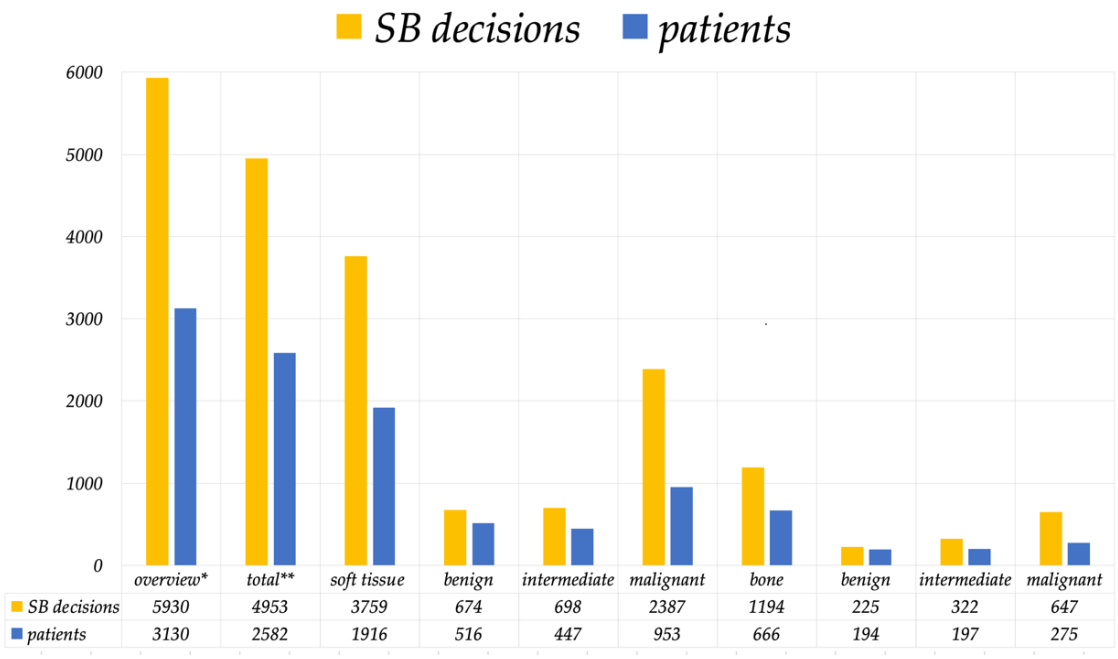


Figure 2. This figure summarizes the number of sarcoma board decisions and patients over a 10-year period. * All evaluations of mesenchymal tumors ** Exclusive metastasis, carcinoma, lymphoma, leukemia, myeloma, and tumor simulator.

During the same 10-year period, one single surgeon performed a total of 1250 surgical interventions on mesenchymal tumors in a total of 1094 patients, who are the subjects of this analysis. There were 484 females and 610 males, with a mean age at surgery of 46.1 years (range: 1 to 91 years) (Figure 3).

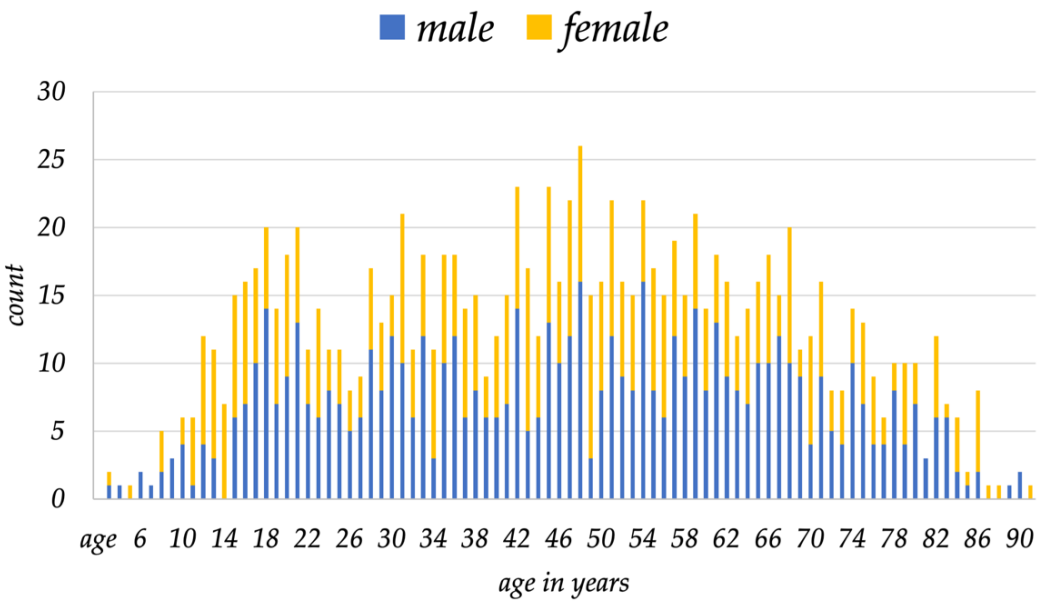


Figure 3. Distribution of gender and age over time of all patients included in this study is shown.

3.2. Tumor Characteristics

In all 1094 patients, there were 628 soft tissue tumors, 339 bone tumors, and 44 metastases treated by surgery. The exact diagnoses are summarized in Table 1.

Table 1. This summary of all tumors included in the analysis over a 10-year period is split according to the diagnoses of the WHO classification.

Soft Tissue	**628**	**Bone**	**339**
Adipocytic	258	Chondrogenic	141
Fibroblastic/myofibroblastic	97	Osteogenic	90
Undifferentiated/unclassified sarcoma	82	Tumors of undefined neoplastic nature	45
Tumors of uncertain differentiation	71	Osteoclastic giant cell rich	24
Nerve sheath tumors	49	Ewing	18
Fibro-histiocytic tumors	21	Notochordal tumors	7
Vascular tumors of soft tumors	14	Undifferentiated high-grade pleomorphic sarcoma	4
Smooth muscle tumors	19	Fibrohistiocytic	3
Chondro-osseous tumors	10	Fibrogenic	2
Pericytic tumors	4	Myogenic, lipogenic, epithelial tumors	2
Skeletal muscle tumors	4	Tumor syndromes	2
		Vascular tumors	1
Non-neoplastic/simulator	62		
Metastasis	44		
Lymphoma myeloma leukemia	12		
Sequelae of prior therapy	8		

Of these tumors, there were 361 benign, 199 intermediate, 409 malignant (34 G1, 85 G2, and 289 G3, respectively), 62 sarcoma simulators, 44 metastases, 12 blood, and 8 sequelae of prior therapy (Figure 4). In total, 266 underwent preoperative radiation therapy, 63 underwent postoperative radiation therapy, and 126 underwent neoadjuvant chemotherapy. The mean size of the tumors averaged 80.3 mm (range: 1 to 550 mm) (Figure 5).

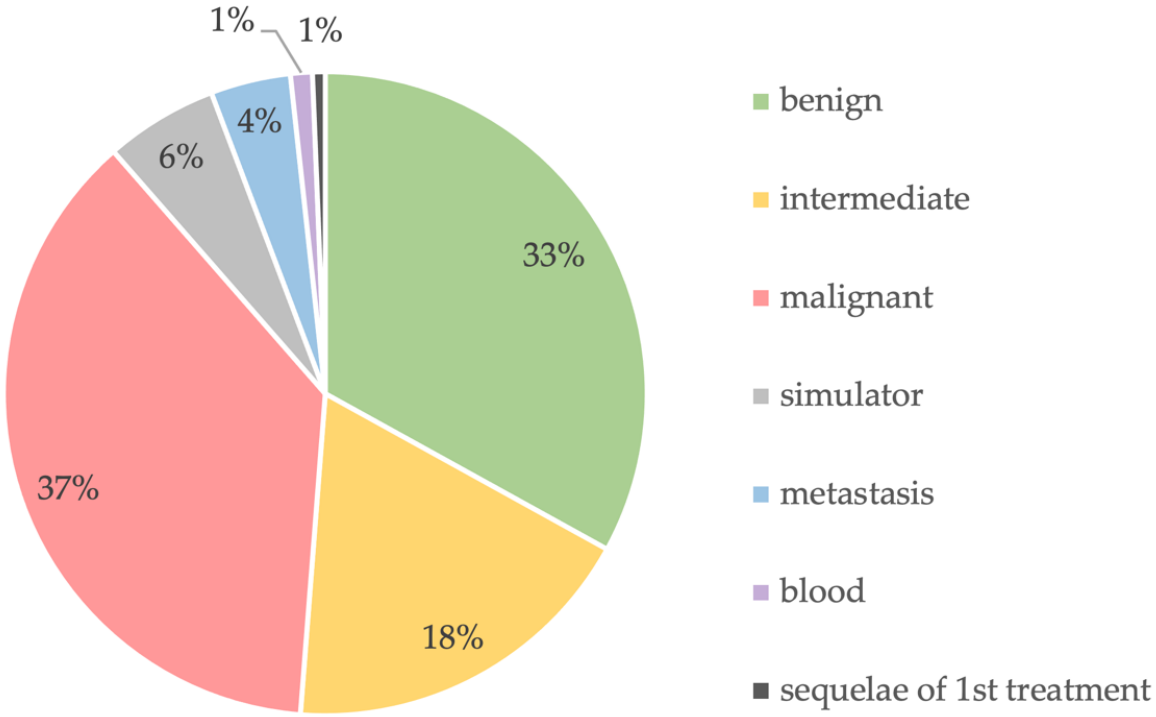


Figure 4. Biological diagnosis of the lesions.

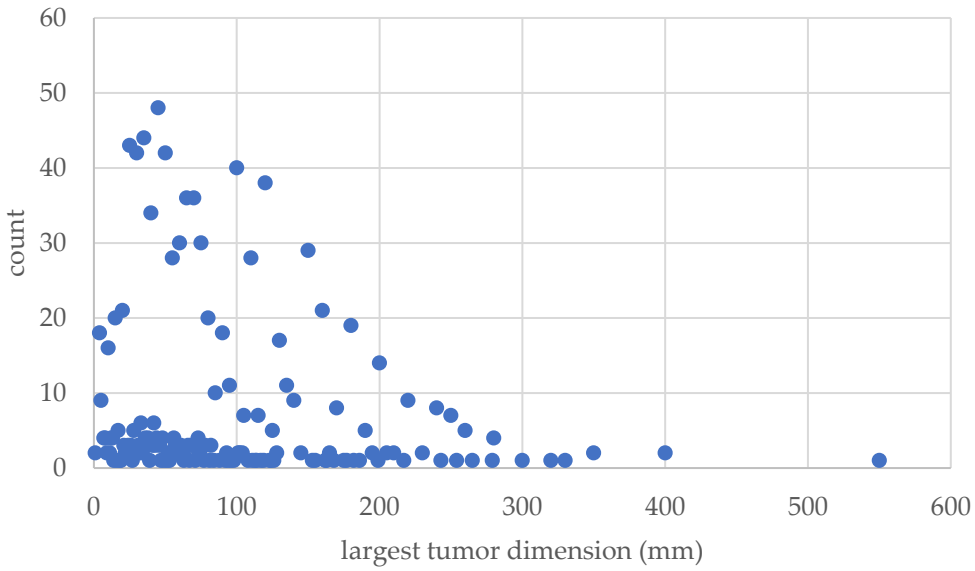


Figure 5. This diagram shows the number and size of the tumors.

Of these interventions, 615 concerned the deep soft tissue (197 benign, 102 intermediate, 281 malignant, 27 simulator, 7 metastasis, 1 blood); 116 cases concerned the superficial soft tissue (45 benign, 12 intermediate, 40 malignant, 18 simulator, 1 blood); and 519 concerned the bone (129 benign, 112 intermediate, 182 malignant, 18 simulator, 46 metastasis, 14 blood, and 18 sequelae of first treatment). From head to toe, 13 of all interventions were located in the head/neck/face region, 301 in the upper extremity, 87 in the torso/chest/abdomen, 159 in the pelvis, and 690 in the lower extremity.

3.3. Surgical Settings

The indication for surgery is an important parameter to describe the complexity of the patient cohort. Of all 1250 surgical interventions, in 996 cases (79.7%), surgery

was indicated for the first time. In total, 56 cases (4.5%) had prior whoops surgery, and 17 cases (1.4%) presented with a pathological fracture. There were 52 first revision surgeries (4.2%) for any cause, and 41 second or more revision surgeries (3.3%). In total, 45 cases (3.6%) underwent surgery for a local recurrence (independent of whether the cases were of primary or referred patients), and 35 surgeries (2.7%) were indicated for more than 2 local recurrences. In total, eight surgeries (0.6%) were performed for other reasons, such as three for regional metastasis, two for systemic recurrence (one intraabdominal and one spine), two for removal of osteosynthesis material after fracture care, and one for a local progression of a multiple myeloma.

The definition of the surgical margin is not uniformly accepted [15], and the surgeon's judgement on the resected margin does not necessarily reflect the pathologist's opinion, nor the shared decision process of the MDT/sarcoma board. In the presented series, the surgeon defined wide/adequate margins in 933 surgeries (95.9%), in 18 marginal (1.8%) surgeries, and 23 intralesional (2.4%) surgeries, and margin status was not applicable in 276 surgeries because there was no sarcoma.

Of all surgeries, 875 were carried out by the sarcoma surgeon alone (70%), whereas 309 surgeries were performed with an expert from another discipline (24.7%), 53 surgeries with 2 additional disciplines (4.2%), and 4 surgeries each with 4 and 5 additional disciplines (0.3% each). In one surgery, namely a forequarter amputation with chest wall resection due to a post-irradiation UPS (undifferentiated pleomorphic sarcoma) infiltrating the brachial plexus, a total of 7 different disciplines were involved (sarcoma, orthopedics, chest, vascular, neuro, plexus, and reconstructive surgery).

3.4. Surgical Techniques

Surgical techniques focus on both resection and reconstruction. Resection techniques depend on the anatomic location and the specific structures that need to be removed. In this series, besides tumor resection itself, additional resection included 1800 surrounding and different types of soft tissues and 489 bone resections, 11 chest/thorax resections, 19 abdominal structures, and 106 sequelae of first treatment (e.g., débridement or prosthesis related resections).

Reconstructions after tumor resection were necessary in a total of 640 cases. They consisted of 319 bony reconstructions, including 94 prostheses, 84 allografts, 79 ORIF (incl. 18 pedicle screws/rods/cages), 24 autografts, 20 cementations (incl. 2 cement spacers), 4 arthrodeses, 2 gore-tex mesh, 1 distraction osteogenesis, and 11 other bone reconstructions (e.g., external fixator or Tikhoff–Linberg hanging bridge reconstruction).

Soft tissue reconstruction consisted of 38 tendon/ligaments, 70 neurovascular structures (56 vessels and 14 nerves), 16 abdominal, and 11 chest wall reconstructions, as well as 159 soft tissue reconstructions for soft tissue coverage (96 pedicle flaps, 22 free tissue transfer, 41 skin-/mesh-graft).

Furthermore, there were 29 sequelae of first treatment (e.g., cementation).

A detailed summary of resected and reconstructured structures is provided in Table 2.

Table 2. This summary provides a detailed overview of performed resections (left) and reconstructions (right).

Resection	Count	Reconstruction	Count
Bone	**489**	**Bone**	**319**
simple curettage	107	cementation	18
rotationplasty (lower extremity)	2	ORIF (incl. bone ankers; removal of OS material)	61
hemi-cortex resection	20	autograft	11
complete bone resection: extra-articular	108	vascularized fibula autograft (based on fibular artery)	10
complete bone resection: transarticular	92	non-vascularized fibula autograft	1
with 3D patient-specific cutting guides	23	allograft chips	45
radiofrequency ablation (RFA); cryotherapy, MR-HIFU	41	bulk allograft	32

Table 2. *Cont.*

Resection	Count	Reconstruction	Count
tendon resection	2	conventional prosthesis	9
ligament resection	1	modular tumor prosthesis	79
forced epiphyseolysis OT (Canadell technique)	1	custom-made prosthesis	2
extra-articular scapulo-humeral resection (Tikhoff–Linberg)	1	growing prosthesis	4
biopsy/gain of diagnostic tissue	12	pedicle screws/rods/cages	18
removal of cement	1	other bone reconstruction	11
resection–replantation (upper extremity)	1	distraction osteogenesis	1
Internal hemipelvectomy	38	artificial bone substitute (Ca-sulfate, etc.)	7
Type I—ilium	15	cement spacer/pseudarthrosis/flail joint	2
Type II—Acetabular	13	arthrodesis	4
Type III—Pubic	4	vascularized epiphyseal transfer (based on tibial anterior artery)	2
Type IV—Sacral	6	Gore-Tex mesh, Trevira, etc.	2
Amputation	39	**Soft Tissues**	**159**
Forequarter	5	skin-/mesh-graft	41
External hemipelvectomy	5	pedicled tissue transfer	96
Upper extremity	5	rectus abdominis	3
Lower extremity	24	rectus abdominis (with skin)	7
Soft Tissues	**1800**	gastrocnemius	10
simple	694	latissimus dorsi	12
tendon resection	23	latissimus dorsi (with skin)	3
ligament resection	5	gracilis	3
resection of funiculus, scrotum, genitals	3	soleus	3
other STS resection	11	ALT	8
muscle resection	419	other muscle flap	47
vessel dissection	225	free tissue transfer	22
nerve dissection	270	latissimus dorsi	8
periosteum resection	41	gracilis	2
bone resection	20	ALT	8
vessel resection	38	other perforator flap	3
nerve resection	50	other free tissue transfer	1
MR-HIFU	1	**Chest wall**	**11**
Chest/Thoracic	**11**	**Abdomen**	**14**
chest wall resection	7	abdominal wall	4
other chest/lung resection	2	colon anastomosis	3
wedge resection	2	bladder	2
Abdomen	**19**	ureter	2
abdominal wall resection	1	other intraabdominal reconstruction	5
kidney	2	**Sequelae of First Treatment**	**29**
suprarenal glands	1	cement spaces implantation	4
ureter	3	partial implantation/replacement	22
bladder	3	complete compartment implantation/replacement	3
colon/rectum	4	**Neurovascular**	**70**
bowel	2	vascular	56
uterus/ovaries	1	artery complete	14
other abdominal resection	2	vein complete	13
Sequelae of 1st treatment	**106**	lympho-venous	21
debridement	27	other vessel reconstruction	8
inlay change	5	neural	14
partial removal of prosthesis	26	nerve reconstruction	8

Table 2. *Cont.*

Resection	Count	Reconstruction	Count
complete removal of prosthesis	3	neurotization/local transfer	2
infection	7	autologous	4
wound healing breakdown	11	**Tendon/Ligament**	**38**
osteosynthesis breakdown	2	autologous tendon transfer	18
fracture	1	allograft tendon reconstruction	2
other	24	local tendon reconstruction	18

4. Discussion

In this article, the authors describe the surgical spectrum of a sarcoma surgeon and provide a web-based means to assess it using a structured interoperable RWDT format. Our group has recently published an article detailing the quality indicators for sarcoma care in a multidisciplinary setting, as well as introducing an interoperable digital platform capable of assessing harmonized, structured data [6]. Achieving global harmonization and scalability of medical data is a crucial step towards achieving precision medicine. Specifically, in this study, our research has focused on the surgical aspects of sarcoma care, which have been integrated into the aforementioned digital platform. The presented parameters include information on patient exposure, tumor characteristics, the surgical setting, and surgical techniques. Such information ultimately allows the definition of the complexity or even the quality of a surgical procedure within an MDT. This will be an important step to establish a new ecosystem to meet the challenges of the precision medicine era [6].

Outcome prediction in medicine with the help of digital transformation and artificial intelligence opportunities will dramatically revolutionize our current treatment approach, but it will largely depend on the availability of structured data sets [17,19]. However, because of the scarcity of sarcomas, and to be able to compare on a large scale at the international level, we need to establish a common language of exchange among experts for data harmonization. It is not enough, for example, to bundle an outcome analysis of all megaprostheses independent of their anatomic localization and (neo-)adjuvant treatments. It is necessary to focus a large-scale analysis on a specific region or clinical circumstances to determine the advantages of subtle differences. The challenge for shared sarcoma care is to, nevertheless, have adequate numbers for an analysis. We therefore need a refined interoperable digital system which allows not only a detailed assessment but also the ability to make comparisons on a large, global scale to compensate for low volume numbers which are inherent with sarcomas. The interoperable digital data platform presented herein may offer a first step in this direction.

Sarcoma surgery meets two great challenges. A sarcoma surgeon has to be technically very skillful and versatile but also needs to have a great understanding of biology. These aspects need to be reflected when the spectrum of sarcoma surgery is assessed. Therefore, we created four main groups. Obviously, from the technical aspects, all specific types of resections and reconstructions matter and are important and need to be reflected in detail in such assessment. Furthermore, the types of tumors, as well as the anatomic regions where the tumors are located, must be reflected as well. We also included indications for surgery and the involved disciplines [18]. The latter is considered important to foster interdisciplinary exchange and to respect increasing technical complexities. Obviously, the current suggestion of surgical exposure presented herein is not comprehensive and may be regularly updated, similarly to how sarcoma pathologists update their WHO classification.

For the resection of sarcomas, the anatomic localization and the biology of the tumor are critically important to define the resection planes. To achieve an oncological and functional outcome in the patient's best interest, it is critically important that sarcoma surgery is carried out with considerations for both biological and technical principles [20,21]. To obtain and improve the biological understanding of these tumors, participation at a weekly MDT's meeting probably represents the minimal requirement because it increases the

exposure to the thinking and approach of other disciplines. Our data, for example, show that interpretations of surgical margins—i.e., how wide is wide?—may continue to vary greatly without universal harmonization of assessment. The surgeons may interpret the margin differently among themselves, but their interpretations may also differ from those of pathologists. This has great consequences for the interpretation of any comparative study and must be addressed. Modern sarcoma surgery [1,9,10,16,22,23], therefore, fosters transdisciplinary collaboration under the direction of surgeons who have a broad biological knowledge and are able to organize a team of surgeons with broad technical skills depending on the anatomic site of the tumor, which is particularly important for reconstruction after tumor resection.

Sarcoma surgery is a critical determinant for a successful treatment and outcome in sarcoma patient care. The German Cancer Society (DKG) defines in their guidelines the minimal surgical interventions per year (n = 15), as well as those in a lifetime experience (n = 50) for the sarcoma surgeon [24]. The Musculoskeletal Tumor Society—MSTS also reported the number of sarcoma surgeries performed per surgeon per year, averaging approximately 35 cases [25]. Although the number of treated patients is important, it is not discriminative enough to determine the entire spectrum of surgical exposures, as sarcoma surgery includes a wide spectrum both anatomically and biologically. The French sarcoma group nicely showed that although the absolute number of performed surgeries is important, the most important discriminator for outcome is the embedding of the surgery within an MDT [2]. This is further confirmed by Baum et al. who questioned the policy of volume-based case thresholds for complex cancer surgeries by reporting risk-standardized mortality rates to be a superior metric of surgical quality compared to volume-based metrics [3,26]. Defining the complexity of surgical procedures will, therefore, be a helpful tool to meet the requirements of the precision medicine era [11,12,18,23,27].

This study has a few limitations. The overall numbers included herein may still be relatively small and concern only one sarcoma surgeon. However, considering the yearly surgical exposure proposed by MSTS or DKG [25,28], the numbers presented herein qualify for a high-volume surgeon as per definition. Furthermore, the data presented herein are considered a starting point which needs to be elaborated on, first to discuss the parameters and then to include data from many sarcoma surgeons globally. Because this RWDT-interoperable digital platform is web-based, any surgeon can store the personal information anonymously within this interoperable digital platform for free, which makes it possible to collect a vast spectrum of information.

5. Conclusions

The spectrum of sarcoma surgery not only is defined by surgical, technical, and biological skills but also critically depends on the integrated understanding of an orchestrated transdisciplinary treatment approach together with non-surgical disciplines. The multidisciplinary team meeting is an integral part of sarcoma surgery. If we aim at improving the quality of sarcoma patient care, it is time to move beyond assessing the raw numbers of surgeries performed. The definition of the quality ultimately assumes the comprehensive assessment of all important transdisciplinary parameters with the help of an interoperable digital platform. If the MDT is accepted as the key component for delivering high-quality care, such a platform has to reflect the interplay of disciplines, which then needs to be expelled as such to meet the precision medicine requirements. In a first step, global harmonization of data assessment on a large scale represents the prerequisite.

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From Intensification to Optimization: Balancing Efficacy, Safety, and Costs in High-Risk Localized Soft Tissue Sarcomas

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Simple Summary: Soft tissue sarcomas (STS) are rare, aggressive cancers that require carefully balanced treatment strategies to improve survival without excessive side effects. Standard treatment for high-risk localized STS typically includes preoperative radiotherapy and surgery. Recent trials have explored intensifying treatment by adding immunotherapy (e.g., pembrolizumab), but these approaches often lead to increased toxicity, prolonged treatment times, and higher healthcare demands. In this study, we evaluated an optimized, short-course preoperative ultra-hypofractionated radiotherapy (uhpRT) using real-world data, highlighting differences between outcomes achieved under everyday clinical conditions versus highly standardized trial environments. Comparing our outcomes with those from a recent randomized controlled trial (SU2C-SARC032) that tested intensified therapy with pembrolizumab, our streamlined uhpRT protocol achieved similar survival outcomes while markedly reducing toxicity, treatment duration, and resource utilization. Our results underline the importance of therapeutic optimization, emphasizing efficacy, safety, and real-world applicability over routine intensification.

Abstract: Background/Objectives: The SU2C-SARC032 randomized controlled trial (RCT) tested pembrolizumab combined with preoperative normofractionated radiotherapy as an intensified treatment for high-risk stage III resectable soft tissue sarcoma (STS), demonstrating a moderate improvement in disease-free survival (DFS) compared to preoperative radiotherapy alone, but accompanied by significantly increased toxicity, prolonged treatment durations, elevated resource source, and limited real-world applicability. To address the gap between highly controlled trial outcomes and routine clinical practice, this comparative analysis evaluated a streamlined ultra-hypofractionated preoperative radiotherapy (uhpRT) protocol using real-world data (RWD) as a potentially more balanced approach. **Methods:** Prospectively collected observational RWD from 54 consecutive patients with Stage III (T2 N0 M0) high-risk resectable STS treated at a single institution with uhpRT (25 Gy in 5 fractions in one week, no systemic therapy, median interval of 14 days to surgery) were analyzed. Survival endpoints (overall survival [OS], DFS, local disease-free survival [LDFS], distant disease-free survival [DDFS]), toxicity, and treatment duration were compared qualitatively with published outcomes from the SU2C-SARC032 trial's intensified pembrolizumab arm and control arm. **Results:** At 2 years, the optimized uhpRT protocol achieved OS (90%), DFS (66%), and DDFS (70%) comparable to the intensified pembrolizumab arm (OS: 88%, DFS: 67%, DDFS (67%)) and clearly exceeded outcomes of the control arm (OS/DFS/DDFS: 85%/52%/52%). Importantly, the uhpRT protocol

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markedly reduced treatment-related toxicities (0% Grade 3/4 events vs. 56% in the intensified trial arm) and total treatment duration (<1 month vs. 3–11 months). **Conclusions:** These findings challenge the necessity of broad treatment intensification for high-risk localized STS, strongly supporting the concept of therapeutic optimization. Given substantial real-world variability in treatment practices and feasibility highlighted by recent research, our findings advocate for treatment strategies that prioritize realistic applicability, patient safety, and value-based care principles over pure intensification.

Keywords: soft tissue sarcoma; ultra-hypofractionated preoperative radiotherapy (uhpRT); systemic therapy; PD-1 checkpoint inhibition; therapy de-intensification; survival outcomes; treatment toxicity; value-based healthcare; real-world evidence; high-risk sarcoma management

1. Introduction

Soft tissue sarcomas (STS) are rare mesenchymal tumors with diverse histological subtypes and anatomical locations, posing challenges in diagnosis, staging, and treatment [1]. In Switzerland, about 330 new cases per year are officially indicated by the National Registration of Cancers (Nationales Krebsregister der Schweiz) [2,3]. High-risk cases, such as Stage III (T2 N0 M0) high-grade sarcomas, are aggressive, with high recurrence and metastasis rates, leading to significant morbidity and mortality [4–6]. Effective STS management requires a multidisciplinary approach, with surgery as the cornerstone for localized disease. Preoperative radiotherapy is a standard adjunct to improve local control in high-risk tumors [7,8]. The role of currently available systemic therapies for non-metastatic STS is still unclear, as chemotherapies such as doxorubicin and ifosfamide offer, based on available limited data, only modest survival benefits and are associated with significant toxicity, thereby limiting their role in routine practice [9–11]. Although treatment intensification, for example via extended systemic therapy or immunotherapy, may appear attractive, these regimens often increase toxicity, treatment duration, and resource demands. Despite advances in multimodal strategies, balancing efficacy and safety—key tenets of value-based healthcare—remains an urgent priority, necessitating the pursuit of optimized (i.e., deintensified) treatment protocols and the generation of real-world evidence [12,13].

Furthermore, the reproducibility of outcomes reported in randomized controlled trials (RCTs) remains uncertain when translated to real-world clinical practice. A recent multicenter sarcoma ring trial highlighted substantial inter-institutional variability in therapy planning and delivery, even when standardized protocols were employed, underscoring the risks of directly extrapolating RCT outcomes to routine care without critical evaluation of real-world feasibility and implementation [14].

The current standard of care for high-risk STS includes surgery combined with preoperative radiotherapy, while recent systemic therapies in use are selectively employed by some centers due to their limited efficacy, toxicity, and resource demands, as supported by the limited body of reliable data [9,15–17]. Recent trials, such as the SU2C-SARC032 RCT, are exploring combining pembrolizumab, an immune checkpoint inhibitor, with radiotherapy [18–21]. To reliably answer whether such intensification benefits patients, big data is required. This multicenter trial addressed a very important innovative question using a straightforward 2-arm protocol to evaluate the implementation of immunotherapy in the curative therapy of STS. The experimental arm (n = 64) of the trial demonstrated a 15% improvement in disease-free survival (DFS) in Grade 2 and 3 tumors compared to the control arm (n = 63, p = 0.06), while overall survival (OS) remained comparable between

the test and control arms [18]. Grade 3 or higher adverse events were observed in 56% of patients in the experimental arm, raising concerns about the feasibility of therapy intensification in routine practice. The trial's stringent inclusion criteria limit its generalizability to broader real-world patient populations. In contrast, in real-world settings, high-risk STS management often involves patients with comorbidities, advanced age, larger tumors, or prior unplanned surgeries, and local recurrences—all conditions typically excluded from clinical trials.

Observational RWD studies complement RCTs by capturing the heterogeneity of real-world populations, offering inclusive assessments of treatment efficacy and safety, and addressing gaps in the trial data arena [22].

Against this backdrop, the present analysis compares real-world evidence from an ultra-hypofractionated preoperative radiotherapy (uhpRT) protocol for high-risk STS with the published SU2C-SARC032 RCT results. Emphasizing an approach aligned with "therapeutic optimization" over intensification, this study underscores the importance of minimizing treatment-related toxicity, shortening total treatment time, and preserving efficacy in a value-based healthcare context.

However, methodological concerns have emerged regarding recent intensified therapy trials, particularly the SU2C-SARC032 trial, which included Grade 2 tumors classified as stage III according to the outdated AJCC 7th edition (2009). According to the current AJCC 8th edition (2017), Grade 2 lesions are no longer classified as stage III. The inclusion of these lower-risk tumors likely skews survival outcomes, inflating the observed effectiveness of intensified systemic therapy. Therefore, real-world analyses that accurately reflect contemporary staging criteria and patient heterogeneity are critical for validating treatment strategies.

2. Materials and Methods

2.1. Study Design

This study analyzed prospectively collected data of a RWD uhpRT RWD cohort of consecutive high-risk STS patients treated at a single institution over a 4.5-year period [23]. The primary objective was to compare these RWD outcomes to the results of the SU2C-SARC032 RCT, a multicenter randomized controlled trial published in November 2024 in The Lancet [18]. The SU2C-SARC032 RCT was chosen as the benchmark for comparison due to its control arm using pre-operative radiation only, rendering it comparable to its own RWD protocol cohort, and due to its clinical relevance, rigorous methodology, and similar timeframe for patient recruitment. All included consecutive RWD patients meeting the same specific eligibility criteria as given in the SU2C-SARC032 trial; however, without exclusions based on age, comorbidities, tumor location, or prior interventions such as unplanned surgeries or previous irradiation. This inclusive approach ensured a representative real-world cohort reflective of the complexities encountered in clinical practice.

2.2. Patient Population

2.2.1. uhpRT Cohort

The uhpRT RWD cohort included all consecutive patients who met the SU2C-SARC032 RCT conditions (resectable Stage III (T2 N0 M0) grade 2/3 STS as according to AJCC 7th edition) and were treated between April 2020 and November 2024 at a single institution. In contrast to the RCT benchmark trial, no exclusions were made based on age, comorbidities, tumor size, location, or prior interventions, resulting in a heterogeneous real-world population. This inclusiveness allowed for the evaluation of treatment efficacy across diverse clinical scenarios, including patients with prior unplanned excisions ("whoops" surgeries), reoperations for locally recurrent disease, and retroperitoneal or trunk wall

lesions. Excluded were 13 patients treated with the same protocol in the same time interval; however, they were diagnosed with G1 lesions.

2.2.2. SU2C-SARC032 RCT Cohort

The SU2C-SARC032 trial enrolled patients with resectable Stage III high-grade STS G2/3 that were required to meet specific fitness thresholds for pembrolizumab and radiotherapy. Exclusion criteria encompassed prior systemic therapy, significant comorbidities, and inadequate organ function. Additionally, patients with retroperitoneal tumors, prior unplanned surgeries, or residual disease were excluded, reflecting the trial's selective design.

2.2.3. Comparison of Inclusion Criteria

The broader inclusion criteria of the uhpRT RWD cohort allowed for the analysis of outcomes in a more heterogeneous population with respect to real-life practice than the controlled SU2C-SARC032 trial. This real-world approach enhances the generalizability of the findings and provides valuable insights into the protocol's performance in less idealized clinical conditions (Table 1).

Table 1. Comparison of Patient Cohorts.

Criteria	uhpRT RWD Cohort [23]	SU2C-SARC032 RCT
Stage	Stage III (T2 N0 M0)	Stage III (T2 N0 M0) *
Tumor Grade	Grade 2/3	Grade 2/3
Age restrictions	None	Specific thresholds for fitness
Comorbidities	No exclusions	Excluded significant comorbidities
Tumor Locations	Includes retroperitoneal or trunk wall	Excluded retroperitoneal
Prior Surgeries	Included unplanned surgeries or recurred disease	Excluded prior unplanned surgeries and recurred disease
Systemic Therapy History	No exclusions	Excluded prior systemic therapy
Residual Disease	included	excluded
Organ Function	No exclusions	Excluded patients with inadequate organ function

* The SARC032 trial used the 7th edition of AJCC from 2009 (and not the most current one), reason why the same criteria herein are also used for the uhpRT cohort.

2.3. Treatment Protocols

The uhpRT RWD cohort followed a predefined streamlined protocol comprising ultra-hypofractionated preoperative radiotherapy, delivering a total of 25 Gy in 5 fractions over one week. Limb-salvage surgery was performed approximately two weeks (median 14 days) following radiotherapy completion. This treatment protocol deliberately avoided systemic therapy to minimize patient burden and enhance clinical feasibility and tolerability.

In contrast, the SU2C-SARC032 trial evaluated two distinct treatment arms:

- **Control Arm:** Patients received conventional normofractionated radiotherapy (50 Gy in 25 fractions over 5 weeks) followed by surgery without systemic therapy.
- **Experimental Arm:** Patients received conventional normofractionated radiotherapy combined with systemic therapy (pembrolizumab), administered over a median of 14 cycles (maximum 17), spanning approximately 3–11 months (Table 2).

Table 2. Comparison of Treatment Protocols [23].

Component	uhpRT RWD Cohort	SU2C-SARC032 RCT Control Arm	SU2C-SARC032 RCT Test Arm
Radiotherapy	25 Gy in 5 fractions (1 week)	50 Gy in 25 fractions [width=10.5 cm] (5 weeks)	50 Gy in 25 fractions [width=10.5 cm] (5 weeks)
Interval (RT-Surgery)	Median 14 days	Median 34 days	Median 36 days
Surgery	Limb-salvage only (100%)	Limb-salvage only (100%)	Limb-salvage only (100%)
Systemic Therapy	none	none	Pembrolizumab: median 14 cycles (max 17)
Toral treatment Duration	<1 month	2.5 months	3–11 months

2.4. Outcome Measures

2.4.1. uhpRT Study Endpoints

The endpoints were chosen according to the SU2C-SARC032 Trial endpoints, in order to comparatively evaluate treatment effectiveness: OS, defined as the time from the start of radiotherapy to death from any cause; DFS, defined as the time from the start of radiotherapy to any recurrence (local, nodal, regional, or distant) or death; LDFS measuring the time to local recurrence, and DDFS measuring the time to distant metastasis. These endpoints were evaluated at two years, with survival probabilities estimated using Kaplan–Meier analysis. Follow-up time was calculated from the start of radiotherapy to the last documented clinical contact or event, and patients lost to follow-up were censored at their last recorded visit. This approach reflects real-world practice and allows for a pragmatic assessment of treatment outcomes.

2.4.2. SU2C-SARC032 Trial Endpoints

In the SU2C-SARC032 trial, DFS was the primary endpoint, defined as the time from randomization to recurrence or death. Secondary endpoints included OS, LDFS, and DDFS, all measured using Kaplan–Meier analysis. The SU2C-SARC032 reached a longer follow-up duration, with a median of 43 months for both the experimental and control arms. This extended follow-up allowed for a more comprehensive assessment of long-term outcomes such as distant metastases and late recurrences.

2.4.3. Alignment and Deviations

While the definitions of OS, DFS, LDFS, and DDFS were consistent across both studies, notable differences existed in follow-up duration and data collection. The uhpRT RWD cohort had a shorter median follow-up of only 30 months, limiting the evaluation of long-term outcomes, whereas the SU2C-SARC032 controlled trial design allowed for more structured follow-up over a median of 43 months. Additionally, the uhpRT study relied on real-world data, introducing variability in patient follow-up intervals, while the SU2C-SARC032 maintained a uniform follow-up schedule. These differences in methodology were carefully considered to ensure that comparisons between the uhpRT RWD cohort and the SU2C-SARC032 trial were kept as valid as possible.

2.5. Statistical Analysis

2.5.1. Cohort Analysis

Kaplan–Meier survival curves were generated for OS, DFS, LDFS, and DDFS in the uhpRT cohort, with median survival times and 95% confidence intervals (CIs) reported. Cox

proportional hazards models were used to assess associations between clinical variables, such as tumor grade, patient age, tumor size, and prior surgeries, and survival outcomes, providing insights into prognostic factors within a real-world population.

2.5.2. Comparison with SU2C-SARC032 Trial

Published summary statistics from the SU2C-SARC032 trial were used for indirect comparisons. Kaplan–Meier survival probabilities and hazard ratios for both trial arms were extracted, and subgroup analyses by tumor grade, age, and tumor size were conducted to align the uhpRT RWD cohort with the SU2C-SARC032 study populations.

2.5.3. Adjustments and Limitations

Due to the lack of access to raw data from the SU2C-SARC032 trial (which was only released 3 years after publication), propensity score matching was not feasible. Sensitivity analyses were conducted to account for known baseline differences, such as tumor size/location or prior interventions. According to the study's Supplementary Materials in The Lancet paper, raw data from the SU2C-SARC032 trial will only be made available in three years, limiting the ability to perform direct comparisons in the current analysis. Despite these constraints, consistent endpoint definitions and Kaplan–Meier methodologies support meaningful qualitative comparisons, providing valuable insights into the effectiveness of the uhpRT protocol.

3. Results

3.1. Patient Characteristics and Treatment Protocols

This comparative analysis included 54 consecutive patients with Stage III (T2 N0 M0) STS treated at a single institution using the uhpRT protocol. Their outcomes were compared with those of 63 and 64 patients in the control and experimental arms, respectively, of the SU2C-SARC032 RCT, a multicenter randomized controlled trial conducted across 20 international institutions. The analysis focuses on survival outcomes, safety, and treatment feasibility, emphasizing differences in baseline characteristics, treatment protocols, and the real-world applicability of the uhpRT protocol compared to the controlled environment of the SU2C-SARC032 RCT (Table 3).

Table 3. Comparison of treatment protocols.

Parameter	uhpRT RWD Cohort [23]	SU2C-SARC032 RCT Control Arm	SU2C-SARC032 RCT Test Arm
Recruitment	04.2020–11.2024 (4.5 y)	11.2017–11.2023 (6 y)	11.2017–11.2023 (6 y)
Interval	Single institution	20 international institutions	20 international institutions
Center			
Study Setup	Prospective RWD	Prospective RCT	Prospective RCT
N of patients	54	63	64
Follow-up, median (months)	30	43	43
Sex			
Female	21 (39%)	24 (38%)	23 (36%)
Male	33 (61%)	39 (62%)	41 (64%)

Table 3. *Cont.*

Parameter	uhpRT RWD Cohort [23]	SU2C-SARC032 RCT Control Arm	SU2C-SARC032 RCT Test Arm
Age	63 (38–86)	60 (26–84)	59 (35–87)
Ethnicity (white)	100%	95%	80%
Stage [1]	III	III	III
TNM			
T2-4 N0 M0	100%	100%	100%
rT2-4 N0 M0	6 (11%)	0	0
Grade			
Grade 2	13 (24%)	20 (32%)	22 (34%)
Grade 3	41 (76%)	43 (68%)	42 (66%)
Histologic Subtype			
Undiff. pleomorphic Sarcoma (UPS)	15 (28%)	48 (76%)	53 (83%)
Dedifferentiated Liposarcoma (DDLS)	12 (22%)	4 (6%)	4 (6%)
Myxofibrosarcoma (MFS)	12 (22%)	6 (10%)	7 (11%)
Undiff./Unclassified Sarcoma (NOS)	0	5 (8%)	0
Myxoid Liposarcoma (MLS)	5 (9%)	0	0
Leiomyosarcoma (LMS)	4 (7.5%)	0	0
Others	3 (5.5%)	0	0
Tumor Volume, median cc (range)	161 (18–3084)	NA	NA
Tumor Size (median cm, range)	10 (7–18)	10 (7–13)	11 (8–14)
Not available	5 (whoops)	NA	NA
Tumor Location			
Lower limb	25 (46%)	38 (60%)	41 (64%)
Lower limb girdle	6 (11%)	6 (10%)	3 (5%)
Upper limb	7 (13%)	9 (14%)	10 (16%)
Upper limb girdle	5 (9%)	10 (16%)	10 (16%)
Retroperitoneal	5 (9%)	0	0
Trunk wall	5 (9%)	0	0
others	1 (2%)	0	0
Previously treated			
Unpanned excision (whoops)	5 (9%)	0	0
Surgery for initial manifestation	6 (11%)	0	0
Previous adj. Radiation Therapy	3 (5.5%)	0	0

Table 3. *Cont.*

Parameter	uhpRT RWD Cohort [23]	SU2C-SARC032 RCT Control Arm	SU2C-SARC032 RCT Test Arm
Radiation Therapy			
(Ultra-)hypofractionation	54 (100%)	2 (3%)	1 (2%)
normofractionation	0	61 (97%)	63 (98%)
Systemic Therapy			
Preoperative Chemotherapy	1 (2%)	0	0
Postoperative Chemotherapy	0	0	0
Pembrolizumab	0	0	100%
(PD-1-ihibitor, max 17, 3-weekly)			(median 14 cycles)
Surgery			
No surgery	0	1	2
Limb salvage	43/43 (100%)	NA	NA
Resection status (R0/1/2)	49 (91%)/5 (9%)/0	NA	NA
amputation	0	NA	NA

[1] based on AJCC 7th edition from 2009, for comparison purposes.

3.1.1. Baseline Characteristics

The median follow-up in the uhpRT RWD cohort was 30.2 months, compared to 43 months in both arms of the SU2C-SARC032 trial. Patients in the uhpRT RWD cohort were slightly older, with a mean age of 63 years (range: 38–86), compared to 60 years and 59 years in the control and experimental arms, respectively. High-grade (Grade 3) tumors were more prevalent in the uhpRT RWD cohort (76%) compared to the trial cohorts (68% and 66%). The uhpRT RWD cohort exhibited greater histological diversity, with undifferentiated pleomorphic sarcoma (UPS) representing 28% of cases, compared to 83% in the SU2C-SARC032 trial arms. Median tumor volumes in the uhpRT RWD cohort measured 161 cm^3, while volumetric data were not reported for the SU2C-SARC032 trial cohorts. Tumor sizes based on the longest diameter did not significantly differ across cohorts.

The uhpRT RWD cohort included real-world complexities not captured in the trial populations, such as prior unplanned excisions ("whoops" surgeries; 9%), reoperations for locally recurrent disease (11%), previous radiotherapy (5%), and retroperitoneal tumor location (9%). These factors reflect the broader inclusiveness of the uhpRT RWD cohort, which offers insights into the performance of the treatment protocol in less idealized clinical settings. This heterogeneity underscores the real-world adaptability and feasibility of the uhpRT protocol compared to the controlled trial environment.

3.1.2. Treatment Protocols

The uhpRT RWD cohort adhered to the predefined ultra-hypofractionated regimen (25 Gy in 5 fractions over one week), followed by surgery at a median interval of 14 days [23]. Only one patient (2%) deviated from the protocol by receiving preoperative chemotherapy due to specific clinical indications. No postoperative chemotherapy was administered.

In comparison, the SU2C-SARC032 trial utilized conventional radiotherapy (50 Gy in 25 fractions over 5 weeks) and included pembrolizumab in its experimental arm, ad-

ministered over 14–17 cycles (approximately 3–11 months). Surgical management was limb-sparing in all groups, with no amputations recorded.

3.2. Survival Outcomes

Survival outcomes of the uhpRT RWD cohort were evaluated and compared with the control and experimental arms of the SU2C-SARC032 trial to assess its effectiveness. Kaplan–Meier curves were generated for OS, DFS, LDFS, and DDFS at two years (Table 4).

Table 4. Details on Disease Control.

Parameter	RWD Cohort	SU2C-SARC032 Control Arm	SU2C-SARC032 Test Arm	*p*-Value RCT Arms
Local Disease-free Survival @ 2y, all	**94%**	**100%**	**97%**	
G2 (*n*)	100% (13)	NA	NA	X
G3 (*n*)	92% (41)	NA	NA	X
Female (*n* = 21)/male (*n* = 33)	94%/93%	NA	NA	X
Age ≤ 65 y/>65 y (*n* = 29/25)	92%/95%	NA	NA	X
Distant Disease-free Survival @ 2y, all	**70%**	**52%**	**67%**	
G2 (*n*)	80% (13)	NA	NA	X
G3 (*n*)	64% (41)	NA	NA	X
Female/male (*n*)	68% (21)/68% (33)	NA	NA	X
Age ≤ 65 y/>65 y (*n*)	58% (29)/68% (25)	NA	NA	X
Disease-free Survival @ 2y, all	**66%**	52%	**67%**	0.035
G2 (*n*)	80% (13)	74% (20)	80% (22)	0.78
G3 (*n*)	60% (41)	41% (43)	60% (42)	0.06
Female/male (*n*)	63% (21)/61% (33)	NA	NA	X
Age ≤ 65 y/>65 y (*n*)	54% (29)/72% (25)	NA	NA	X
Overall Survival @ 2y, all	**90%**	**85%**	**88%**	
G2 (*n*)	100% (13)	NA	NA	X
G3 (*n*)	86% (41)	NA	NA	X
Female/male (*n*)	94% (21)/86% (33)	NA	NA	X
Age ≤ 65 y/>65 y (*n*)	88% (29)/91% (25)	NA	NA	X

3.2.1. Overall Survival (OS)

The 2-year OS rate for the uhpRT RWD cohort was 90%, comparable to the experimental (88%) and the control arm (85%; $p = 0.28$, trial control vs. test arm) of the SU2C-SARC032 trial (Figure 1).

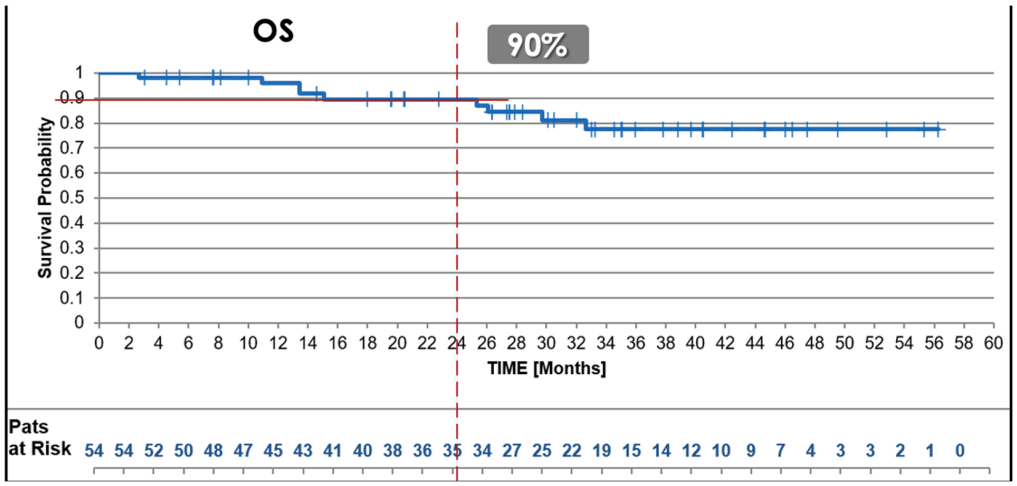


Figure 1. Overall Survival. Kaplan–Meier survival curves depicting 2-year Overall Survival (OS) in the uhpRT real-world cohort compared qualitatively to outcomes of the control and intensified pembrolizumab arms from the SU2C-SARC032 trial. The uhpRT protocol demonstrated comparable OS rates despite the shorter treatment duration and absence of systemic therapy.

3.2.2. Disease-Free Survival (DFS)

The 2-year DFS rate for the uhpRT RWD cohort was 66%, compared to 67% observed in the experimental arm of the SU2C-SARC032 trial and 52% (p = 0.035, trial control vs. test arm) reported in the control arm (Figure 2).

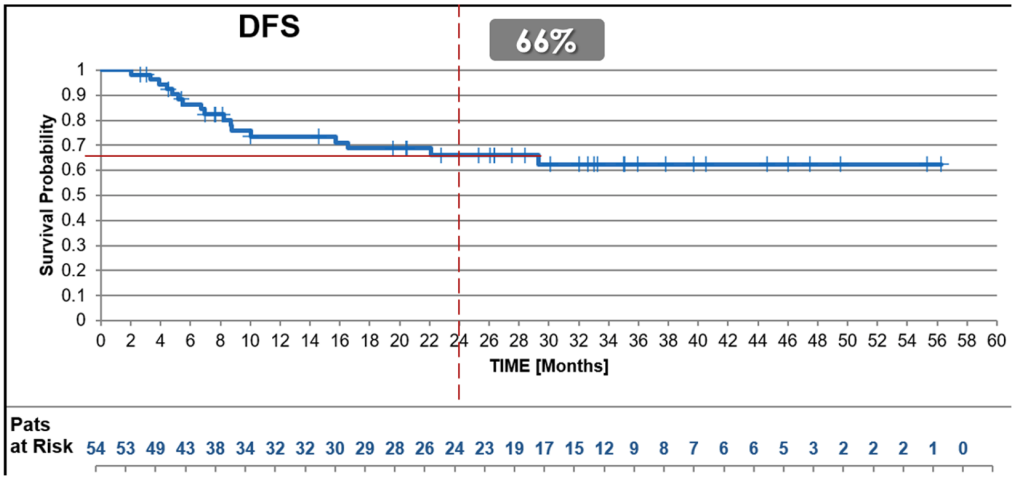


Figure 2. Disease-free Survival. Kaplan–Meier survival curves illustrating 2-year Disease-Free Survival (DFS) in patients treated with the uhpRT protocol compared with the control and intensified pembrolizumab arms of the SU2C-SARC032 trial. DFS rates in the uhpRT RWD cohort closely matched those of the intensified treatment arm and significantly exceeded those of the control arm.

3.2.3. Local Disease-Free Survival (LDFS)

The uhpRT RWD cohort achieved a 2-year LDFS of 94%, higher than the approximately 85% reported in both the control and experimental arms of the SU2C-SARC032 trial, as according to Figure 3 in the article, while 100% for the control arm and ~96% (2 failures) for the permbrolizumab test arm as according to the description in the text (Figure 3).

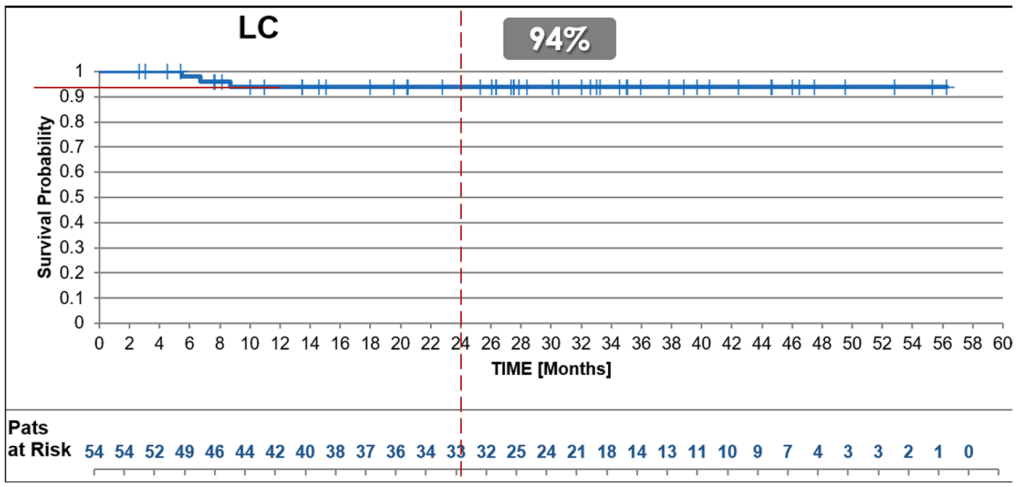


Figure 3. Local Disease-Free-Survival. Kaplan–Meier curves showing 2-year Local Disease-Free Survival (LDFS) outcomes for the uhpRT RWD cohort in comparison with published LDFS results from the SU2C-SARC032 trial. The uhpRT RWD cohort exhibited excellent local control rates, surpassing outcomes of both control and intensified treatment arms.

3.2.4. Distant Disease-Free Survival (DDFS)

The 2-year DDFS for the uhpRT RWD cohort was 70%, closely matching the 67% observed in the experimental arm of the SU2C-SARC032 trial and surpassing the 52% (p = 0.08, trial control vs. test arm) reported in its control arm (Figure 4).

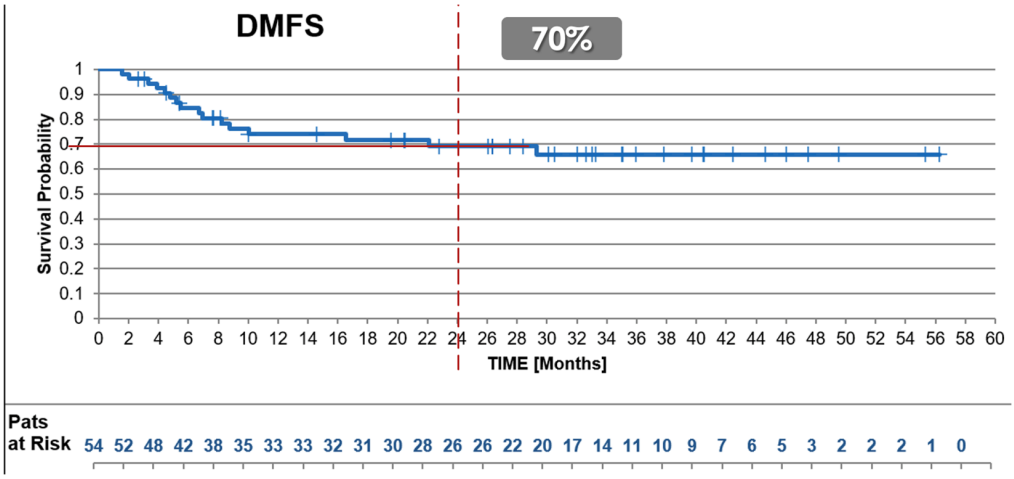


Figure 4. Distant-Disease-Free Survival. Kaplan–Meier survival curves presenting 2-year Distant Disease-Free Survival (DDFS) of the uhpRT RWD cohort versus the SU2C-SARC032 trial cohorts. The uhpRT protocol demonstrated comparable efficacy in preventing distant metastases, mirroring outcomes achieved with intensified pembrolizumab treatment and surpassing the control arm.

3.3. Safety and Adverse Events

The safety profile of the uhpRT protocol was limited, comparable to that of the SU2C-SARC032 trial, as in the RCT, no differentiation between early and late-term effects was indicated. The own evaluation included acute radiotherapy toxicity, late-term toxicity, and wound complication rate. The findings emphasized the markedly superior tolerability of the uhpRT protocol, particularly as it avoids the systemic toxicities associated with pembrolizumab (Table 5).

Table 5. Summary of safety outcomes.

Parameter	RWD Cohort	SU2C-SARC032 Control Arm	SU2C-SARC032 Test Arm	*p*-Value RCT
Treatment Times				
Radiation Therapy, weeks	1	5	5	X
End of Radiation Therapy to Surgery (median days)	14	34	36	X
Pembrolizumab, median cycles (max 17, 3-weekly)	0	0	14	X
Total Treatment Time, months (TTT)	<1	2.5	3–11	X
Acute RT Toxicity				
G0	52 (96%)	NA	NA	X
G1	2 (4%)	NA	NA	X
G2	0	NA	NA	X
Wound Complication Rate (acc. CAN-NCIC-SR2 trial)	12%	NA	NA	X
Late-term Toxicity				
G3/4	0	21 (31%)	39 (56%)	X
At least 1 serious adverse event	0	13 (19%)	31 (47%)	X

3.3.1. Radiation-Related Early Side Effects

Early radiation-related side effects in the uhpRT RWD cohort were minimal. Most patients (96%) experienced no early skin reactions (Grade 0), while the remaining 4% exhibited only mild skin reactions (Grade 1). No cases of moderate or severe acute toxicity (Grade 2 or higher) were reported. Although detailed acute toxicity data were not explicitly published for the SU2C-SARC 032 trial, reported rates of severe adverse events (Grade 3/4) were high, with 31% in the control arm and 56% in the experimental arm. These findings highlight the superior short-term tolerability of the uhpRT protocol.

3.3.2. Wound Complications

The uhpRT RWD cohort demonstrated a low wound complication rate of 12%. This result supports the feasibility of the 'short interval' surgical approach utilized in the uhpRT protocol due to the excellent early tolerance. Importantly, the shortened interval between the completion of radiotherapy and surgery (median 14 days) did not appear to compromise wound healing. While comparable data on wound complications from the SU2C-SARC032 trial were not explicitly reported, the observed rate in the uhpRT RWD cohort reflects a favorable balance between treatment efficiency and surgical outcomes.

3.3.3. Late-Term Effects

Late-term effect data following the uhpRT RWD cohort revealed no instances of any severe (Grade 3 or 4) toxicity during the still short study period—as expected considering the relatively lower radio-biological effective dose of 5 × 5 Gy as compared to the normofractionated schedule in the RCT (: equivalent doses EqD2 for late responding normal tissues (a/b = 2 Gy): 44 Gy vs. 50 Gy). This contrasts with the experimental arm of the SU2C-SARC 032 trial, where 47% of patients experienced at least one serious adverse event, likely attributable to pembrolizumab. The absence of late-term severe toxicity so far in the uhpRT RWD cohort reinforces the protocol's potential to minimize long-term treatment-related complications.

3.3.4. Overall Adverse Events

The uhpRT RWD protocol exhibited a notably superior safety profile compared to the SU2C-SARC032 trial. None of the patients in the uhpRT RWD cohort experienced Grade 3/4 toxicities or serious adverse events during the study period. In contrast, the SU2C-SARC032 trial reported substantial toxicity, with 31% of patients in the control arm and 56% in the experimental arm experiencing Grade 3/4 adverse events. Additionally, at least one serious adverse event occurred in 19% and 47% of patients in the control and experimental arms, respectively. These findings underscore the efficacy of the uhpRT RWD protocol in achieving disease control while significantly reducing the risk of severe treatment-related complications, further supporting its applicability in real-world clinical settings.

3.4. Subgroup Analysis

Due to the modest sample size, all subgroup analyses presented below are exploratory, intended primarily for hypothesis generation and cautious interpretation. Statistical validation (e.g., *p*-values) was not performed, and the following observations should not be considered conclusive.

3.4.1. Tumor Grade

Patients with Grade 2 tumors (n = 13) in the RWD cohort showed favorable survival outcomes, achieving a 2-year OS of 100% and DFS of 75%. In contrast, patients with Grade 3 tumors (n = 41) had slightly lower outcomes, with a 2-year OS of 86% and DFS of 55%. Although direct comparisons with the SU2C-SARC032 trial were not feasible due to unavailable subgroup data, these observations support tumor grade as a clinically relevant prognostic indicator.

3.4.2. Patient Age

The uhpRT protocol demonstrated similarly effective outcomes across age groups, with younger patients (<65 years) showing a 2-year OS of 89% and older patients (≥65 years) 87%. DFS was comparably balanced, with rates of 63% for younger and 61% for older patients, indicating that age alone may not significantly influence outcomes within this treatment protocol.

3.4.3. Tumor Volume

Patients with tumors larger than the median size (161 cm^3) exhibited slightly reduced local (91% vs. 97%) and distant (67% vs. 77%) disease-free survival rates compared to smaller tumors. This observation aligns with clinical expectations—larger tumors typically correlate with higher metastatic risk—but must be interpreted cautiously given limited subgroup sizes, lack of statistical validation, and inherent selection bias (exclusion of metastatic cases at baseline). Future larger-scale studies are necessary to confirm these observations definitively.

4. Discussion

This comparative analysis demonstrates that our optimized uhpRT protocol, devoid of systemic therapy, achieves comparable short-to-intermediate-term survival outcomes to the intensified pembrolizumab regimen assessed in the SU2C-SARC032 randomized controlled trial (RCT). Our findings provide strong evidence that treatment optimization—characterized by shorter durations, substantially lower toxicity, and reduced healthcare resource consumption—may offer significant clinical and economic advantages over therapy intensification in high-risk localized soft tissue sarcomas.

The chosen 5-fraction ultra-hypofractionated regimen (25 Gy over 1 week) was based on existing evidence demonstrating comparable efficacy and improved acute tolerability relative to conventional 5-week normofractionated radiotherapy [23–27] (regarding [23,24]: please see also Tables 1 and 3). Additionally, the shorter regimen potentially leverages favorable immunological effects typically associated with hypofractionated schedules ($\leq$8 fractions), which may enhance local and systemic antitumor immune responses [28]. Indeed, larger fraction sizes have been reported to potentiate immunogenic cell death, highlighting a mechanistic basis for combining short-course radiotherapy with immunotherapeutic strategies if needed [29–33]. While the SU2C-SARC032 trial importantly addressed the innovative question regarding immunotherapy intensification, its preliminary results, though noteworthy for a ~15% absolute improvement in disease-free survival (DFS), revealed substantial increases in toxicity, prolonged treatment duration, and higher resource requirements. The reported DFS benefit was found statistically significant when summarizing G2 and G3 cases, while the G3 subgroup (high risk subgroup, as according to the 2017 AJCC 8th edition) itself was not found significantly different among the control and test arm (p = 0.06), G2 cases showed no differences (p = 0.78) (Table 4). Notably, the extended duration of pembrolizumab treatment (up to 17 cycles spanning nearly one year) in the SU2C-SARC032 trial introduces an additional potential bias. This prolonged systemic exposure could artificially delay recurrence, thus inflating disease-free survival rates without necessarily reflecting a genuine long-term therapeutic benefit. By comparison, our optimized uhpRT protocol, designed explicitly to minimize patient burden and duration of therapy, addresses this issue by demonstrating comparable disease control within a significantly shorter treatment timeframe. Specifically, 56% of patients in the intensified regimen experienced severe (Grade 3/4) toxicities, raising critical questions regarding its broader applicability and necessity, particularly in real-world clinical settings [34–36]. The median follow-up time in our uhpRT RWD cohort was 30 months, which is shorter than that reported in the SU2C-SARC032 trial (43 months). This limits the assessment of long-term outcomes, particularly late recurrences, distant metastases, and late toxicity. However, approximately 80% of soft tissue sarcoma recurrences—both local and distant—are known to occur within the first three years after treatment [37], suggesting that our findings provide a valid estimate of mid-term disease control [37].

These outcomes reflect broader concerns outlined by Braik et al. regarding the unclear benefit and potentially disproportionate risks associated with systemic therapy intensifi-

cation in localized soft tissue sarcoma [9]. We acknowledge the recent CTOS consensus (September 2024), which advises against adopting hypofractionated preoperative radiotherapy outside of clinical trials [38]. However, our uhpRT program began in March 2020 and has, from the outset, been implemented within a structured real-world framework, with prospective documentation of toxicity and patient-reported outcomes. This approach supports responsible, data-driven adaptation of care models and may contribute complementary evidence toward future refinement of consensus guidelines. The recently proposed Common Sense Oncology principles further support this critical approach to clinical trial design and reporting, advocating for endpoints that directly translate into meaningful patient benefits, such as overall survival and health-related quality of life (HRQOL). These principles underline the necessity for clear communication regarding absolute clinical benefits, realistic toxicity profiles, and overall patient burden, thus reinforcing the importance of prioritizing treatment strategies that provide genuine value rather than purely statistical advantages [12,39].

In stark contrast, our uhpRT protocol exhibited no severe adverse events (Grade 3/4), highlighting substantial gains in patient safety and tolerability [23,24,38]. In contrast, the pembrolizumab arm of the SU2C-SARC032 trial reported severe (Grade 3/4) adverse events in 56% of patients, with nearly half experiencing serious adverse events (SAEs), significantly impacting patient quality of life. The observed low wound complication rate (12%) is consistent with our previously published experience in normofractionated preoperative RT and likely reflects both meticulous surgical technique and radiation planning [40]. Notably, PTVs were manually edited to minimize exposure of skin, bone, and joints, and underwent systematic double-review. The long-term collaboration of the same surgical-radiation team (>20 years) may have further contributed to the consistent mitigation of early complications. Importantly, no radiation-induced bone fractures have occurred to date, likely due to strict avoidance of circumferential or extended bone exposure during PTV delineation. Based on estimated α/β ratios of 2 for late-responding tissues and ~4 for sarcoma tumor control, the 5 $\times$ 5 Gy regimen corresponds to an EqD2 of approximately 44 Gy and 37.5 Gy, respectively. The BED for 5 $\times$ 5.0 Gy of ~56 Gy is somewhat lower than that for 25 $\times$ 2.0 Gy with ~66 Gy, including the time correction. The substantially shorter total treatment time (1 vs. 5 weeks) compensates at least in part for the lower BED. Our observed 2-year LC rate of 94% underscores the efficacy of this protocol when implemented with rigorous QA and multidisciplinary coordination. However, in the comparator trial, quality-of-life data were not comprehensively reported. These toxicity findings highlight the critical importance of balancing survival outcomes against treatment-related morbidity, further underscoring the advantages of a safer and more patient-centered approach, such as our uhpRT protocol. These findings underscore the clinical relevance of optimizing locoregional strategies such as radiotherapy, while recognizing that innovations in systemic therapy for STS are urgently needed and must be developed through rational, patient-centered trial designs, as highlighted in the broader Common Sense Oncology framework [12,13]. By significantly shortening total treatment duration to less than one month, our approach also addresses practical limitations inherent to intensified regimens, such as prolonged hospital stays, increased patient burden, reduced compliance, and greater financial toxicity. Adopting optimized regimens, such as uhpRT, could significantly decrease both direct and indirect healthcare costs, thus aligning with global efforts to implement sustainable, value-based healthcare practices [41–43].

Furthermore, the inclusivity of our real-world data cohort, comprising patients with comorbidities, recurrences, prior interventions, and diverse anatomical tumor sites, reinforces the generalizability and real-world relevance of our findings [44–48]. However, this patient heterogeneity may impact outcome comparisons with more selectively enrolled

trial populations. Indeed, extrapolating the results from highly controlled clinical trial settings to routine practice without consideration of real-world variability is problematic, as demonstrated by the sarcoma ring trial [14]. This trial revealed significant discrepancies between institutions in treatment planning, despite uniform guidelines. Therefore, it is imperative to not only compare outcomes between therapeutic strategies but also to document and evaluate the exact treatments delivered across institutions. Without capturing these variances, outcome comparisons may equate fundamentally different practices, thus 'comparing apples to oranges' rather than providing a meaningful basis for clinical decision-making [39]. Additionally, the shorter median follow-up of 30 months in our cohort, compared to 43 months in the SU2C-SARC032 trial, may limit full assessment of late toxicities and long-term control. This limitation underscores the urgent need for international collaborative research networks specifically designed to improve accrual rates, enhance patient enrollment efficiency, and facilitate rapid generation of statistically robust evidence [49–52]. Our analysis thus provides valuable insights into treatment efficacy and feasibility within less idealized, everyday clinical scenarios. This approach aligns strongly with value-based healthcare principles, prioritizing patient outcomes, reducing treatment burden, and enhancing healthcare sustainability and equity [41–43].

Future investigations could further delineate the potential immunologic synergy of ultra-hypofractionated radiotherapy. Integrating immunotherapy with short-course RT in prospective studies may clarify whether such combinations can enhance disease control without incurring excessive toxicity. Additional research should also investigate the economic implications and long-term sustainability of optimized regimens, driving clinical practice toward evidence-based, patient-centered, and economically responsible sarcoma care. Including comprehensive patient-reported outcome measures (PROMs) alongside standard clinical endpoints will be essential to capture the broader impact of therapy on quality of life, functional recovery, and patient satisfaction [53].

5. Conclusions

Our real-world comparative analysis demonstrates that an optimized ultra-hypofractionated preoperative radiotherapy (uhpRT) protocol achieves short-to-intermediate-term survival outcomes comparable to the intensified pembrolizumab regimen explored in the SU2C-SARC032 phase III trial, but with substantially reduced toxicity, treatment duration, and resource demands.

These findings critically challenge the routine use of intensified systemic immunotherapy for high-risk localized soft tissue sarcomas, suggesting that the modest improvement in disease-free survival reported in the trial, combined with significantly increased toxicity, does not yet justify clinical adoption at this time. Instead, our results strongly support optimized, patient-centered treatment strategies consistent with value-based healthcare principles, highlighting the uhpRT approach's efficiency, reduced toxicity, and potential immunological advantages.

Given the persistent high risk of distant metastases, further well-powered international trials remain essential to clearly define subgroups who might benefit from systemic immunotherapy. Moreover, as underscored by the sarcoma ring trial findings, future studies must rigorously document treatment delivery variability in real-world practice to ensure meaningful comparisons between therapeutic interventions. Adhering to Common Sense Oncology principles will further enhance the clinical relevance and applicability of future trial results, ultimately guiding oncology practice towards patient-centered, sustainable, and evidence-based care. Until stronger evidence emerges, intensified systemic treatments should remain cautiously and selectively applied based on individualized risk-benefit assessments. Furthermore, despite the observed improvement in disease-free survival in

the pembrolizumab trial, no corresponding benefit in overall survival (OS) was demonstrated (88% pembrolizumab vs. 85% control, $p = 0.28$). Given the substantial increase in toxicity without OS benefit, the routine adoption of pembrolizumab in this setting remains unjustified outside clinical trials.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Scientific Article

Preoperative Ultrahypofractionated Radiation Therapy for Soft Tissue Sarcomas: Low Rate of Wound Complications

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Purpose: Normofractionated preoperative radiation therapy (nRT) with 50 Gy applied in 25 fractions represents the most widely used radiation therapy (RT) regimen in combined local treatment of soft tissue sarcomas (STSs). STSs are characterized by a low α/β ratio of 4 to 5 Gy, which may translate into a higher sensitivity for hypofractionation. Increasing data from cohorts and phase 2 trials on ultrahypofractionated RT (uhRT) regimens are available. We prospectively assessed our preoperative uhRT sarcoma patient cohort with a focus on short-term wound complications (WCs).

Methods and Materials: This is a prospective registry analysis of a single-center patient cohort, treated from 03.2020 to 10.2023 with uhRT (25 Gy in 5 fractions in 1 week). The same radiation oncologists (G.S./C.G.) and surgeon (B.F.) performed the treatment (61/61 and 58/60), as well as the same reference pathologist (B.B.) confirmed all histopathologic diagnoses. WC (according to CAN-NCIC-SR2 trial) and intermediate local control (LC) rates were assessed and compared with outcome data of a previously published cohort of 67 extremity/trunk sarcoma patients treated with nRT by the same authors (7% WC, 98% LC at 3 years).

Results: After a mean/median follow-up of 19/19 months (range, 0-46), LC at 1.5 years was 94%. Surgery was performed at a mean/median of 20/16 days (range, 4-60) after uhRT completion. WC were observed in 7/60 operated patients (12%), and in 5/51 (10%) extremity/trunk lesions. Early tolerance was excellent, limited to G0 to G1, even in 3 patients with prior RT to the same region. Clear resection margins were achieved in 55/60 patients (92%). Pathologic necrosis of ≥95% was reported in 5% and 75% achieved less than 50% necrosis.

Conclusions: These results show low rates of WC and high LC for uhRT and are comparable with our previously published nRT data. This study supports the routine use of preoperative uhRT for STS.

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Introduction

Ultrahypofractionated radiation therapy (uhRT) is noninferior regarding efficacy and toxicity compared with normofractionated radiation therapy (nRT) in tumor

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entities such as prostate, breast, or rectal cancer.[1-3] Building up on these experiences, uhRT is increasingly being studied for curative combined treatment of soft tissue sarcoma (STS).[4] Several cohort and phase 2 studies show promising results for uhRT with ranging fractionation schedules.[5−18]

STSs are rare heterogeneous tumors with various malignant subtypes, mostly in the upper and lower extremities, trunk wall, or retroperitoneum.[19] Standard treatment of large (≥5 cm) and/or subfascial-located STS is based on surgical resection and radiation therapy (RT) in order to achieve complete remission.[20] The addition of adjuvant RT to surgery in STS translates into roughly 30% reduction of local recurrence probability, whereas no effect is evident on metastatic spread or overall survival rates.[21] Preoperative RT is favored over postoperative RT because of substantially reduced late side effects. In addition, potential tumor downsizing prior to surgery may be beneficial.[22,23] However, twice more wound healing complications are reported following preoperative nRT using nonmodulated techniques (35% vs 17%).[22] The technological evolutions of linear accelerators through intensity modulated radiation therapy (IMRT)[24] and volumetric modulated arc therapy (VMAT) allow highly conformal dose delivery, which translates to an optimized sparing of surrounding normal tissues and, in consequence, substantially less side effects.[25] Preoperative nRT in sarcoma patients using IMRT/VMAT has been reported to reduce related wound healing complications.[26,27] The additional use of image guided radiation therapy allowing reduced RT planning target volumes (PTVs) may further improve tolerance while not compromising disease control.[28]

The historically most widely used preoperative nRT scheme includes a total dose of 50 Gy delivered in 25 fractions (f) over 5 weeks.[20] Radiobiological evaluations in STS found a low α/β ratio (<10), suggesting STS to be more susceptible to increased fraction sizes.[29] Recent reports show a low average α/β ratio of 2 to 4 Gy with a wide distribution between different sarcoma subtypes, even suggesting further differentiation between subtypes regarding fractionation schemes.[30]

Using uhRT, the treatment time of RT is reduced from 5 to 1-1.5 weeks as treatment sessions decreased from 25 to 5. Based on these findings, uhRT shows promise in significantly shortening the total treatment time (TTT) for the entire combined therapy, reducing it from approximately 3 to 4 months to just 1 month. Provided at least comparable outcomes, uhRT is consequently economically beneficial because it reduces direct and indirect treatment costs for patients, hospitals, and insurances.[31] Current guidelines based on historic practices suggest surgical resection being delayed at least for 4 to 8 weeks after RT completion.[20,22] Back in 2014, Koseła-Paterczyk et al[5] reported uhRT followed by immediate surgery showing lower wound healing complications (22%). Similarly, Parsai et al[10] reported acceptable toxicity (18%).

Increasing reports on mild hypofractionated or uhRT data from phase 1/2 studies and patient cohorts consistently confirm comparable outcomes with preoperative nRT for wound complications (WCs) and disease control.[4]

However, the current literature on uhRT for STS shows noninferiority compared with nRT. Surveys among multidisciplinary sarcoma experts recently showed that only 10% of sarcoma centers regard 5 fractions (25-30 Gy) as the standard treatment of STS.[32]

At our center, preoperative uhRT for STS was implemented in March 2020; patients were consecutively enrolled in this prospective registry. This outcome analysis includes a comparison with relevant uhRT literature and own data from a previously published extremity/trunk-only cohort treated with preoperative nRT.[27]

Methods and Materials

Patient cohort

Starting in March 2020, a prospective registry was set up with predefined planning constraints and outcome parameters. Until October 2023, 61 consecutive patients received uhRT with 5 × 5 Gy, of which 3 underwent previous RT. All RTs were performed or supervised by authors G.S. and/or C.G. at the Department of Radiation Oncology, Cantonal Hospital Lucerne. Surgery was performed by author B.F. unless the patient requested external treatment.

All histologic diagnoses were confirmed by reference pathologist author B.B. Initial tumor staging included magnetic resonance imaging (MRI) of the primary lesion and computed tomography (CT) of the chest with or without abdomen. The indication for preoperative RT was discussed and determined in all instances during the weekly Swiss Sarcoma Network (SSN; swiss-sarcoma.net) multicenter sarcoma board meeting. This board comprises multidisciplinary multicenter sarcoma specialists, encompassing surgeons, radiation oncologists, oncologists, diagnostic radiologists, and pathologists.

Preoperative RT

Margins

Definition of PTV/gross tumor volume (GTV) was extrapolated from RTOG 0630.[33] Fusion of MRI image with planning CT was performed to best identify GTV and surrounding edema zone, which was systematically included in the PTV.

Contouring

- GTV: tumor volume on MRI without peritumoral edema
- Final GTV: GTV + peritumoral edema

- PTV: final GTV + margins up to 1.5 cm in all directions, +3 to 4 cm in longitudinal direction.

In order to spare the surrounding normal tissues, particularly bone and noninvolved skin, individual manual PTV editing has been performed in all patients.

Bolus material ("flab")

In patients with superficial tumors, a bolus material (1 cm thickness) was placed to reach the prescribed dose to the affected skin area. To combat any possible microscopic spread caused by the initial biopsy, a bolus was positioned over the biopsy incision.

RT delivery

The standard RT modality was VMAT with a treatment application based on image guided radiation therapy. Depending on anatomic extension, the use of conformal 3-dimensional (3D) RT was explored (VMAT-equivalent planning target volume dose coverage).[27] In these cases, comparative planning was used to ensure the best possible approach was chosen. In all patients, uhRT was applied on consecutive workdays. The prescribed total dose was delivered with 95% isodose and a max dose (Dmax) of 107% to the PTV. If no bolus was placed, Dmax to the skin was 25 Gy. Doses of >20 Gy to long bones were limited to half the cortical circumference. Of 30 cases with tumors close to the femur or humerus, 4 showed bony tumor invasion. Excluding these 4 cases, dose constraints included Dmax of <26 Gy to the bone.

Surgery and histopathologic analysis

If logistically possible, we opted for prompt surgical intervention after RT, ideally within the first 2 weeks after RT completion. At the patient's request, 2 patients were operated on externally. Initial diagnosis and excised specimens were histopathologically confirmed and examined on microscopic margins and tumor necrosis by author BB. An unplanned previous excision without histopathologic confirmation of diagnosis and/or without prior MRI or CT ("*whoops* lesions") was performed externally in 9 patients (15%). One patient who experienced a "*whoops*" surgery, resulting in a large residual mass, developed significant local and distant disease progression under RT and was in consequence treated palliatively with chemotherapy. This patient died of progressive local and distant disease undergoing no further surgery. The remaining 60/61 cases were assessable to the WC analysis.

Chemotherapy

Chemotherapy was delivered in 2/61 uhRT patients prior to RT and surgery. No simultaneous systemic treatment was performed during RT. In the event of new metastatic progression following RT and surgery, the use of chemotherapy was evaluated on a case-by-case basis and not further studied in this analysis.

Follow-up

Clinical follow-up (FU) after surgery was performed every 3 months in the first 2 to 3 years and later expanded to every 6 months. Surveillance included MRI of the primary tumor site and a CT of the thorax. The choice of imaging in metastasized patients was made based on their individual situation and needs.

Outcome definitions

The primary goal was to assess early WC rates in the first postoperative 120 days, according to the Canadian NCIC SR2 trial.[22] These include seroma aspiration, antibiotics, revision surgery for wound repair, secondary vacuum-assisted closure, and major wound infections. In addition, early/intermediate disease control and histopathologic necrosis were assessed.

Statistical analysis

When feasible, standard descriptive statistics (mean/median/range) were used. Kaplan-Meier survival curves were used for local recurrence, distant metastatic-free survival, and overall survival. Metastatic-free survival is defined by the absence of distant progression whereby patients with previous metastatic disease were excluded from the related analysis.

Results

Patient and disease characteristics of the current uhRT and previously published nRT cohort[27] are shown in Table 1.

Radiation treatment and tolerance

Fifty-four of 61 lesions were irradiated with VMAT, 7 using 3D-conventional techniques with IMRT-equivalent dose distribution. All patients completed the prescribed short course uhRT. In 1/26 cases with a tumor near the femur or humerus but without bone involvement, the maximum dose to the cortical bone was 26.6 Gy, surpassing the prescribed Dmax of <26 Gy.

Early actinic reactions were limited to G0 to G1 dermatitis (grade 0-1 skin reaction, National Cancer Institute

Table 1 Patient and disease characteristics of the current uhRT vs previously published nRT cohort[27]

Parameters	uhRT	nRT[27]
No. of patients	61	67
Total RT dose	25 Gy	50 Gy
Dose/fraction	5 Gy	2 Gy
Prescribed RT duration	1 wk	5 wk
Mean/median FU (mo)	19/19	37/33
Diagnosis		
Myxofibrosarcoma	14	6
Myxoid liposarcoma	8	21
Dedifferentiated liposarcoma	7	2
Leiomyosarcoma	5	3
Unclassified pleomorphic	17	17
Others	10	18
M+ at primary staging	6	N/A
N+ at primary staging	3	N/A
Previous local treatment	15/61 (25%)	14/67 (21%)
"*Whoops*" surgery	9 (15%)	14 (21%)
Previous surgery, no RT	3 (5%)	N/A
Previous surgery + RT	3 (5%)	0
Locally Tx-naive patients	46/61 (75%)	53/67 (79%)
Induction chemotherapy	2	N/A
Mean/median (range) interval RT surgery (wk)	2.9/2.3 (0.6-8.6)	7.3/7 (3-12)
TTT (RT start to date of surgery, d)	26/23 (10-75)	N/A
Resection status		
R0	55	66
R1	5	1
R2	0	0
No surgery	1	0
LVA	11	0
%Tumor necrosis, mean/median (range)	29/15 (0-100)	N/A

Abbreviations: FU = follow-up; LVA = lymphaticovenous anastomosis; M+ = distant metastasis; N+ = nodal metastasis; N/A = not available; nRT = normofractionated radiation therapy; RT = radiation therapy; Tx = therapy; TTT = total treatment time; uhRT = ultrahypofractionated radiation therapy.

Common Terminology Criteria for Adverse Events), even among all 3 patients with previous RT to the same region. Radiation-induced late effects (>3 months after RT) related to RT were not observed based on consequent FU visits performed by the involved surgeon (author B.F.).

Surgery

Immediate surgical intervention was anticipated, ideally within 14 days, based on the capacity of the operating room (OR) and the availability of the surgeon. En bloc resection of macroscopic tumor was performed 0.6 to 8.6 weeks after uhRT completion by author B.F. Longer intervals from completion of uhRT until surgery were mainly defined by COVID-19 pandemic–related lack of OR capacity.

Histopathologic findings

Surgical margins

Metric margins are shown in Table 2. Marginal resection (R1) was reported in 5/60 operated patients. In 2

Table 2 Analysis of surgical margins

Parameters	Clear margins (RO)				Marginal resection (Rl)	Intralesional resection (R2)	No surgery
	0-1 mm	>1-2 mm	>2-5 mm	>5 mm			
All (61)	28	9	7	11	5	0	1
"*Whoops*" surgery (9) *5/9 with residual tumor*	3	0	0	4	1	0	1
Previous surgery, no RT (3)	1	0	0	1	1	0	0
Previous surgery + RT (3)	2	0	0	0	1	0	0
Locally naive (46)	22	9	7	6	2	0	0

Abbreviation: RT = radiation therapy.

cases, external surgery was performed according to the patient's wishes. Clear margins were achieved in 55/60 (92%), with margins of 0 to 1 mm in 28/60 (47%) patients. Clear margins were achieved in 11/14 (79%) patients with prior "*whoops*" surgery or initial surgery with or without radiation for previous sarcoma.

Table 3 Characteristics of operated patients affected by WC

Parameters	N	WC (%)	Characteristics of WC affected patients
Primary site			
Extremity/chest wall	51	5/51 (10%)	1/5: following previous IC 1/5: following *whoops* surgery of foot lesion, with previous wound healing disorder, because of substantial arteriosclerosis, 91 y 1/5: following fourth OP for third LR
Pelvic/retroperitoneal/abdominal wall	9	2/9 (22%)	Very large abdominopelvic PTVs (1487 cm^3 and 2960 cm^3)
Previous treatment			
"*Whoops*"	8	1/8 (13%)	
Previous surgery, no RT	3	1/3 (33%)	
Previous surgery + RT	3	0/3 (0%)	
Induction chemotherapy	2	1/2 (50%)	
None	44	4/44 (9%)	
Time between RT and surgery (wk)			
0-2	12	1/12 (8%)	
2-4	37	3/37 (8%)	
4-8	10	3/10 (30%)	
8<	1	0/1 (0%)	
Surgical characteristics			
Surgical flab transplants	25	4/25 (16%)	
LVA	11	2/11 (18%)	1/2 following IC, 1/2 following fourth surgery for recurrence
Flab (= prescription dose to skin)			
Yes (>15 cm^3)	37	4/37 (11%)	
No	23	3/23 (13%)	
TOTAL	60	7/60 (12%)	

Abbreviations: IC = induction chemotherapy; LR = local recurrence; LVA = lymphaticovenous anastomosis; OP = operation; PTV = planning target volume; RT = radiation therapy.

Table 4 Characteristics of WC

Patients	PTV (cm^3)	PTV (cm^3)	Bolus material (cm^3)	Anatomic l ocalization	Time between RT and surgery (d)	WC postsurgery (d)	Duration of WC (wk)	Previous treatment	Surgical flab	Type of troubles	Management of troubles	Outcome of WC
Pat. 1	89	24	100	Foot	33	14	8	None	No	Necrosis	VAC	Ad integrum, no consequences
Pat 2	894	147	84	Dorsal thigh	14	22	4	None	No	Seroma, infection	Wound revisions, debridement, VAC	Ad integrum, no consequences
Pat 3	1171	31	0	Lateral Thigh	30	34	4	3 × previous surgery	No (flap for revision)	Extensive seroma, prolonged wound healing	D ebridement, VAC, flap plastic	Ad integrum, no consequences
Pat 4	2960	1195	0	Abdominal wall	21	6	5	None	Yes	Seroma, infection	Wound revision	Ad integrum, no consequences
Pat 5	1487	156	60	Fossa ischiorektalis	36	10	12	None	Yes	Seroma, infection + ileus	Debridement VAC + laparotomy	Ad integrum, no consequences
Pat 6	1445	390	158	Medial thigh	24	40	0.5	Induction chemotherapy	Yes	Seroma, dehiscence, fistula	Wound revision, debridement	Ad integrum, no consequences
Pat 7	170	11	12	Foot	9	11	6	"*Whoops*" surgery	Yes	Sepsis, prolonged wound healing even prior to RT because of peripheral vascular disease	Debridement (2 ×), antibiotics	Ad integrum, no consequences

Abbreviations: GTV = gross tumor volume; Pat = patient; PTV = planning target volume; RT = radiation therapy; VAC = vacuum-assisted closure; WC = wound complication.

Tumor necrosis

In one case, necrosis was not assessable because no surgery was performed. In the second case, a skin leiomyosarcoma was previously treated by "*whoops*" surgery resulting in an insufficient amount of tumor residuum for necrosis analysis. The 2 patients treated with preoperative induction chemotherapy showed a necrosis rate of 80% and 90%. Further analysis focuses on patients without prior chemotherapy. The percentage of tumor necrosis was mean/median 29%/15% (range, 0-100) following preoperative uhRT. Five of 57 (9%) cases achieved ≥90% necrosis, and 3/57 (5%) achieved ≥95% necrosis. Nine of 57 (16%) achieved between 50% to 90% necrosis, and 43/57 cases (75%) achieved less than 50% necrosis.

Wound complication rate

Despite conservative approaches with seroma aspiration and antibiotics, all observed wound complications led to secondary revision in the first 3 months after primary surgery and occurred in 7/60 patients (12%) (Table 3).

All affected patients experienced complete WC healing after a mean/median 5.6/5 (range, 0.5-12) weeks from onset (Table 4). There is no significant difference related to PTV, GTV, and bolus deposit (*P* value, 0.82, 0.66, and 0.66) between patients with wound complications and such with none. The area of skin covered by bolus material had a volume (cm^3) of mean/median 127/84 cm^3 (range, 17-500) among patients without WC compared with mean/median 101/92 cm^3 (range, 60-158) in patients with WC. Small boluses less than 15 cm^3 were excluded from analysis because they only covered the incision area of the biopsy. PTV among patients without WC was mean/median 1075/816 (range, 65-4350) compared with patients with WC mean/median 1174/1171 (range, 89-2960). GTV among patients without WC was mean/median 361/168 (range, 2-1923) compared with patients with WC mean/median 279/147 (range, 11-1195).

Disease control

Staging before treatment showed 8/61 (13%) patients with nodal and/or distant metastatic disease. Therefore, these were excluded from the analysis of metastatic-free survival. At the time of analysis, 8/61 patients have died, 6/8 from STS; 10 patients are alive with metastatic disease (Fig. 1). Local recurrence (LR) developed in 3/60 operated patients, 4 to 8 months after uhRT, with related LR-free survival of 94% at 1.5 years (Fig. 1). All 3 patients with local failure received diagnoses of high-grade (G3) STS. Two were in the medial thigh with a GTV of over 1100 cm^3. The third was in the arm, treated with R1 resection externally, constituting the patient's second LR. Minimal resection margins were <1 mm throughout of which one was classified as R1. None of them had previous "*whoops*" surgery.

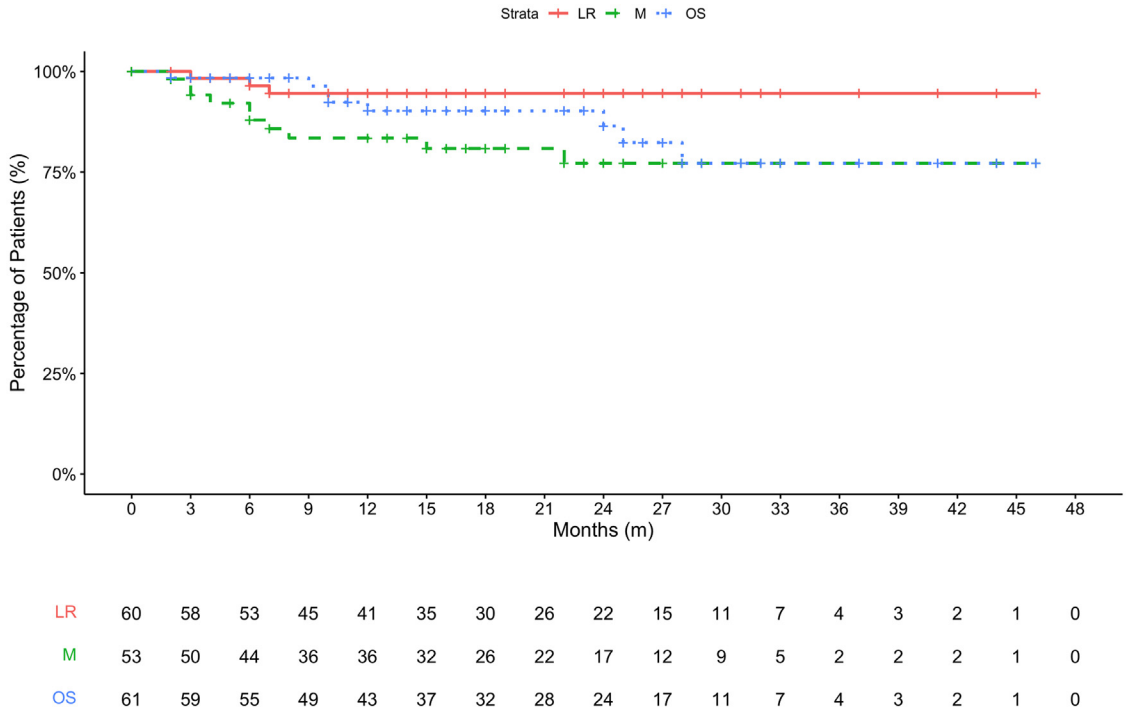


Figure 1 Kaplan-Meier survival curves for local recurrence (LR), distant metastatic-free survival (M), and overall survival (OS).

Table 5 Characteristics of selected nRT and uhRT studies

		Author (y), study name	Study	Interval	n	RT (technique)	Chemotherapy	R0	WC	Time RT to surgery	LC @ y (median FU)
nRT	1	O'Sullivan et al[22] (2002) CAN-NCIC-SR2: Phase III	Phase 3	1994-1997	94	25 × 2 Gy/5 wk (2/3D)	-	84%	35%	3-6 wk	93% @ 5 y (3.3 y)
	2	Canter et al[34] (2010)	Prosp cohort	2000-2009	25	25 × 2 Gy/5 wk (3D)	-	84%	28%	4-6 wk	100% @ 3 y (1.6 y)
	3	Shah et al[35] (2012)	Prosp cohort	2000-2010	30	25 × 2 Gy/5 wk (3D)	-	80%	23%	4-6 wk	100% @ 5 y (3.3 y)
	4	Wang et al[28] (2015) RTOG-0630	Phase 2	2008-2010	79	25 × 2 Gy/5 wk (3D 25%/IMRT 75%)	-	76%	37%	4-8 wk	94% @ 2 y (3.6 y)
	5	Studer et al[27] (2018)	Prosp cohort	2008-2016	67	25 × 2 Gy/5 wk (IMRT)	-	97%	7%	6-8 wk	98% @ 3 y (2.8 y)
uhRT	1	Koseła-Paterczyk et al[5] (2014)	Phase 2	2006-2011	272	5 × 5 Gy/5 d (3D or IMRT)	22%	79%	32%	Immediate	81% @ 3 y (2.9 y)
	2	Koseła-Paterczyk et al[18] (2016)	Phase 2	1999-2014	32	5 × 5 Gy/5 d (3D)	-	90%	22%	3-7 d	90% @ 5 y (5 y)
	3	Kubicek et al[8] (2018)	Phase 2	N/A	13	5 × 7-8 Gy (Cyber-Knife)	21%	100%	29%	4-8 wk	93% @ 9 mo (9 mo)
	4	Kalbasi et al[11] (2020)	Phase 2	2014-2016	52	5 × 6 Gy/5d (IMRT 76%/3D 20%/Elec-tron 4%)	-	82%	32%	2-6 wk	94% @ 2 y (2.4 y)
	5	Parsai et al[10] (2020)	Retrosp cohort	2016-2019	16	5 × 6 Gy/5 d (IMRT/VMAT)	6%	63%	31%	0-7 d	100% @ 1 y (0.9 y)
	6	Koseła-Paterczyk et al[6] (2020) NCT03816475	Phase 2	2015-2019	27	5 × 5 Gy/5 d (3D 62%/IMRT)	-	93%	28%	5-10 wk	100% @ 3 y (2.3 y)
	7	Gobo Silva et al[12] (2021) NCT02812654	Phase 2	2015-2018	18	5 × 5 Gy/5 d (3D or IMRT)	Yes	83%	33%	4-8 wk	94% @ 3 y (2.4 y)
	8	Koseła-Paterczyk et al[7] (2016/Update 2021)	Phase 2	2010-2017	311	5 × 5 Gy/5 d (3D 96%/IMRT 4%)	30%	84%	31%	2-4 d	86% @ 5 y (4.8 y)
	9	Spalek et al[9] (2021) NCT03651375	Phase 2	2017-2019	46	5 × 5 Gy/5 d (IMRT 52%/VMAT 41%/3D 7%)	Yes	72%	34%	6-8 wk	93% @ 2 y (2 y)
	10	Potkrajcic et al[14] (2021)	Retrosp cohort	2018-2020	18	5 × 5 Gy/5 d (3D 83%/VMAT 7%)	-	78%	28%	4.1 wk (median)	92% @ 6 mo (5 mo)

(*continued on next page*)

Table 5 (*Continued*)

	Author (y), study name	Study	Interval	n	RT (technique)	Chemotherapy	R0	WC	Time RT to surgery	LC @ y (median FU)
11	Savjani et al[15] (2021) UCLA	Phase 2	2016-2018	52	5 × 6 Gy/5 d	-	80%	27%	N/A	93% @ 3 y (3 y)
12	Bedi et al[16] (2021) NCT02634710	Phase 2	2016-2020	32	5 × 7 Gy/10 d (1 × /48 h) (3D/ or MRT)	31%	91%	25%	4-6 wk	100% @ 3 y (3 y)
13	Leite et al[13] (2021)	Phase 2	2015-2019	25	5 × 8 Gy/10 d (1 × /48 h) (IMRT/VMAT)	20%	96%	28%	4-12 wk	100% @ 2 y (1.8 y)
14	Mayo[17] (2023)	Prosp cohort	2016-2020	22	5 × 6 Gy/5 d (IMRT 9%/VMAT 91%)	5%	82%	41%	0-5 d	100% @ 2 y (2 y)
15	Current Study (2023)	Prosp cohort	2020-2023	61	5 × 5 Gy/5 d (IMRT 11%/VMAT 89%)	3%	92%	12%	2.3 wk (median)	94% @ 1.5 y (1.6 y)

Abbreviations: FU = follow-up; IMRT = intensity modulated radiation therapy; LC = local control; VMAT = volumetric modulated arc radiation therapy; Prosp = prospective; Retrosp = retrospective; WC = wound complication rate.

Discussion

This analysis assessed WC rate and early/intermediate LC following preoperative uhRT in sarcoma patients. We found low WC rates and early LC, comparable with our data from a nRT cohort.[27] When focusing solely on current cases in the extremities and trunk to ensure comparability, the prevalence of WC was similar in both cohorts (10% vs 7%). When interpreting the reported WC and LC rates, it is important to consider that 15/60 (25%) patients had undergone either prior "*whoops*" surgery or initial surgery with or without radiation for a previously diagnosed STS.

Apart from its nonrandomized settings, this work has limitations in terms of sample size, number of events, and the short FU period for assessing LC.

The use of preoperative uhRT for STS has been increasing over the past years. Study protocols show some heterogeneity regarding fractionation, additional use of chemotherapy, and the time interval between RT and surgery. Authors reporting on uhRT before 2020 often opted for 5 × 5 Gy. Over the past few years, different groups published 5 × 6 to 8 Gy schemes, with smaller sample sizes and shorter FU (Table 5).

WC rates were reported to be 18% to 34% following uhRT using 5 × 5 Gy, 11% to 32% following moderate hypofractionated RT (mhRT),[36–38] and 30% to 36% following nRT. The latter was partly treated in the pre-IMRT era, whereas our own collective is based on VMAT (-equivalent) treatment plans and restrictive PTV definitions recommended by the RTOG-0630 trial.[28,33] The listed 6 analyses using higher doses (5 × 6-8 Gy) resulted in WC rates between 24% and 32% and LC rates of 93% to 100%. Following uhRT, our own WC rate falls within the lower range of the spectrum.

A substantial number of our operated patients had narrow surgical resection margins of 0 to 1 mm (28/60) and 0 to 2 mm (37/60). Although often associated with increased concerns regarding the possibility of residual cancer cells, these narrow resection margins appear to indicate the compensatory effect of uhRT.

Reported uhRT LC rates range between 80% and 100% at 3 to 5 years after primary treatment and compare with roughly 93% in the prospective randomized nRT trials at 3 to 5 years FU. Previously published uhRT LC rates match well with our own results of 94% after a still short mean FU of 1.5 years.[4] Trials using mhRT show slightly lower local control, although the variability is high. Using 8 × 3.5 Gy treatment scheme as Ryan[39] in 2008, MacDermed[40] in 2010, Pennington[41] in 2018, and Lu[37] in 2018, LC between 87% and 89% was achieved at 2 to 5 years. With a short FU time of 16 months (median), Guadagnolo[38] published in 2022 promising results using a dose of 42.75 Gy in 15 fractions on 119 patients, resulting in 93% LC at 2.5 years.

Roohani et al[4] stated in a recent systematic review (2022) that uhRT translates to reduced rates of acute toxicity compared with nRT. This is strongly supported by our own cohort with no G2 or higher acute actinic effects (in 2 cases with involved skin). Kao[42] published a recent meta-analysis on preoperative uhRT of prospective studies stating uhRT being feasible and well tolerated.

Using uhRT reduces the radiation treatment time by 4 weeks, increasing patients' comfort and economic efficiency.[31] Substantially less acute (skin) reaction allows for immediate surgery after uhRT and avoids the onset of fibrotic changes. This shortens the TTT to 2 to 3 weeks instead of 2 to 3 months. In addition, this approach makes preoperative radiologic restaging unnecessary. In 2014, Koseła-Paterczyk first described immediate surgery after uhRT for STS, which was also incorporated into the treatment scheme of Parsai in 2020 and Mayo in 2023.[5,10,17] Immediate surgery is reported as a safe option, considering the very high short-term treatment tolerance.[43] This is confirmed by our own cohort results.

Tumor necrosis has been reported as a predicting parameter for local and distant control, as well as overall survival.[40,44–47] We achieved a median necrosis rate of 15%, lower than that in comparable studies with conventional fractionation (25%/30%/35%/59%).[34,35,46,48] Following an interval of 41 days from RT (using 7 × 5 Gy with 31% received neoadjuvant chemotherapy) to surgery, Bedi et al[16] published similar results with 12.5% of cases achieving ≥90% necrosis compared with 9% in our cohort. We achieved complete pathologic necrosis at ≥95% in 5% of our patients compared with other publications using preoperative ifosfamide/doxorubicin chemotherapy, with 19%[41] and 24%.[9] We explain our low rate of substantial necrosis by the absence of chemotherapy and a shorter interval between RT completion and surgery (median 16 days). There are no data on the necrosis rate and its significance after neoadjuvant uhRT without chemotherapy and immediate surgery.

Conclusion

Our analysis shows low WC and high LC rates of preoperative uhRT and nRT in patients with STS. uhRT translates to a TTT of roughly 1 month compared with 3 to 4 months in nRT, reducing the treatment burden on patients and medical facilities, besides increased economic efficiency.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT (OpenAI) in order to draft and edit text. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ultrahypofractionated Versus Normofractionated Preoperative Radiotherapy for Soft Tissue Sarcoma: A Multicenter, Prospective Real-World-Time Phase 2 Clinical Trial

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Simple Summary: Soft tissue sarcomas are rare cancers that are often treated with a combination of surgery and preoperative radiotherapy to reduce the risk of cancer returning. Traditionally, this radiotherapy is delivered over five weeks, which can be challenging for patients due to the long treatment time and potential side effects. This study investigates a shorter, one-week radiotherapy option to determine if it provides similar results in terms of cancer control, survival and wound healing. By comparing these two treatment schedules, we aim to explore whether the shorter approach can offer a safe and effective alternative that might reduce the burden on patients and healthcare systems. If successful, this shorter treatment could improve patient convenience and resource efficiency, offering a new option in sarcoma care that aligns with modern goals for patient-centered, efficient cancer treatments.

Abstract: Background/Objectives: The historically most commonly used preoperative radiotherapy regimen for soft tissue sarcomas (STSs) consists of 50 Gray (Gy) delivered in 25 fractions over 5 weeks, achieving excellent local control, but with significant challenges due to prolonged treatment duration and early side effects. Reducing therapy duration while maintaining optimal local and distant control would be highly beneficial for patients. We aimed to investigate the outcome of an ultrahypofractionated radiotherapy (uhRT) regimen which may represent a shorter and more patient-friendly alternative. **Methods:** This multi-center, open-label, phase 2 clinical trial with a clustered cohort design was conducted within the Swiss Sarcoma Network (SSN). Adult patients (aged $\geq$ 18 years) with STS of the extremities or superficial trunk and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3 were included. Participants were assigned to either normofractionated radiotherapy (nRT) at 50 Gy in 25 fractions or uhRT at 25 Gy in 5 fractions. Data were collected prospectively in real-world-time clinical settings. The primary outcome was local recurrence-free survival (LRFS), with overall survival (OS) and wound complications as secondary outcomes. **Results:** Between March 2020 and October 2023, 138 patients were included in the study; 74 received nRT and 64 received uhRT. The median follow-up times were 2.2 years for uhRT and 3.6 years for nRT. The LRFS rates at 1 year were 97.0% for nRT and 94.8% for uhRT ($p = 0.57$). The two-year LRFS rates were 91.9% and 94.8%, respectively ($p = 0.57$). The one- and two-year OS rates were 97.1%/86.3% and 98.2%/88.8%, respectively ($p = 0.72$). The wound complication rate was comparable between the nRT (12.0%) and uhRT (12.5%) groups ($p = 0.99$). **Conclusions:** UhRT for STSs offers an effective and safe alternative to traditional nRT, with comparable early LRFS, OS and wound complication rates. Given the two-year median follow-up, which is critical for evaluating

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local recurrence, uhRT shows promise as a shorter and more convenient treatment regimen. UhRT may be a safe and effective alternative treatment option to traditional nRT.

Keywords: soft tissue sarcoma; ultrahypofractionated radiotherapy (uhRT); normofractionated radiotherapy (nRT); preoperative radiation therapy; clinical trial; wound complications; local control rate

1. Introduction

Soft tissue sarcomas (STSs) are a rare, heterogeneous group of malignant tumors originating in the connective tissues, including muscles, fat and nerves, presenting diverse histological types and aggressiveness [1]. Standard therapy involves surgical resection supplemented by radiotherapy, which has been shown to significantly reduce the risk of local recurrence [2,3]. Radiotherapy should be administered preoperatively, aiming to sterilize adjacent tissues and thereby improve local control.

Advancements in radiotherapy technologies have substantially improved the precision and efficacy of treatments for STSs. Techniques such as IMRT (Intensity-Modulated Radiotherapy) and VMAT (Volumetric Modulated Arc Therapy) have optimized the delivery of radiation by enabling highly conformal dose distributions that closely match the planning target volume (PTV)'s three-dimensional shape [4]. This allows for maximized radiation delivery to the PTV while better sparing surrounding healthy tissues, which is crucial in reducing the incidence of side effects such as would complications.

Radiation dose fractionation has evolved alongside these technological advancements. The currently most used normofractionated radiotherapy (nRT) administers approximately 2 Gy per fraction over several weeks [5,6]. Recently, hypofractionated (hRT) and ultrahypofractionated (uhRT) regimens have emerged as promising alternatives [7–11]. UhRT delivers higher doses per fraction in fewer sessions over one to two weeks. This approach is based on radiobiological evidence suggesting that STSs have a low α/β ratio, resulting in higher sensitivity to larger radiation doses per fraction. Hypofractionated radiotherapy has been shown to effectively induce immunogenic tumor cell death, releasing tumor-associated antigens and damage-associated molecular patterns. Furthermore, due to an increased expression of Major Histocompatibility Complex I, antigen recognition is promoted. Another potential mechanism of action of hypofractionation is the induction of bystander cells [12,13]. Due to the reduced treatment duration, uhRT represents a more efficient and potentially less burdensome alternative therapeutic regimen for the treatment of STSs. Additionally, uhRT could enhance resource utilization and decrease healthcare costs.

Several studies have shown that uhRT can achieve comparable outcomes to nRT [8,10,11,14–24]. Research at MD Anderson Cancer Center demonstrated the safety and convenience of a three-week mild hypofractionated preoperative regimen without increasing major wound complications [25].

However, comprehensive real-world-time (RWT) data comparing uhRT and nRT in STSs are lacking, potentially hindering the broader adoption of uhRT in clinical practice. This study aimed to compare the efficacy of uhRT versus nRT in treating STSs.

2. Materials and Methods

2.1. The Study Design and Participants

This study was a multi-center, prospective real-world-time, open-label, phase II clinical trial with a clustered cohort design (cluster randomization). Treatment decisions were based on institutional preference and influenced by external factors such as the COVID-19 pandemic. One center exclusively administered uhRT since March 2020 [26,27]. The inclusion criteria were as follows: adults (aged $\geq$ 18 years) with STS of the extremities or superficial trunk with an estimated life expectancy of at least six months who had received preoperative radiotherapy; an ECOG performance status of 0 to 3; a histological diagnosis of intermediate-to-high-grade STS or high-risk low-grade STS according to the

FNCLCC classification; and the technical possibility of gross-total macroscopic resection a determined by the interdisciplinary tumor board MDT/SB. Patients were excluded if they had received radiotherapy post-operatively or for palliative purposes.

An experienced specialized sarcoma surgeon (BF) performed all operations in both treatment groups. Indications of preoperative radiotherapy were made upon the recommendations of the same interdisciplinary tumor board. All uhRT treatment delineations of the cases were performed/supervised by the same radiation oncologists (GS, CG). This study complies with the principles of the Declaration of Helsinki and was approved by the Kantonale Ethikkomission Zurich, Switzerland (BASEC-Nr. 2019-01107 on 24 August 2021; registered on clinicaltrials.gov under NCT04300257). All participants provided written informed consent.

2.2. Treatment

Patients were treated with either nRT (50 Gy in 25 fractions in 5 weeks) or uhRT (25 Gy in 5 fractions in 1 week). The gross tumor volume was initially defined based on preoperative co-registered MRI and adjusted for peritumoral edema. The PTV (planning target volume) incorporated an omnidirectional margin of 1.5 cm and a longitudinal margin of 3–4 cm. Individual manual editing of the PTV was routinely performed to spare non-affected tissue, particularly bone and non-involved skin. If tumors were adjacent to the skin or if a biopsy was performed prior to radiotherapy, bolus material of 1 cm thickness was applied to ensure adequate dose delivery. Radiotherapy was administered using Volumetric Modulated Arc Therapy or Intensity-Modulated Radiation Therapy, complemented by Image-Guided Radiotherapy.

2.3. Data Collection

Data were prospectively collected using Sarconnector®/SHAPEHUB® (v1.1), a real-world-time digital interoperable platform shared across all participating institutions of the Swiss Sarcoma Network [26,27]. This platform collects demographic details, clinical characteristics, treatment specifics and outcomes in a structured and harmonized manner.

2.4. Outcome Measures

The primary outcome of this study was local recurrence-free survival (LRFS). The secondary outcomes were overall survival (OS) and wound complications within 120 days after surgery. Wound complications included revision surgery, vacuum-assisted closure and major infections as per the Canadian NCIC SR2 trial standards [5,25]. Early/intermediate disease control (Table 1) was also assessed according to clinical and imaging follow-ups.

Table 1. Definitions of major and minor wound complications.

Category	Definition/Examples
Major Wound Complications	Secondary operations required under general or regional anesthesia for wound treatment.
	Readmission to the hospital for wound care.
	Invasive procedures for wound management.
	Deep wound packing to an area of a wound measuring at least 2 cm in length.
	Prolonged dressing changes or repeat surgery for revision of a split-thickness skin graft.
	Wet dressings for longer than 4 weeks
Minor Wound Complications	Wound-edge necrosis requiring topical treatment such as silver sulfadiazine cream.
	Minor infections treated with oral antibiotics
	Prolonged dry dressing not reaching the extent or duration of “prolonged dressing changes” defined under major complications.

Regular follow-up assessments were scheduled every 3 months during the first 2–3 years, and subsequently every 6 months. These evaluations involved MRI scans of the primary tumor site and CT scans of the thorax to detect local recurrence and metastasis. For patients with metastatic disease, imaging and follow-up assessments were scheduled according to the recommendations of the interdisciplinary tumor boards.

2.5. Statistical Analysis

Continuous variables are presented as the median and interquartile range (IQR), and categorical variables as the frequency and percentage. Comparisons between nRT and uhRT were conducted using Pearson's Chi-squared test for categorical data and the Wilcoxon rank-sum test for continuous data. The predicted overall survival was estimated using the Sarculator [28]. Variables that were needed to calculate the predicted survival using the Sarculator were not available for all patients. In these cases (n = 35), the predicted survival was calculated using Persarc [29]. Survival outcomes were analyzed using the Kaplan–Meier method. Differences in survival times over the whole study period were assessed using the log-rank test, while differences in survival probabilities at certain time points were tested using a Z-test. The hazard ratios (HRs) and 95% Confidence Intervals (CIs) for OS and LRFS were estimated using Cox proportional hazards regression, adjusted for the predicted overall survival as estimated by the Sarculator or Persarc [28,29]. The odds ratios (ORs) and 95% CIs for wound revision rates were calculated using logistic regression, adjusted for the predicted overall survival. All *p*-values were two-tailed, with an alpha value of 0.05.

2.6. Quality Control

Quality control measures to ensure the accuracy and reliability of data were implemented within the Sarconnector®/SHAPEHUB® [26,27]. Validation checks for completeness and correctness were systematically performed. Outliers and anomalies were reviewed by clinical experts to ensure data validity.

3. Results

3.1. Patients Characteristics

Of 138 patients undergoing preoperative radiation therapy for STSs, 74 (53.6%) received nRT, while 64 (46.4%) were treated with uhRT. The patient characteristics are presented in Table 2. A higher proportion of patients with FNCLCC high-grade (G3) tumors were treated under the uhRT protocol compared to the nRT protocol (70% vs. 48%, $p = 0.007$). The predicted 5-year overall survival rates as determined by the Sarculator and Persarc prognostic tools did not differ significantly between the groups ($p = 0.10$) [29–32]. Supplementary Table S1 presents the diagnoses of the included patients stratified by therapy group.

Table 2. Patient characteristics.

Characteristic	Overall, N = 138 [1]	Normofractionation, N = 74 [1]	Ultrahypofractionation, N = 64 [1]	*p*-Value [2]
Gender				0.83
Female	63 (46%)	33 (45%)	30 (47%)	
Male	75 (54%)	41 (55%)	34 (53%)	
Age	59 (49, 73)	59 (50, 74)	61 (49, 72)	0.90
Depth				0.31
Epifascial	22 (16%)	9 (12%)	13 (20%)	
Retroperitoneal	4 (2.9%)	3 (4.1%)	1 (1.6%)	
Subfascial	112 (81%)	62 (84%)	50 (78%)	
Size	83 (59, 120)	87 (65, 121)	74 (52, 110)	0.14

Table 2. *Cont.*

Characteristic	Overall, N = 138 [1]	Normofractionation, N = 74 [1]	Ultrahypofractionation, N = 64 [1]	*p*-Value [2]
Grading				0.007
G1	13 (9.4%)	6 (8.1%)	7 (11%)	
G2	37 (27%)	27 (36%)	10 (16%)	
G3	72 (52%)	30 (41%)	42 (66%)	
(Unknown)	16 (12%)	11 (15%)	5 (7.8%)	
Necrosis	40 (10, 90)	60 (10, 90)	20 (5, 69)	0.002
Indication				0.11
First presentation	119 (86%)	67 (91%)	52 (81%)	
Recurrence	19 (14%)	7 (9.5%)	12 (19%)	
Hyperthermia	1 (1.0%)	1 (2.8%)	0 (0%)	0.4
Boost	2 (2.0%)	2 (5.6%)	0 (0%)	0.13
Predicted 5y OS using Sarculator or Persarc	0.78 (0.66, 0.88)	0.77 (0.63, 0.85)	0.82 (0.68, 0.90)	0.10
Status				0.40
AWD	32 (23%)	16 (22%)	16 (25%)	
DOD	31 (23%)	20 (27%)	11 (17%)	
NED	75 (54%)	38 (51%)	37 (58%)	
Wound revision	17 (12%)	9 (12%)	8 (13%)	0.93

[1] n (%); Median (IQR). [2] Pearson's Chi-squared test; Wilcoxon rank-sum test; Fisher's exact test. Legend: AWD—alive with disease; DOD—dead of disease; NED—no evidence of disease.

3.2. Local Recurrence-Free Survival

The median follow-up time for LRFS was 2.2 years (95% CI 2.0–2.5) in the uhRT group and 3.6 years (95% CI 2.8–4.3) in the nRT group. Local recurrence occurred in 8 (10.8%) of 74 patients in the nRT group, and in 4 (6.3%) of 64 patients in the uhRT group. The LRFS estimates at one and two years are shown in Figure 1. The one-year LRFS rates were 97.0% (95% CI 92.9–100.0) in the nRT group and 94.8% (95% CI 89.2–100.0) in the uhRT group ($p = 0.57$). The two-year LRFS rates were 91.9% (95% CI 85.4–99.0) for nRT and 94.8% (95% CI 89.2–100.0) for uhRT ($p = 0.57$). The log-rank p-value was 0.93. The HR for LR following uhRT relative to nRT was 0.54 (95% CI 0.11–2.76, $p = 0.46$).

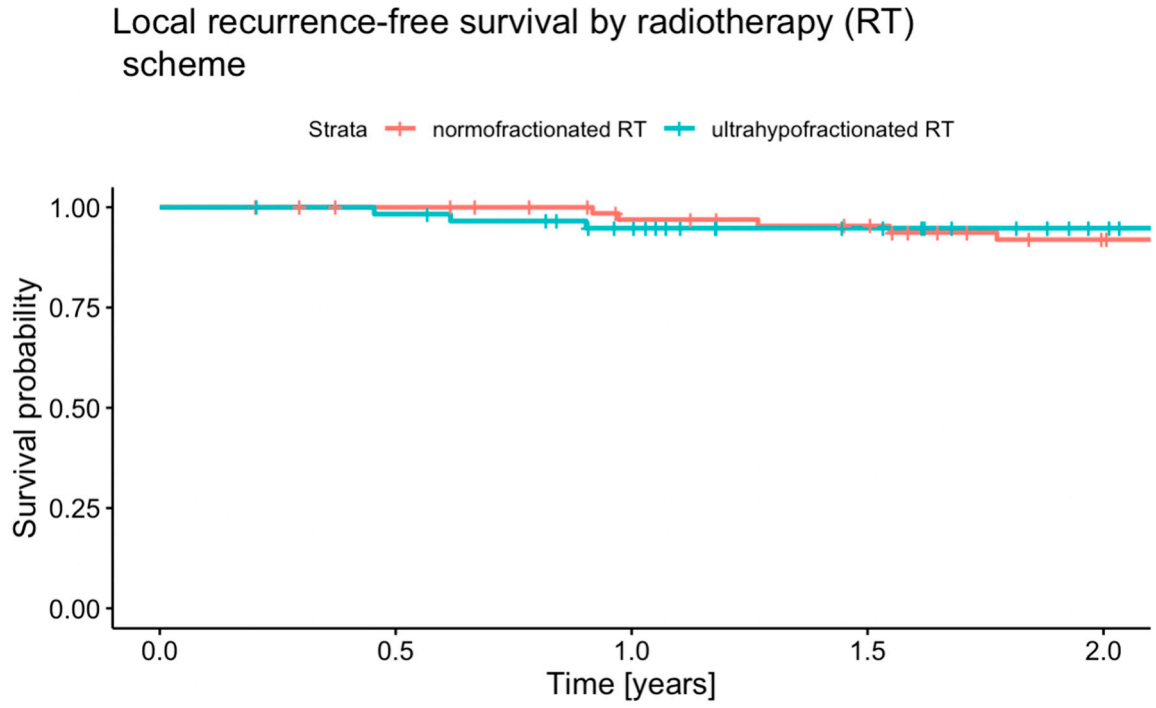


Figure 1. Kaplan–Meier plot of local recurrence-free survival stratified by therapy group.

3.3. Overall Survival

The median follow-up times for OS were 2.3 years (95% CI 2.1–2.8) in the uhRT group, and 4.2 years (95% CI 3.4–4.8) in the nRT group. Deaths from any cause occurred in 19 (25.7%) of 74 patients in the nRT group, and 11 (17.2%) of 64 patients in the uhRT group. The one-year OS rates were 97.1% (95% CI 93.2–100.0) in the nRT group and 98.2% (95% CI 94.8–100.0) in the uhRT group (Figure 2, $p = 0.69$). At two years, the OS rates were 86.3% (95% CI 78.3–95.0) for nRT and 88.8% (95% CI 80.7–97.7) for uhRT ($p = 0.72$; log-rank $p = 0.82$). The HR for death following uhRT relative to nRT was 1.62 (95% CI 0.62–4.24, $p = 0.33$).

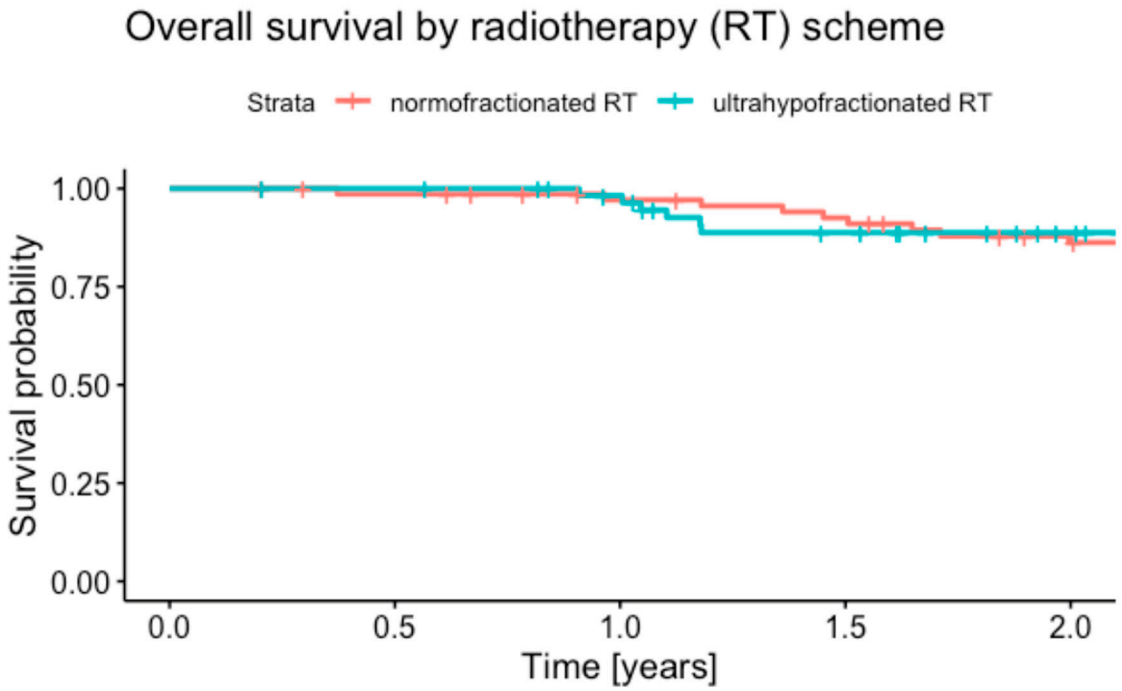


Figure 2. Kaplan–Meier plot of overall survival stratified by therapy group.

3.4. Wound Revision

A total of 9 (12.0%) of 74 patients in the nRT group and 8 (12.5%) of 64 patients treated with uhRT underwent wound revision ($p = 0.42$). The OR for uhRT compared to nRT was 0.80 (95% CI 0.24–2.59, $p = 0.71$).

4. Discussion

The present study is the first prospective observational study comparing uhRT and nRT for STS. Our results demonstrated no significant differences in LRFS, OS and wound complication rates between the uhRT group and the nRT group.

In this study, the two-year rates were 92% in the nRT group and 95% in the uhRT group, comparable with the rates reported in the current literature (Table 3) [7,10,25,33]. While nRT regimens, as reported in prospective studies by Canter et al. and Shah et al., achieved local control rates of approximately 100% at 3–5 years, they reported significant wound complication rates ranging from 23% to 35% [34,35]. Similarly, the phase III study of O'Sullivan et al. reported a 92% local control rate at 3.3 years with a 35% wound complication rate [5]. Two phase II studies of moderately and ultrahypofractionated schedules by Guadagnolo et al. and Bedi et al. also noted 31% and 25% wound complication rates, respectively [11,25]. The two existing phase II studies of ultrahypofractionated regimens demonstrated comparable results: Kosela et al. reported an 81% local control rate at 3 years with a 32% wound complication rate, while Kalbasi et al. achieved a 94% local control rate at 2 years with a 31% wound complication rate [14,15]. Our study validated the

uhRT results in comparable local control rates to the nRT and hRT regimens. Notably, our study noted a wound complication rate of 12.5% in the uhRT group and 12% in the nRT group, significantly lower than previously reported rates after nRT and hRT, but consistent with our own historical control of an nRT cohort [6].

Table 3. Characteristics of previous studies assessing different radiotherapy regimens.

Fractionation Type	Study	Design	Number of Patients	Total Dose	Dose/Fraction	Duration (Weeks)	Wound Complication Rate	Local Control
nRT	Canter et al. (2010) [36]	Prospective	25	50	2	5	28%	100% at 3-years
	Shah et al. (2012) [35]	Prospective	30	50	2	5	23%	100% at 5 years
	O'Sullivan et al. (2022) [5]	Phase III	94	50	2	5	35%	92% at 3.3 years
	Studer et al. (2018) [6]	Retrospective	67	50	2	5	7%	98% at 3 years
hRT	Guadagnolo et al. (2022) [25]	Phase II	120	42.75	2.85	3	31%	-
uhRT	Kosela-Paterczyk et al. (2016) [17]	Phase II	32	25	5	1	29%	90% at 5 years
	Kalbasi et al. (2020) [15]	Phase II	52	30	6	1	32%	94% at 2 years
	Bedi et al. (2022) [11]	Phase II	32	35	7	1	25%	100% at 3 years
	Present study (2024)	Comparative Phase II	64 (of 138)	25	5	1	12%	94.8% at 2.2 years

The evidence provided herein supports that uhRT may serve as a viable alternative treatment regimen for patients with STSs. A regimen with high therapeutic efficacy at a shorter treatment duration, such as uhRT, may reduce the treatment burden and encourage patient compliance. Additionally, the increased implementation of uhRT into clinical practice may lead to efficient resource allocation and reduced healthcare costs [15,25].

While prospective randomized trials are the gold standard, prospective real-world-time (RWT) data, collected during routine clinical practice, may mirror the treatment outcomes in diverse, real-world populations and provide more generalizable results. Furthermore, the prospective nature of RWT allows for the accurate and complete collection of follow-up data. A combination of machine learning and causal inference can help to infer individualized treatment effects [37,38].

Another interesting area of research involves nanoparticles which might be incorporated into a multimodal treatment regimen for sarcomas in the future [39,40].

This study has several limitations. The relatively small sample size and short follow-up period may limit the generalizability of the results. Although the cluster design and the lack of intersurgeon variability mitigate some biases, the non-randomized nature of treatment assignment remains a limitation. Future studies, including target trial emulations and randomized controlled trials, will be necessary to validate the long-term safety and efficacy of uhRT for the treatment of STSs. Furthermore, the follow-up time of the present study cohort was limited. Moreover, the quality of life of the included patients was not formally assessed. However, we plan to publish an extended follow-up and quality of life assessment in the future.

Our results indicate that uhRT, delivering 25 Gy in five fractions over one week, achieved similar local control, short-term overall survival rates and wound complication rates to nRT. The reduced treatment duration associated with uhRT offers substantial benefits in terms of patient convenience, compliance and healthcare costs. Therefore, uhRT

may serve as an alternative radiotherapy regimen for the treatment of STSs. While our study provided level 2b evidence which encourages the adoption of uhRT for the treatment of STSs, larger randomized controlled studies with longer follow-up periods will be necessary to validate our results.

5. Conclusions

Our study presents uhRT as a promising alternative to nRT in the preoperative treatment of soft tissue sarcoma, with comparable rates of local control, survival and wound complications over the short term. The shorter duration of uhRT offers meaningful advantages for the patient experience and may improve healthcare resource utilization. However, the study's non-randomized design and clustered approach warrant cautious interpretation.

These findings suggest that uhRT could be integrated as a patient-centered, efficient option in sarcoma care, aligning with the modern goals of value-based healthcare. Further randomized trials with extended follow-up are essential to confirm long-term outcomes and to refine the role of uhRT within sarcoma treatment protocols.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers16234063/s1, Table S1: Diagnoses of included patients according to therapy group.

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Article

Diagnosis-Related Outcome Following Palliative Spatially Fractionated Radiation Therapy (Lattice) of Large Tumors

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Simple Summary

Lattice Radiotherapy (LRT), a spatially fractionated stereotactic radiotherapy (SBRT) technique, has shown promising results in the palliative treatment of large tumors. The focus of our first analysis of 56 lesions >/=7cm was on the extent of shrinkage following palliative LRT. We herewith present an updated analysis of our single-center LRT cohort, with a focus on LRT outcome across histopathological diagnosis and applied LRT regimen. Based on the meanwhile 66 patients treated for 81 lesions, we found a failure rate to LRT in ~10% of cases, stable disease (+/−10% of pre-treatment volume) in ~10–20%, and shrinkage in ~75% of treated lesions, with a mean effect duration of > 7 months, i.e., mostly life-long in palliative patients with very large tumors with an overall survival rate of mean/median 7.7/4.6 months (0.4–40.2). In addition, the probability of shrinkage/partial remission across the most frequent histologies (carcinoma, sarcoma, and melanoma) and the extent of shrinkage in carcinomatous vs. sarcomatous lesions were similar, maybe with a lower extent of shrinkage in melanoma. The effectiveness of one fraction stereotactic LRT vs. five fraction simultaneous integrated boost-LRT was also found to be comparable.

Abstract

Background: Lattice Radiotherapy (LRT), a spatially fractionated stereotactic radiotherapy (SBRT) technique, has shown promising results in the palliative treatment of large tumors. The focus of our first analysis of 56 lesions >/=7cm was on the extent of shrinkage following palliative LRT (mean 50%) and assessment of its effect duration (: mean 6 months). Herewith we present an updated analysis of our single-center LRT cohort, with a focus on LRT outcome across diagnoses and applied LRT regimens. Methods: We assessed the clinical outcome following LRT in 66 patients treated for 81 lesions between 01.2022 and 05.2025. LRT protocols included simultaneous integrated boost (sib-) LRT in 49 lesions (5 × 4–5 Gy to the entire mass with sib of 9–13 Gy to lattice vertices). Alternatively mainly in pre-irradiated and/or very large lesions—a single-fraction stereotactic LRT (SBRT-LRT) of 1 × 20 Gy to vertices only was delivered to 26 lesions. In six cases with modest response to single fraction SBRT-LRT, the sib-LRT schedule was added 4–8 weeks later. Results: The median age was 68 years (18–93). Main tumor locations were abdomino-pelvic (n = 34) and thoracic (n = 17). Histopathological diagnoses included carcinoma (n = 34), sarcoma (n = 31), and melanoma (n = 16). 31% of all lesions have been previously irradiated. 73% of cases underwent concurrent or peri-LRT systemic therapy. The mean/median overall survival (OS) time of the cohort was 7.6/4.6 months (0.4–40.2), 11.9/5.8 months in 16/66 alive, and 6.4/4.3 months in deceased patients, respectively. 82% of symptomatic patients reported immediate subjective improvement (PROM), with a lifelong response duration in most cases. Progressive disease (PD: >10% increase in initial volume) was found in 9%,

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stable disease (SD +/−10% of initial volume) in 19% of scanned lesions, and shrinkage (>10% reduction in initial volume) in 75%, with a mean/median tumor volume reduction of 51/60%. The extent of shrinkage was found to be 11–30%/31–60%/61–100% in 38/24/38% of lesions. Response rates (PD, SD, shrinkage) following the two applied LRT regimens, as well as those related to sarcoma and carcinoma diagnoses, were found to be comparable. Treatment tolerance was excellent (G0-1). Conclusions: Palliative LRT provides rapid subjective relief in ~80% of symptomatic patients. Radiologic shrinkage was stated in 75% of FU-scanned lesions, with a lifelong effect duration in most patients. LRT was found effective across histologies, with a similar extent of shrinkage in carcinoma and sarcoma following 1F SBRT- and 5F sib-LRT regimens, respectively.

Keywords: LRT; lattice radiation therapy; SFRT in large tumors; clinical results following LRT

1. Introduction

The palliative treatment of very large tumors remains a major challenge in oncology. These lesions are often characterized by poor vascularization, hypoxic subregions, and numerous pre-treatments, including previous radiation, limiting normal tissue tolerance of re-radiation.

Lattice Radiotherapy (LRT), a form of spatially fractionated radiation therapy (SFRT), has emerged as a promising strategy to address these challenges. By integrating high-dose sub-volumes ("vertices") within the gross tumor volume (GTV), LRT aims to achieve enhanced tumoricidal effects while maintaining tolerable dose distributions across critical structures. The underlying rationale is supported by radiobiological insights into immunogenic modulation, bystander effects, and vascular disruption mechanisms triggered by steep intratumoral dose gradients [1–13].

Since first LRT reports ~15 years ago, there is increasing but still limited clinical knowledge reported in the literature. SFRT has over decades been used for many patients with favorable and encouraging outcomes; however, this modality remains insufficiently understood. Many questions on SFRT/LRT remain open, like ideal geometric arrangements, dosage, dose-volume arrangements, and time interval for decision to repeat LRT—beside the lack of knowledge regarding underlying immuno-biological mechanisms of action. A comprehensive critical review on the recent status of clinical and preclinical studies and knowledge gaps has been recently published by Prezado et al., addressing clinical physical as well as immunobiological aspects and open questions on SFRT [1].

Our formerly published clinical outcome data demonstrated the effectiveness and favorable safety of LRT in a heterogeneous cohort of 45 patients with 56 large (>/=7 cm) tumors treated in a palliative setting [2]. LRT yielded encouraging rates of symptom relief and radiologic response, persisting for a mean of 7.7 months. In the meantime, the clinical application of LRT at our center has continued to expand, supported by increasing familiarity with the LRT concept and clinical outcome and growing multidisciplinary interest. A summary of published clinical LRT results up to 2023 has been listed in Table 1 of our previous report [1]. Additional clinical reports on LRT published in the literature since then are listed in Table 1 of this work [3–13], mirroring an increasing interest in/spectrum of LRT indications, while orchestrated multi-center trial activities are still scant.

A recent publication informs about the formation of the Radiosurgery Society, GRID, LATTICE, Microbeam, and FLASH (GLMF) Working Groups as a framework for these efforts, focused on advancing the understanding of the biology, technical/physical parameters, trial design, and clinical practice of these new radiation therapy modalities [14].

Table 1. Summary of selected clinical outcome reports over the last two years.

Autor [Ref], Y	Interval	Type	N Pat	N lesions	Intention	Schedules	Diagnosis, Inclusion	FU	Result	>/=1FU Imaging (CT, MRI, PET-CT)
Kinj R et al. [3], 2023	-	**Case report**	1	1	curative boost	60 Gy, sequential 1 × 12 Gy SBRT-LRT	NSCLC	surgery	ypT0ypN0	-
Ferini G et al. [4], 2024	05.2021–11.2023	**Prosp. Cohort**	8	8	palliative	1F SBRT-LRT, sequential 5–15 F	large inoperable breast tumors	NA	4 CR, 3 PR; 100% ORR	Yes
Xu P et al. [5], 2024	06.2022–06.2023	**Retrosp. Cohort**	19	19	palliative	2–3 × 12 Gy SBRT-LRT	advanced HNC lesions >5 cm	median 10 mo.	16/19 regression, 3 progression	Yes (1 mo. post)
Parisi S et al. [6], 2024	-	**Case report**	1	1	curative	1 × 10 Gy SBRT-LRT to 1 sphere, sequential 60 Gy/30 f whole breast	Inflammatory breast cancer	6 mo.	CR (plus trastuzumab)	Yes (6 mo.)
Amendola B et al. [7], 2024	01.2013–12.2021	**Retrosp. Cohort**	20	20	curative	3 × 8 Gy SBRT-LRT, sequential 21–25 × 1.8 Gy +/− boost	advanced bulky cervical cancer	median 19 mo.	+ Boost: 70% CR − Boost: 44% CR	Yes (median 19 mo.)
Liu T-F et al. F et al. [8], abstract, 2024	-	**Case report**	1	1	palliative	1 × 20 Gy SBRT-LRT, sequential 45 Gy/25 F	Malignant thymoma	surgery	ypT1aN×, 5 mo. FU: LC	Yes (5 mo.)
Raiden B et al. [9], abstract, 2024	06.2020–01.2024	**Retrosp. Cohort**	63	63	palliative	1 × 12–18 Gy SBRT-LRT, sequential 20 to 72 Gy/5–30 F	bulky tumors	mean 6 mo. (1–28)	55% stable disease, 34% partial response, 8% complete response, 3% progression	Yes (mean 6 mo.)
Ahmed SK et al. K et al. [10], 2024	12.2019–06.2022	**Retrosp. Cohort**	53	61	palliative	1 × 16–20 Gy SBRT-LRT, sequential consolidative EBRT	Metastatic or unresectable sarcoma	median 7.4 mo.	60% symptom relief; 35% SD 55% PR 10% PD	Yes (median 6 mo.)
Amarell K et al. [11] abstract, 2024	2019–2023	**Retrosp. Cohort**	13	13	palliative	1 × 15–20 Gy SBRT-LRT	Large tumors	median 2.8 mo.	75% SD 25% PD	8/13 (median 6.9 mo.)
Majercakova K et al. [12], 2025	2020–2024	**Retrosp. Cohort**	15	15	palliative	EBRT 45–54 Gy or 20–25 Gy/4–5F or 30 Gy/10 F, sequential 1 × 20 Gy SBRT-LRT	bulky inoperable sarcoma, no-extremity	median 10 mo.	67% stable disease (RECIST)	Yes (1–2mo post)
Iori F et al. [13], 2025	11.2021–08.2023	**Retrosp. Cohort**	20	20	palliative	Sib-LRT with 20/>50 Gy in 5F	solid tumors >/=4.5 cm		79% response rate @ 3 mo., 54% shrinkage	Yes (3 mo.)
own cohort, 2025	01.2022–05.2025	**Prosp. Cohort**	66	81	palliative	Sib-LRT (20–25 Gy/9–13 Gy in 5 f (n = 49) SBRT-LRT 1 × 20 Gy to vertices only (n = 26), Combination (n = 6)	Carcinoma (34)/Sarcoma (31)/Melanoma (16), >/=7 cm	median 6 mo. (1–40)	19% SD 75% shrinkage >10% 9% PD 8% CR	Yes (in 63/81 lesions)

Li et al. analyzed the effectiveness and safety of LRT in large tumors >five cm in a systematic review and meta-analysis based on single-arm clinical studies [15]. Pooling 187 patients treated for 209 lesions out of seven eligible publications, the authors found the three-month complete response rate and partial response rate were 36.67% and 42.49%, respectively, while the three-month progressive disease rate was 7.10%. The tumor volume was reduced by 48.95%. The pooled 6-month overall survival rate was found to be 79.27%, with a median response time of 4.25 months. The pooled rates of mild and moderate-to-severe adverse events were 19.40% and 3.37%, respectively.

The following analysis represents an update of our single-center expanded patient cohort with extended FU. The focus was on consistency of LRT effectiveness across histologies and different LRT regimens applied in patients with limited or no alternative therapeutic options.

2. Materials and Methods

2.1. Patients (Table 2)

A total of 66 patients with 81 large lesions (≥7 cm diameter) were treated in palliative intent between January 2022 and May 2025. Histopathological diagnoses included carcinoma (n = 34), sarcoma (n = 31), and melanoma (n = 16). Median gross tumor volume (GTV) was 415 cc (range: 33–4027 cc). In 63/81 (78%) lesions, at least one follow-up (FU) imaging was available for volumetric analysis.

Prior radiation was documented in 31% of all lesions.

Systemic therapy was administered in 73% of cases; progress of lesions under systemic therapy led to referral for LRT in most cases.

Ethical approval has been applied by the Local Ethical Commission (No. AO _2023-00061, EKNZ).

Table 2. Characteristics of the cohort.

Parameter	N
N patients	66
N lesions treated with LRT	81
age, mean/median (range)	65/68 y (18–93)
Localization of lesions	• 34 abdomino-pelvic/retroperitoneal • 10 pleuro-pulmonal • 7 abdomino-thoracic wall • 7 sternal/pelvic bones • 6 axilla • 6 lower extremity • 5 cervical • 3 breast • 2 inguina • 1 upper extremity
Histopathol diagnosis of lesions	• 34 carcinoma • 31 sarcoma • 16 melanoma
Lesion size, mean/median (range)	
• diameter	• 14/12.5 cm (7–28)
• gross tumor volume (GTV)	• 814/415 cc (33–4027)
previous local Radiation Therapy	25/81 lesions (31%), mean/median 22/15 m (2–90) prior to LRT
Systemic Therapy	
• previous +/−post	• 59/81 lesions
• during LRT	• 3/81
• none	• 19/81
LRT schedules	
• (A): 1 × 20 Gy SBRT (vertices only)	• N = 26
• (B): 5 × 4–5 Gy/9–13 Gy SIB-LRT (to entire mass)	• N = 49
• (C): (A) supplemented by (B)	• N = 6
LRT characteristics, mean/median (range)	
• PTV2 to entire mass (0–5mm margin to GTV)	• 1072/689 cc (87–4460)
• PTV1 (vertices)	• 5.8/4.2 cc (0.35–36)

Table 2. *Cont.*

Parameter	N
• % PTV1 of PTV2	• 0.7/0.5 % (0.05–4)
• N vertices	• 10/7 (1–82)
FU mean/median (range), in months	
• All patients (n = 66)	• 7.7/4.6 (0.4–40.2)
• Alive (n = 16/66)	• 11.9/5.8 (1.3–40.2)
• Deceased (n = 50/66)	• 6.4/4.3 (0.4–36)

2.2. LRT

Our Lattice Radiation Treatment (LRT) protocol includes the following regimens (*):

(A) single-fraction stereotactic LRT (SBRT-LRT, n = 26) of 20 Gy to vertices only, as reported by Jiang et al. and Dincer et al. [16,17];

(B) simultaneous integrated boost LRT (sib-LRT, n = 49) applying 5 × 4–5 Gy to the entire mass with sib of 9–13 Gy to lattice vertices, as described by Duriseti et al. [18];

(C) combination: (A), followed by (B)—after typically 4–8 weeks: realized in only 6/81 lesions, aiming to improve treatment response to (A).

Detailed information regarding LRT contouring/planning has been reported in our former publication [2].

2.3. Indication for Palliative LRT/Inclusion Criteria

All patients treated with LRT were referred for palliative radiation therapy evaluation of large tumors >/= 7cm. In all cases surgical intervention was either not feasible or not indicated, and systemic therapy was not indicated/not possible/not effective anymore. For several of these patients with exceptionally large tumors, omission of any palliative radiotherapy has been considered upon the availability of LRT as an option at our site. Another criterion is given by the anatomical situation—i.e., the possibility to place vertices without increasing risk for normal tissue damage: flat long-axis tumors were considered not eligible and not included in the program. Also, tumors encasing neurovascular bundles or intestinal loops were strictly excluded.

(*): When we started our LRT program, regimen (A) was mainly used for very large and/or previously irradiated lesions. This single-fraction SBRT-LRT regimen was then found to be clinically similarly effective as regimen (B), while most convenient for palliative patients. This observation led us to the standard application of the single-fraction SBRT-LRT regimen (A) as the regimen of first choice—if anatomically feasible, followed by regimen (B) in cases of unsatisfactory response to regimen (A). The definition of 'unsatisfactory' included no or <10% of volumetric response and no subjective benefit. The condition for any further LRT (vs. best supportive care) was always the patients' wish/interest and general condition.

2.4. Definition of Volumetric Response

FU-imaging was available from 63/81 lesions (78%). The following definitions of response were used (decision was against the RECIST score, which is only based on diameter of lesions):

- progressive disease (PD): >10% increase in initial volume; please note: clinically obvious PD was also counted for lesions with no FU scans;
- stable disease (SD): +/−10% of initial volume—taking the uncertainty given by edema reactions following LRT into account;
- shrinkage (>10% reduction in initial tumor volume);
- complete remission (CR): no residual tumor in diagnostic scans.

2.5. Follow Up

Clinical and radiological FU was conducted on an individualized basis, tailored to the individual needs of these palliative patients, i.e., FU imaging was not performed solely for analytical purposes, resulting in incomplete radiographic FU (63/81 lesions were examined with at least 1 magnetic resonance imaging or computed tomography scan, accounting for 78% of cases). In consequence, time-related volumetric change analysis was not assessable in defined time intervals. Clinical FU was assessed at our department (physical or phone call visits) and based on chart notes from other involved disciplines.

2.6. PROMS (Patient Reported Outcome Measure)

PROMS were collected from all patients able to state their experienced symptom changes, using a Visual Analogue Scale (VAS, ranging from 0 = no symptoms, to 10 = unbearable symptoms), Table 3.

Table 3. PROM assessment.

PROM Assessment	N Patients (N Lesions)
Asymptomatic before LRT	5 (5)
PROM not assessable	6 (6)
No change post LRT	8 (8)
Progress/worse	2 (2)
Substantial subjective benefit	45 (60)
SUMMARY	45/55 (82%) symptomatic patients able to provide PROMs experienced fast substantial durable benefit

3. Results

The mean/median overall survival (OS) of the cohort was 7.7/4.6 months (0.4–40.2); the respective OS of 16 alive patients (07.2025) was 11.9/5.8 (1.3–40.2), and 6.4/4.3 months for 50 deceased patients. Table 4 shows detailed characteristics of treated lesions related to histology. Sarcomatous lesions were characterized by the largest mean/median volumes.

All included lesions measured >/=7cm in diameter.

Table 4. Characteristics of treated lesions.

Parameter	Carcinoma	Sarcoma	Melanoma	All
N lesions	**34**	**31**	**16**	**81**
• metastatic1	31	24	16	*n* = 71
• primary	3	7	0	*n* = 10
Initial volume (cc)				
• mean	702	922	763	780
• median	343	880	248	415
• range	33–3418	88–3704	66–4027	33–4027
Initial diameter (cm)				
• mean	13	17	12	14
• median	11	16	10	12.5
• range	7–28	7–28	7–22	7–28

3.1. Subjective Benefit/PROMS

Eighty-five percent of symptomatic patients (45/55) reported fast relief of symptoms, Table 3, with a life-long duration of this effect in most cases, which is supported by the objective duration of volumetric shrinkage as shown in Figure 1: 9/37 initially shrunk lesions with >1 FU scan showed re-growth; four of these nine lesions remained smaller than initially, i.e., in only 5/37 (14%) a 'clinically relevant' failure during the observed FU time or lifetime was found.

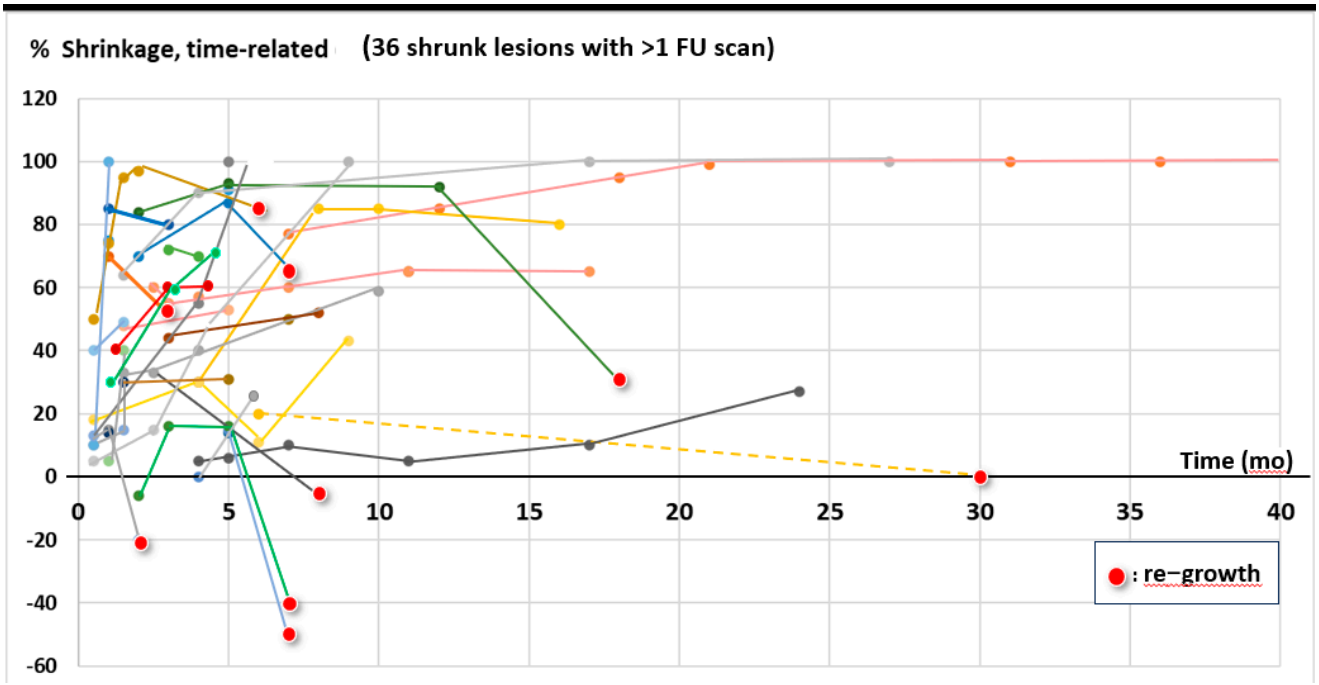


Figure 1. Time-related documentation of shrinkage among patients with shrunk lesions with available imaging: 9/37 initially shrunk lesions with >1 FU scan showed re-growth (red points); of importance: 4/9 lesions remained smaller than pre-LRT, i.e., only 5/37 (14%) developed 'clinically relevant' failure during the observed FU time or lifetime of patients.

The FU time, based on last available imaging of depicted 37 lesions with at least 2 FU scans was mean/median 9.2/5.0 months (1–40).

3.2. Radiologic/Volumetric Response, Table 5, and Figure 2

Nine percent of all 81 lesions and six percent of all FU-scanned lesions, respectively, failed to respond to LRT (progressive disease, PD: increase of >10% of pre-therapeutic volume). Nineteen percent of all lesions with at least one FU scan showed stable disease (SD, defined as +/−10% volume change compared to the pre-LRT volume); the remaining 75% of FU-scanned lesions showed ≥10% shrinkage as compared to the initial volume—mostly already in the first FU (i.e., mean 2.8 months post-LRT), with a mean/median maximum tumor volume reduction of 47%/63% after 5.5 months. Regarding the extent of shrinkage, about one-third of cases reached 11–33%, 34–66%, and 67–100% shrinkage (Figure 3). The duration of volumetric response was mean/median 9.2/5.0 months (1–40) at the time of this analysis. While the number of shrunk lesions/response rate was similar between all three assessed histologies (Figure 4), the EXTENT of shrinkage seemed lower in melanomatous compared to carcinomatous and sarcomatous lesions (Figure 5)—however, this observation is to be taken with caution considering the small and unbalanced sample sizes.

Table 5. Volumetric response, related to histopathologic diagnosis.

Parameter	Carcinoma	Sarcoma	Melanoma	All Analyzed Lesions
FU imaging available	**23/34 (68%)**	**28/31 (90%)**	**12/16 (75%)**	**63/81 (78%)**
Volumetric response to LRT				
• PD (>10% of initial cc)	3/34 (9%)	3/31 (10%)	1/16 (6%)	7/81 (9%)
• SD (+/−10% of inital cc)	5/23 (22%)	5/28 (18%)	2/12 (17%)	12/63 (19%)
• Shrinkage (<10% of initial cc)	17/23 (74%)	20/28 (71%)	10/12 (83%)	47/63 (75%)

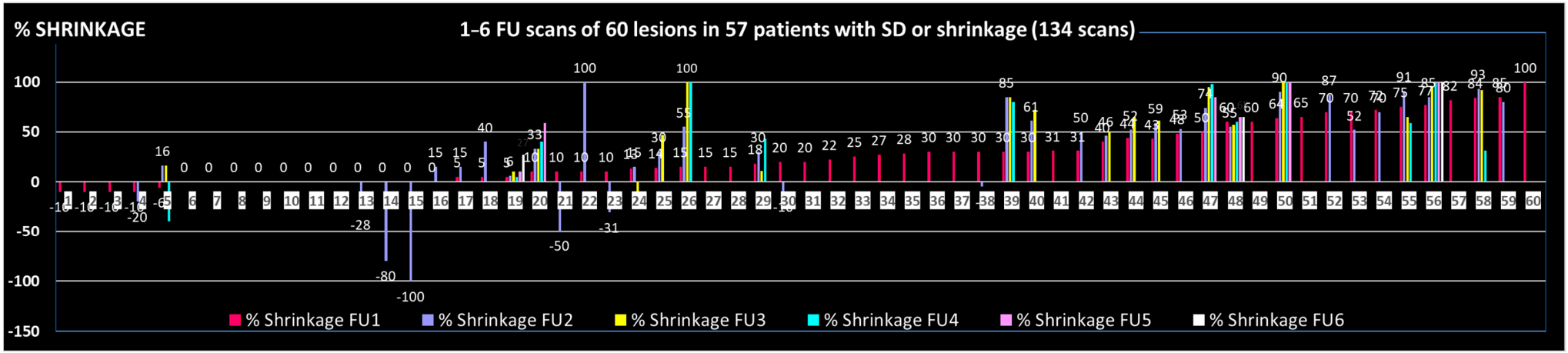


Figure 2. Development of the tumor volume in 60 lesions with stable disease (SD) or shrinkage, assessment based on one to six FU scans/lesion.

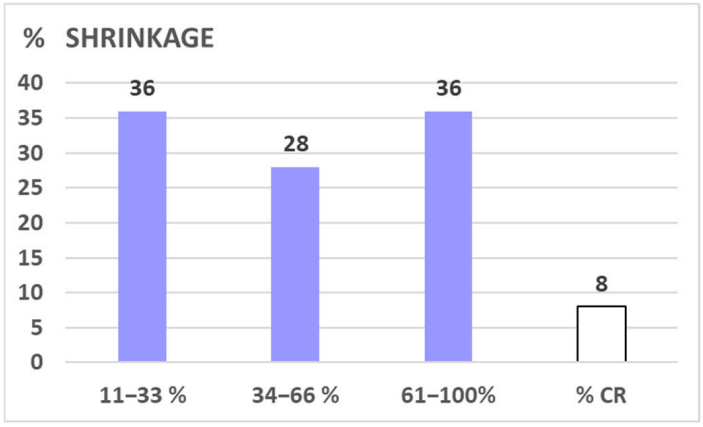


Figure 3. Shows the EXTENT of shrinkage in % in 47 shrunk lesions among patients with shrunk lesions and with available imaging: about one third of lesions each was found to shrink 1/3, 2/3, and ~3/3. In eight percent of our cohort, macroscopic radiologic complete remission was stated.

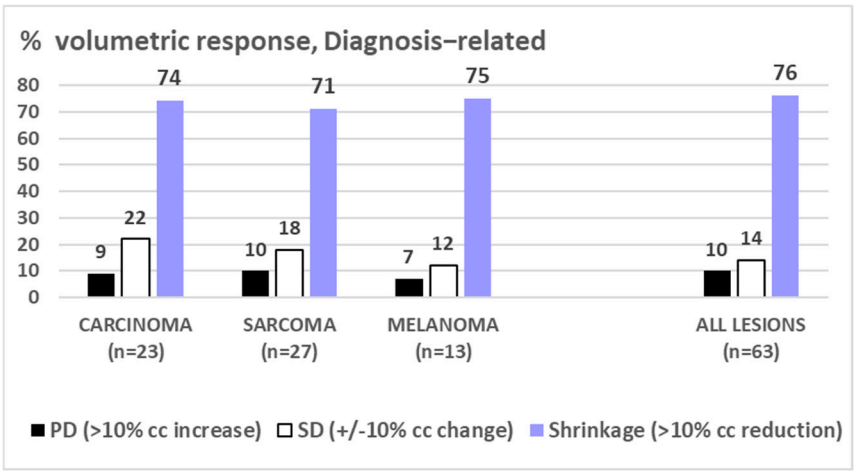


Figure 4. Shows very similar PERCENTAGE of response (PD/SD/Shrinkage) to LRT among the assessed histopathological diagnoses, assessment among patients with shrunk lesions or stable disease and with available imaging.

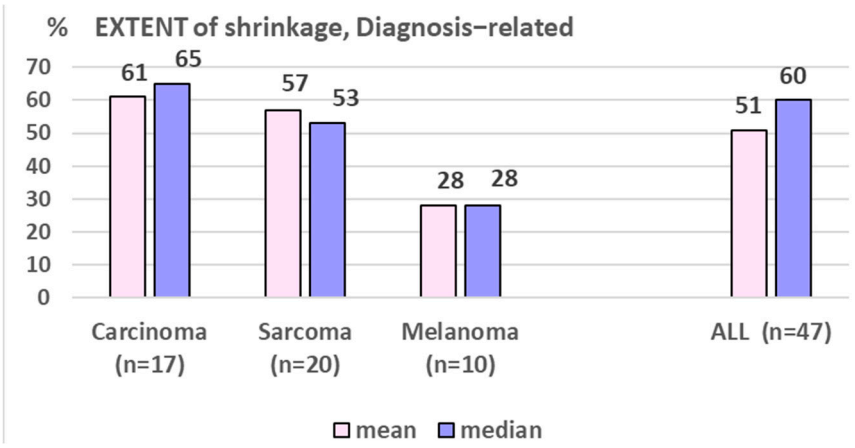


Figure 5. Shows the diagnosis-related EXTENT of shrinkage in %, which seems lower in melanomatous lesion. Assessment among patients with shrunk lesions and with available imaging.

The volumetric response as related to the two used LRT regimens is shown in Table 6: shrinkage and extent of shrinkage (Figure 6) was found very comparable, encouraging to

primarily go for the 1F SBRT-LRT regimen. Depicted in Figure 7A–D are four representative case illustrations before and after LRT using the one fraction SBRT-LRT regimen.

Table 6. Outcome, related to LRT Regimen.

Parameter (N Total)	SBRT-LRT (A) (1 F, to Vertices)	SIB-LRT (B) (4–5 F, to Entire Mass)	Combined (A) followed by (B)
N patients (66)	**24**	**36**	**6**
N lesions (81)	**26**	**49**	**6**
FU imaging available (64)	**21/26 (81%)**	**39/49 (76%)**	**4/6 (66%)**
initial volume, mean/median cc (range)	1118/543 (33–4027)	733/435 (54–3704)	403/489 (81–1289)
previous RT (25)	12/26 (46%)	9/49 (18%)	4/6 (66%)
Volumetric response to LRT			
• PD (: >10% increase in initial cc)	5/21 (24%)	1/39 (3%)	3/4 (75%)
• SD (: +/−10% of inital cc)	4/21 (19%)	8/39 (21%)	0/4
• Shrinkage (: >10% decrease)	12/21 (57%)	30/39 (77%)	1/4 (25%)
• **EXTENT** of shrinkage, % (mean/median (range)	53/50% (15–100)	55/39% (14–100)	-
DOD, *n* = 49/66 (74%)	15/24 (63%)	28/36 (78%)	6/6 (100%)
OS, mean/median (range), in mo.	4.7/3.2 (1–23)	8.5/5.8 (0.4–40.2)	7.4/7.5 (3.7–11.6)

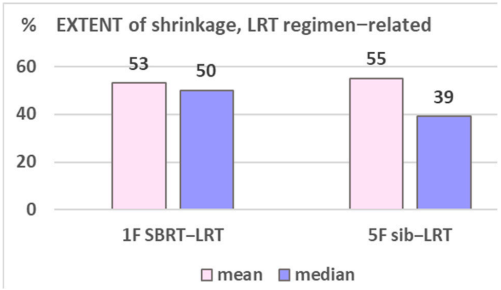


Figure 6. Shows the comparable LRT regimen-related EXTENT of shrinkage. Assessment among patients with shrunk lesions and with available imaging.

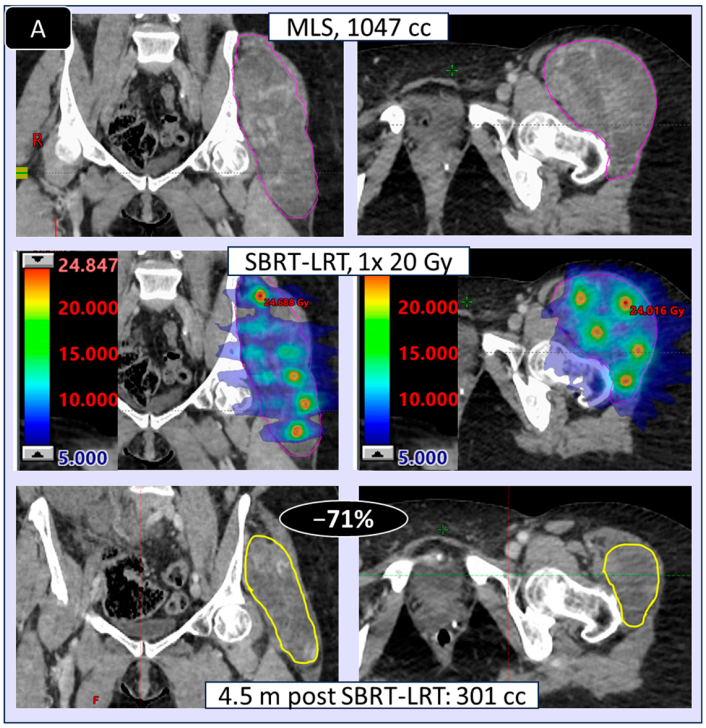


Figure 7. *Cont.*

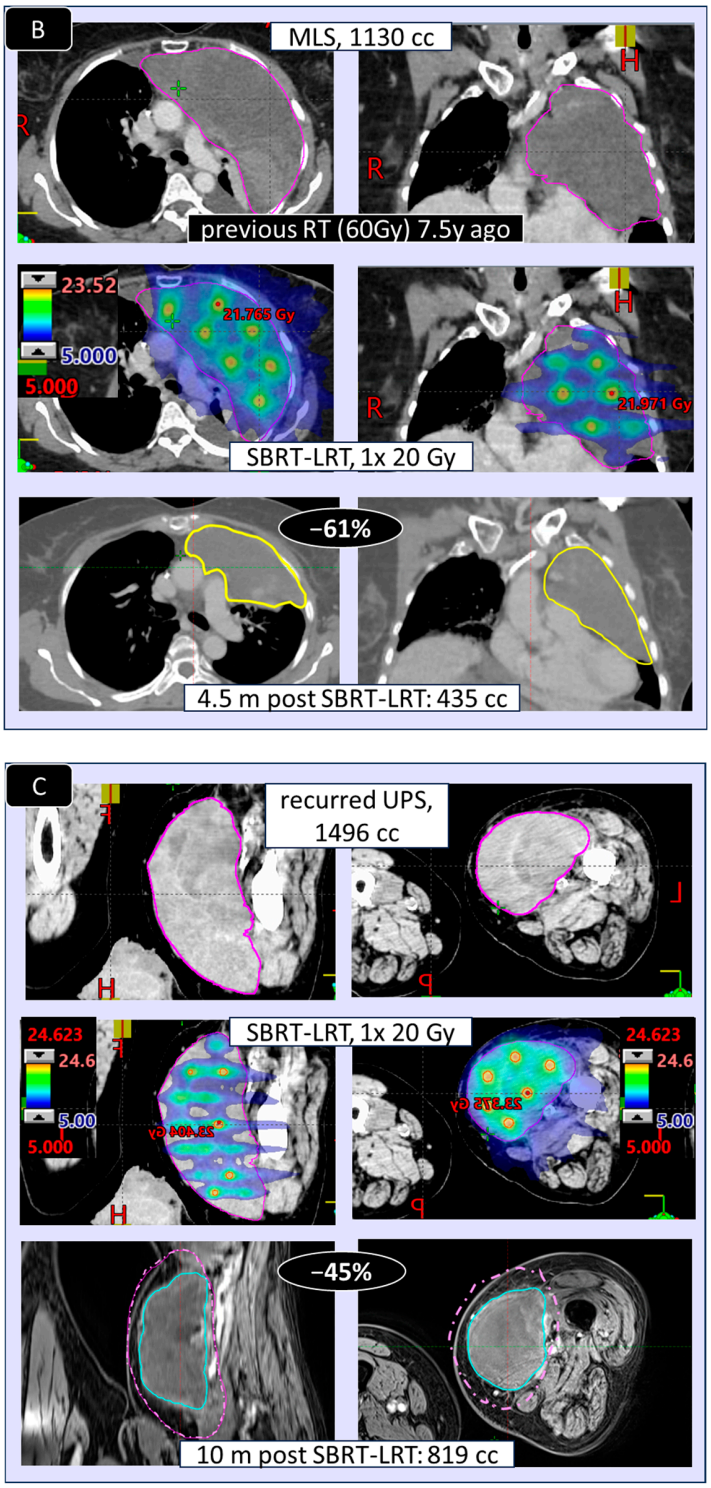


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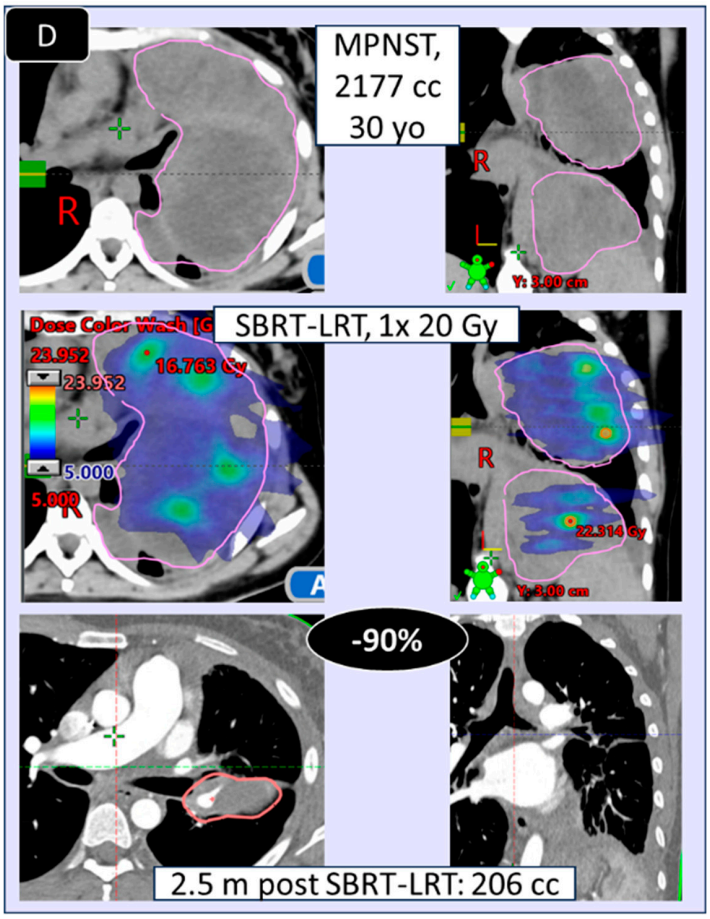


Figure 7. (**A**–**D**): Representative examples of large tumors treated with SBRT-LRT in one fraction (MLS: myxoid liposarcoma; UPS: undifferentiated pleomorphic sarcoma; MPNST: malignant peripheral nerve sheet tumor).

3.3. Toxicity

All patients completed the prescribed short-course LRT. Early tolerance was excellent (Grade 0–1), with only two cases of Grade 2–3 dermatitis due to tumors involving the skin; no late toxicity was assessed so far. Most patients felt some mild to moderate fatigue during a few days post LRT, several reported immediate better overall well-being.

4. Discussion

This update analysis of a single-center cohort treated with palliative LRT represents to our best knowledge the first report on outcome comparison of different LRT regimens and across histopathologic entities. We found similar response rates in carcinomatous, melanomatous, and sarcomatous lesions (~75% shrinkage), while the mean extent of shrinkage seemed higher in carcinoma and sarcoma (~50% of initial volume) as compared to melanoma (~28%), Figure 5; however, this is to be taken with caution considering the unbalanced and still small sample sizes. In addition, as 'sarcoma' is a collective term, sarcoma entity-related response to LRT is currently entirely unknown. LRT reports on melanomatous lesions are very scant and limited to case reports, not allowing any comparative analysis with their own small subgroup.

Regarding LRT in sarcoma, besides the cohort of 26 patients with 31 lesions presented here, we found two additional cohorts (53 and 15 cases) with bulky sarcomatous tumors treated with LRT [10,12]—taken together, 94 patients were treated for 110 lesions. After a median FU of 6–10 months, the rate of SD was >60% (difficult to compare, as different definitions of SD were used), with a high percentage of subjective benefit (PROM).

The previously reported duration of subjective and volumetric beneficial effects [1] has been confirmed (mean 7.7 months), i.e., a lifelong effect can be expected in most patients of such palliative cohorts.

In addition, we compared two different LRT regimens used. While the SBRT single fraction LRT (regimen A) represents the three-dimensional (3D) version of the original GRID therapy, as also reported by Jiang et al. and Dincer et al. [16,17], the sib-LRT (B) represents an innovative version of a historic classic and still widespread palliative regimen, using homogeneously calculated 5 × 4–5 Gy RT with a high-dose integrated boost (sib) as described by Duriseti et al. [18]. The sib-LRT regimen covers the entire tumor mass with an effective, broadly used palliative dose in five fractions, while -according to new immunological findings—small isolated hot spots (vertices) enforce protection of immunologically relevant cells in the microenvironment and increase building of neoantigens around the hot spots.

Comparing the two applied regimens (A) and B), different characteristics of the two sub-groups are to consider: the one fraction regimen (A) was initially mainly used for very large lesions (mean 1118 vs. 733 cc) and/or for previously irradiated tumors (46% vs. 18%), Table 6. The very comparable response, despite these unbalanced features, encouraged us to routinely start LRT treatment with regimen (A), which is most convenient for palliative patients. The SBRT-LRT single-fraction regimen may be supplemented by regimen (B) if needed, and vice versa, or by normo-fractionated external beam RT as used by several centers.

The presented update analysis may add two new findings in the field of knowledge: similar volumetric response in carcinoma and sarcoma and similar volumetric response following the two applied regimens.

Limitations of this analysis are the small unbalanced sample sizes, preventing from reliable statistical analyses. The so-named 'carcinoma' and 'sarcoma' subgroups are collective terms encompassing different disease entities—any related subgroup response specifications are missing. One of the key limitations is the erratic, unplanned imaging time intervals, as well as the sub-cohort with no FU-imaging due to situational disease-/end-of-life-related reasons. In addition, there is no complete long-term FU of the cohort available (i.e., 16/66 patients were still alive at the time of this analysis).

In summary, the following clinical outcome characteristics following LRT may so far hypothetically be drawn from literature and own analyses:

- ~80% of symptomatic patients experience fast subjective relief, in most cases life-long
- progressive disease/treatment failure in ~10%;
- stable disease in ~10–20% (defined as +/−10% volume change);
- shrinkage (>10% shrinkage, partial to rarely complete response) in ~>70% of cases, with the following:
    - mean ~50% volume reduction (extent of shrinkage);
    - shrinkage of 11–33%/34–66%/67–100% in ~1/3 of cases each;
    - complete response (CR) in ~5-<10%;
    - in ~15% regrowth of initially shrunk lesions to a larger than pre-treatment volume (Figures 1 and 2);
    - response to LRT independent of pre-therapeutic size of lesions [2];
    - response to LRT independent of previous RT vs. RT-naïve lesions [2];
    - mostly fast onset of shrinkage (days to weeks) following LRT;
    - mean expectable shrinkage duration of 9 months, i.e., statistically a ~life-long benefit in palliative patients with large tumors (based on the assessed cohort with a mean/median OS of 7.7./4.6 mo);
    - similar probability of shrinkage/PR across the most frequent histologies;
    - similar extent of shrinkage in carcinomatous vs. sarcomatous lesions, maybe lower extent of shrinkage in melanoma—further analyses on larger samples are required;

- likely similar effectiveness of 1F SBRT-LRT vs. 5F sib-LRT—further analyses on larger samples are required.

5. Conclusions

LRT offers a highly effective and well-tolerated palliative approach for patients with large, inoperable tumors. This extended analysis confirms prior findings of rapid symptom relief and robust tumor response in ~80% of cases with an effect duration of mean at least half a year.

In addition, LRT was found comparably effective in sarcomatous and carcinomatous lesions using a single fraction of SBRT-LRT or five fraction of sib-LRT. This is, to our best knowledge, the first clinical LRT report proving comparative response benefit across histologic subtypes and different LRT regimens.

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Informed Consent Statement: All patients completed and signed the official LUKS General Informed Consent (GIC).

Data Availability Statement: Data may be requested – please address the corresponding author (no publicly archived dataset available).

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

SFRT	Spatially Fractionated Radiation Therapy
LRT	Lattice Radiation Therapy
FU	Follow up
mo.	Month
SBRT-LRT	Stereotactic Body Radiation Therapy-LRT
SIB	Simultaneously Integrated Boost
SIB-LRT	Simultaneously Integrated Boost-LRT
F	Fraction (of radiation therapy)
PD	Progressive Disease
CR	Complete Response
SD	Stable Disease
OS	Overall survival
ORR	Overall response rate
DOD	Dead of Disease
MLS	Myxoid liposarcoma
UPS	Undifferentiated pleomorphic sarcoma
MPNST	Malignant peripheral nerve sheet tumor

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Article

Improving Sarcoma Outcomes: Target Trial Emulation to Compare the Impact of Unplanned and Planned Resections on the Outcome

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Simple Summary: In this study, we aimed to understand the association between two types of surgeries on sarcoma outcomes: surgeries that were planned with a clear understanding of the cancer (planned resections) and those that were performed unexpectedly, without prior knowledge that the tumor was cancerous (unplanned resections). Using the novel Target Trial Emulation framework, we assessed how these surgeries impact local recurrence-free survival, metastasis-free survival, cancer-specific survival, and overall survival. Our study found that patients who had unplanned surgeries were more likely to experience their cancer recur at the surgery site. However, there was not a substantial difference in how long patients survived after either type of surgery. Our findings highlight the importance of immediately referring patients to specialized sarcoma treatment centers where unplanned resections are less likely to occur to improve treatment outcomes and provide evidence to guide better management strategies for sarcoma.

Abstract: This study follows the Target Trial Emulation (TTE) framework to assess the impact of unplanned resections (UEs) and planned resections (PEs) of sarcomas on local recurrence-free survival (LRFS), metastasis-free survival (MFS), cancer-specific survival (CSS), and overall survival (OS). Sarcomas, malignant tumors with mesenchymal differentiation, present a significant clinical challenge due to their rarity, complexity, and the frequent occurrence of UEs, which complicates effective management. Our analysis utilized real-world-time data from the Swiss Sarcoma Network, encompassing 429 patients, to compare the impact of UEs and PEs, adjusting for known prognostic factors through a multivariable Cox regression model and propensity score weighting. Our findings reveal a significantly higher risk of local recurrence for UEs and a short-term follow-up period that showed no marked differences in MFS, CSS, and OS between the UE and PE groups, underlining the importance of optimal initial surgical management. Furthermore, tumor grade was validated as a critical prognostic factor, influencing outcomes irrespective of surgical strategy. This study illuminates the need for improved referral systems to specialized sarcoma networks to prevent UEs and advocates for the integration of TTE in sarcoma research to enhance clinical guidelines and decision-making in sarcoma care. Future research should focus on the prospective validations of these findings and the exploration of integrated care models to reduce the incidence of UEs and improve patient outcomes.

Keywords: sarcoma; unplanned "whoops" resection; planned resection; Target Trial Emulation (TTE); local recurrence; metastasis-free survival; overall survival; multidisciplinary teams (MDT); benchmarking in healthcare; digital twin in medical research

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1. Introduction

Sarcomas are malignant tumors distinguished by their mesenchymal differentiation [1] with an incidence of 5 cases per 100,000, classifying them as rare diseases [2]. The misdiagnosis and subsequent unplanned whoops resection (UE) of sarcomas, under the presumption of benignity, constitutes a significant clinical challenge, particularly in the case of smaller, superficial sarcomas in younger patients [3,4]. An average rate of 33% for UE among sarcoma patients, with observed rates ranging from 18% to 53%, was reported in a comprehensive review encompassing 33 studies and underscored the complexity and variability of sarcoma management practices [5]. However, an extensive study from Japan including a nationwide cancer registry with 8761 patients reported a rate of only 11% for UE [6]. The term UE itself encompasses a broad spectrum of scenarios in the literature, lacking a universally accepted (and standardized) definition. Studies have variously described UEs as the removal of a tumor without adequate preoperative diagnostics and consideration of surgical margins or any surgery conducted without specialized evaluation and planning based on the surgeon's initial diagnosis. This diversity reflects the multifaceted nature of sarcoma diagnosis and the critical need for precise planning to avoid adverse outcomes [5,7–9].

The reasons for UE of sarcomas are manifold, primarily based on four key aspects. The overall rarity of sarcomas and, additionally, their subdivision into approximately 70 subgroups, each with distinct clinical and therapeutic differences; the intrinsic complexity of sarcomas, due to which, conventional diagnostic criteria for malignant tumors are not always directly applicable; the complex diagnostic process involving conventional macroscopy, immunohistochemistry, and molecular genetics, the latter requiring high professional expertise; and the significant disparity in expertise observed in rare diseases like sarcomas [2]. Another contributing factor may arise from the often-prolonged diagnostic intervals between the first physician visit and the engagement of an expert [10].

The impact on the clinical outcome following UE has not been conclusively studied. It is assumed that UEs are linked to reduced local recurrence-free survival (LRFS) compared to planned oncologic resections (PEs), while no disparity is evidenced concerning metastasis-free survival (MFS) and cancer-specific survival (CSS) [4,11–13]. Furthermore, there is an established correlation between residual tumor presence in the re-resected specimen and reduced LRFS, as well as overall survival (OS) [13–17]. Given the significant prevalence of residual tumors observed in 31–74% of cases following UE [5], it is reasonable to anticipate a reduction in LRFS and OS post-UE.

There is no uniform agreement on how to best approach patients after UE [18–20]. The UK guidelines recommend considering re-resection for UE with positive resection margins (R1/R2), highlighting the procedure's potential to improve OS rates and extend MSFS [18,19,21]. Research, including a study by Nakamura et al., has shown similar survival and local recurrence rates between PE and UE, followed by subsequent re-resection [22]. Despite these benefits, corrective surgeries often require more complex reconstructive techniques, such as skin grafts, flaps, or even limb amputation [8], raising the critical question of whether re-resection should be universally applied to all UEs or only a select subset [20]. This unresolved dilemma highlights a significant gap in our current treatment paradigms, underscoring the pressing need for innovative research approaches that can elucidate and guide these crucial decisions in sarcoma care.

While retrospective studies certainly have provided valuable insights into the outcomes of surgical interventions for sarcomas, their inherent limitations, such as the inability to establish causality and control for confounding factors, have left critical questions unanswered. The gold standard of clinical studies, a randomized controlled trial (RCT), faces unsurmountable ethical hurdles when it comes to comparing UE versus PE, due to the direct impact on patient care and treatment decisions [23]. This critical juncture in sarcoma research underscores the urgent need for alternative methodologies that can offer the precision and reliability of RCTs without their ethical implications.

Target Trial Emulation (TTE) has emerged as a novel methodological framework that addresses these challenges [23–25]. By emulating the design principles of RCTs and utilizing real-world-time data, TTE allows for the ethical and rigorous exploration of treatment outcomes, effectively bypassing the ethical concerns tied to randomizing surgical treatment options [25]. Leveraging real-world-time data to approximate the causal inference of RCTs, TTE can also minimize potential selection biases typically associated with observational studies [25]. This innovative approach not only bridges the methodological divide but also opens up new avenues for exploring the nuanced impacts of surgical strategies on sarcoma patient outcomes. Adopting TTE, this represents a pivotal advancement in clinical research, enabling the investigation of UEs versus PEs with a level of scientific rigor previously deemed unattainable.

In brief, this study aims to assess the association between UE (compared to PE) and LRFS, MFS, CSS, and OS by emulating a target trial. By pioneering a methodological alternative to traditional RCT's, we aim to shed new light on the implications of surgical strategies for sarcoma, potentially guiding more effective treatment pathways. This exploration promises to not only advance our understanding but also stimulate further research into the nuanced impacts of surgical decisions on patient outcomes in sarcoma care.

2. Materials and Methods

To uphold the quality in sarcoma care and to foster interdisciplinary exchanges, the Swiss Sarcoma Network (SSN) (https://www.swiss-sarcoma.net/, accessed on 31 May 2024) collects patient data longitudinally across the therapeutic continuum of soft tissues and bone tumors, creating a multi-center, high-quality real-world-time (RWT) data warehouse [26,27]. The current data repository, Adjumed.ch (Adjumed Services AG, Zurich, Switzerland; www.adjumed.ch, accessed on 10 October 2023), hosts the dataset, which is anticipated to transition to a new management system, Sarconnector® (BF&PH, Zurich, Switzerland) to function as a dynamic real-world-time data (RWT) warehouse for automated analysis [28].

The SSN data warehouse encompasses the data from 2104 patients registered by SSN members from 2018 to 2023, as illustrated in Figure 1. All sarcoma patients who underwent either UE or PE and received treatment (whether initial or follow-up) at the University Hospital Lucerne (LUKS) or the Cantonal Hospital Winterthur (KSW) were consecutively included (n = 477). In 87 cases, the inclusion criteria were not met: no index surgery was planned (n = 85), death occurred before the index surgery (n = 1), and no data on the index surgery were available (n = 1). Exclusion criteria were a history of any malignant neoplasm within the past 5 years (n = 36), any history of leukemia (n = 2), and age below 16 years (n = 10). Furthermore, desmoid tumors were not included in this study. The final cohort for analyzing the outcome of UE versus PE included 429 patients.

The observation period began at the point of the initial surgical intervention, either UE or PE, referred to as time zero, and ended with the occurrence of the predefined outcomes (local recurrence, metastasis, or death) or date of last patient contact. Due to the real-world-time structure of our data, time zero—the point of initial surgical intervention—can occur before the official start of the study inclusion period. This situation arises when a patient with a recurrence is enrolled in the study, potentially leading to an overestimation of the incidence of local recurrence in the presented cohort. Tumor reappearance at the original site was captured as local recurrence, tumor spread to a different site as metastasis, and mortality was subdivided into all-cause and death due to sarcoma. All consecutive patients were presented to the SSN-MDTB (Multidisciplinary Tumor Board) to determine their recommended individualized treatment strategy.

Utilizing the methodology of TTE, this study incorporated the principles of RCT to real-world-time data [23,25]. This approach involved the prior development of a target trial protocol (Table 1), creating a multivariable Cox regression model and implementing propensity score weighting to approximate the randomization process of a RCT. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented. The proportional hazards

assumption in the Cox proportional hazards regression was verified using Schoenfeld residuals. The linearity assumption for the included covariates was checked using Martingale residuals. Regarding the heterogeneity of the study population, adjustments were made for known prognostic factors in a multivariable Cox regression model, including the tumor biological behavior, grade, size, and sarcoma classification, as well as the anatomical region of the tumor. Sarcoma classification is divided into axial (including head, neck, trunk, visceral, intraperitoneal, and retroperitoneal) and appendicular (encompassing upper and lower extremity). Biological behavior serves as an index for the inherent biological characteristics and clinical behavior, encompassing their growth pattern, invasiveness, metastatic potential, and potential response to treatment. These include three stages: benign, intermediate, and malignant, with benign soft tissue tumors not represented in this study. The propensity score was designed to equalize the distribution of baseline variables across the treatment arms—UE and PE—by being assigned in weights of the inverse probability of treatment assignment based on the aforementioned covariates.

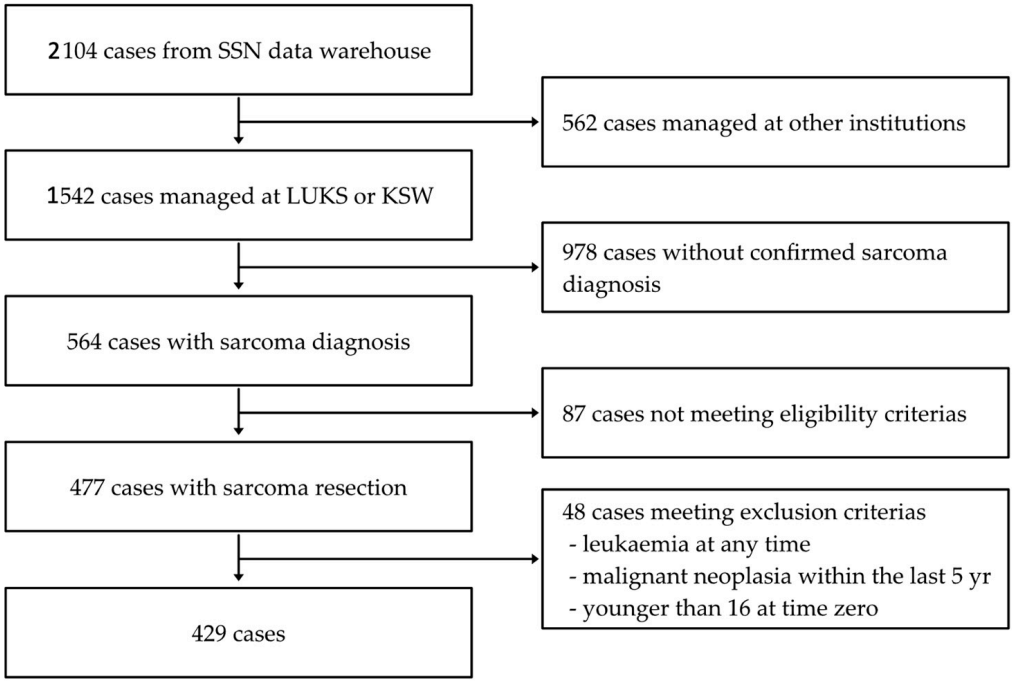


Figure 1. Flowchart.

To ensure the statistical analysis's reliability, sensitivity analyses were performed, adjusting for additional variables such as age, sex, tumor volume (cm^3), and resection status. The influence of chemotherapy and radiotherapy with curative intent on the outcome was also examined. Additionally, the subsets of patients without atypical lipomatous tumor (ALT) and dermatofibrosarcoma protuberans (DFSP) were analyzed. Because 76 cases had time zero prior to 2018 and were partly subsequently captured, an additional sensitivity analysis was designed to include only cases with time zero from 2018 onwards (See Appendix A Tables A1–A4).

Kaplan–Meier curves were employed to visually compare the time-to-event data between the UE and PE groups.

Statistical analysis was done using R statistical software (Posit, PBC, Boston, MA, USA, Version 4.3.2) [29]. A p-value < 0.05 was considered statistically significant.

Table 1. Target trial protocol—based on Edouard L. Fu 2023 [25].

Protocol Element	Target Trial	Emulation with Observational Data from the LUKS/KSW
Eligibility criteria	Patients which had a surgery with curative intent due to any kind of sarcoma. Sarcoma could be diagnosed before or due to this resection.	Same as target trial
Exclusion criteria	All Patients who met the following exclusion criteria: • malignant neoplasia within the last 5 years • any leukemia at any time in patient's medical history • younger than 16 at time zero	Same as target trial
Treatment strategies	1. Planned sarcoma resection 2. Unplanned Whoops resection	Same as target trial
Treatment assignment	Randomization, double-blinded	Eligible individuals are assigned at baseline to treatment strategy that their data are consistent with. To emulate randomization, we evaluated the probability of each patient being assigned to their group and adjusted for the following baseline variables: Biological behavior, sarcoma classification (SST, DST, bone *), anatomic region, tumor size, and grade.
Outcomes	Primary outcome: LRFS Secondary outcomes: MFS, CSS, and OS	Same as target trial
Causal estimation	The effect of UE on MFS, LRFS, CSS, and OS.	Same as target trial
Start and end of follow-up	Starts at the first surgical intervention after the randomization. Ends at occurrence of end point, administrative censoring, or 5 years of follow-up.	Starts at time zero (first surgery due to sarcoma regardless of whether the first surgery was a UE or a PE). Ends at occurrence of end point or administrative censoring.
Statistical analysis	Intention-to-treat analysis, non-naïve per protocol analysis	TTE with multivariable Cox regression and propensity scores

* Including osteosarcomas and Ewing sarcomas.

3. Results

This study included 429 patients: 106 (24.7%) underwent UE and 323 (75.3%) underwent PE. The patient characteristics are presented in Tables 2 and 3. The median follow-up time was 1.9 years (1st quartile (Q1), 3rd quartile (Q3); 0.8 years, 3.7 years). In the UE group, 58.4% had a reoperation, with a residual tumor present in resectate in 75.8% after reoperation. In nine cases, achieving R0 status during reoperation was not feasible due to local circumstances, and among these cases, six subsequently developed a local recurrence. Of the patients who underwent UE, 25.5% had reoperation alone, 33.0% received reoperation along with radiotherapy within 6 months, and 6.6% were treated with radiotherapy alone within 6 months. UE sarcomas were generally smaller (median 46.5 mm versus 94 mm), more frequently located superficially (35.8% versus 9.6%), and were often of lower grade (47.5% versus 30.2%). Notably, patients with dedifferentiated liposarcoma more commonly underwent PE (3.8% versus 11.1%).

Table 2. Characteristics of the study cohort stratified by treatment group.

	All	PE	UE	*p*-Value
n	429	323	106	-
Gender				
Male, *n* (%)	229 (53.4)	167 (51.7)	62 (58,5)	0.26
Female, *n* (%)	200 (46.6)	156 (48.3)	44 (41.5)	0.26
Age in years, median (Q1, Q3)	63 (51, 74)	63 (53, 74)	63.5 (47, 75)	0.45
Sarcoma classification				
SST, *n* (%)	69 (16.1)	31 (9.6)	38 (35.8)	<0.001
DST, *n* (%)	317 (73.9)	256 (79.3)	61 (57.5)	<0.001
Bone, *n* (%)	43 (10.0)	36 (11.1)	7 (6.6)	0.20
Diagnosis *				
Myxoid liposarcoma, *n* (%)	28 (6.5)	24 (7.4)	4 (3.8)	0.26
Dedifferentiated liposarcoma, *n* (%)	40 (9.3)	36 (11.1)	4 (3.8)	0.02
Leiomyosarcoma, *n* (%)	47 (11.0)	31 (9.6)	16 (15.1)	0.15
Atypical lipomatous tumor	63 (14.7)	51 (15.8)	12 (11.3)	0.34
Undifferentiated/unclassified sarcoma	64 (14.9)	52 (15.8)	12 (11.3)	0.27
Tumor size (largest diameter) in mm, median (Q1, Q3)	80 (50, 129)	94 (60, 143)	46.5 (27, 79)	<0.001
Anatomic region				
Axial, *n* (%)	201 (46.9)	152 (47.1)	49 (46.2)	0.91
Appendicular, *n* (%)	228 (53.1)	171 (52.9)	57 (53.8)	0.91
Biological behaviour				
Intermediate, *n* (%)	112 (26.1)	78 (24.2)	34 (32.1)	0.13
Malignant, *n* (%)	317 (73.9)	245 (75.9)	72 (67.9)	0.13
Grade [§] (time zero)				
1, *n* (%)	138 (34.5)	91 (30.2)	47 (47.5)	0.004
2, *n* (%)	73 (18.3)	58 (19.3)	15 (15.2)	0.46
3, *n* (%)	189 (47.3)	152 (50.5)	37 (37.4)	0.03
Resection status (time zero) [†]				
R0, *n* (%)	253 (63.1)	241 (78.8)	12 (12.6)	<0.001
R1/R2, *n* (%)	148 (36.9)	65 (21.2)	83 (87.4)	<0.001
Local recurrence, *n* (%)	82 (19.1)	56 (17.3)	26 (24.5)	0.27
Metastasis at diagnosis, *n* (%)	23 (5.4)	20 (6.2)	3 (2.8)	0.22
Metastasis at follow-up, *n* (%)	111 (25.9)	100 (31.0)	11 (10.4)	<0.001
Death				
Overall, *n* (%)	71 (16.6)	61 (18.9)	10 (9.4)	0.25
Cancer-specific, *n* (%)	61 (14.2)	54 (16.7)	7 (6.6)	0.01

The percentages relate to the *n*-values listed in the first row of the respective columns. * Only 5 common diagnoses in our study cohort are listed. [§] The grade corresponds to the FNCLCC system. [†] R0 status is determined by histological examination. Unlike R2, R1 status is characterized by a negative postoperative MRI finding. To distinguish between R1 and R2 statuses, the surgical report was also reviewed.

Table 3. Characteristics of the UE group.

	n (%)
Reoperation	62 (58.4)
Resection status (reoperation)	
R0	51 (48.1)
R1	8 (7.5)
R2	1 (0.9)
Tumor residual in the resectate after reoperation (histopathological)	44 (75.8) *
Reoperation with radiotherapy [†]	27 (25.5)
Reoperation only	35 (33.0)
Radiotherapy only	7 (6.6)
Reoperation	62 (58.4)

* Out of the 62 reoperations after UE, only 58 histopathological reports were available. The percentages are based on these 58 histopathological reports. [†] Radiotherapy initiated within the first 6 months following UE only.

3.1. Impact on Local Recurrence-Free Survival

An analysis of the association between UE and LRFS, as shown in Table 4, indicated that patients with UE had significantly higher hazards of local recurrence (HR 7.49 (2.88, 19.49), $p < 0.001$) compared to patients that underwent PE. In this regard, the sensitivity analysis (see Appendix A Table A1) revealed no impact on the significance. Figure 2 presents the Kaplan–Meier curve for LRFS by treatment group. Grades 2 and 3 compared to grade 1 were significantly associated with local recurrence, HR 8.03 (1.09, 59.04), $p = 0.04$ and HR 8.50 (1.21, 59.48), $p = 0.03$, respectively. Biological behavior, sarcoma classification, grade, and anatomical region did not significantly influence the local recurrence risk.

Table 4. Multivariable propensity score weighted Cox regression for LRFS.

Characteristics	HR	95% CI	*p*-Value
UE	7.49	2.88, 19.49	<0.001
Biological Behavior			
Intermediate	—	—	
Malignant	1.75	0.26, 11.67	0.56
Sarcoma classification			
SST	—	—	
DST	1.44	0.50, 4.16	0.50
Bone	1.06	0.24, 4.70	0.93
Bone (versus DST) *	0.74	0.23, 2.37	0.61
Anatomic region			
Appendicular	—	—	
Axial	1.96	0.80, 4.77	0.14
Largest tumor diameter (mm)	1.00	1.00, 1.01	0.03
Grade			
1	—	—	
2	8.03	1.09, 59.04	0.04
3	8.50	1.21, 59.48	0.03
3 (versus 2) *	1.06	0.56, 1.99	0.86

* After releveling, bone was compared to DST, and grade 3 was compared to grade 2.

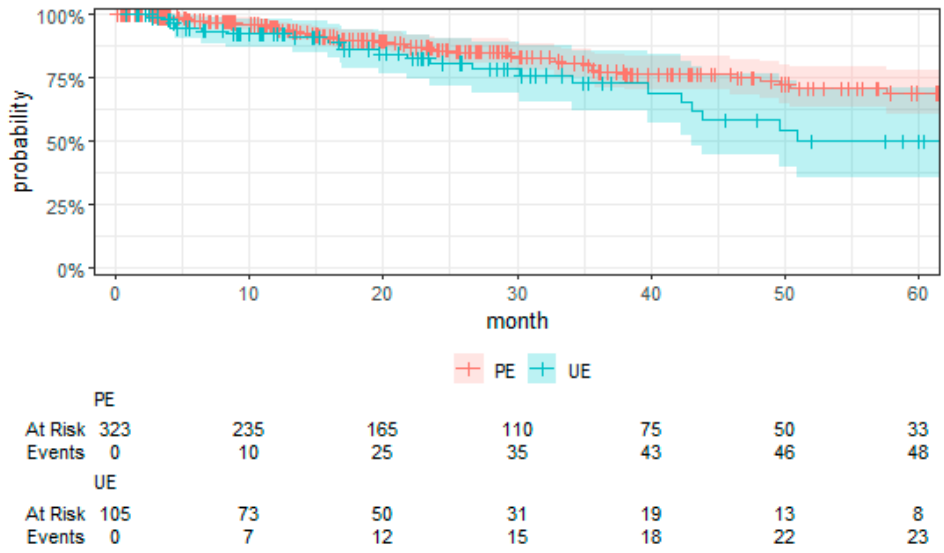


Figure 2. Kaplan–Meier plot of LRFS with the 95% confidence interval.

3.2. Impact on Metastasis-Free Survival

The examination of UE's association with MFS revealed no significant difference in MFS when compared to PE (HR 1.42 (0.40, 4.98), $p = 0.58$) (See Table 5). The sensitivity analysis (see Appendix A Table A2) revealed no impact on this result. Figure 3 presents the Kaplan–Meier curve for MFS by treatment group. Bone sarcomas had a higher hazard of

metastasis compared to SST (HR 4.40 (1.29, 15.02), $p = 0.02$), with a similar trend observed for DST (HR 2.51 (0.85, 7.35), $p = 0.09$). High-grade sarcomas (grade 3) demonstrated a substantially higher hazard of metastasis compared to low-grade sarcomas (grade 1) (HR 11.20 (1.32, 95.20), $p = 0.03$), as did grade 3 compared to grade 2 (HR 3.87 (1.68, 8.94), $p < 0.001$).

Table 5. Multivariable propensity score weighted Cox regression for MFS.

Characteristics	HR	95% CI	*p*-Value
UE	1.42	0.40, 4.98	0.58
Biological Behavior			
Intermediate	—	—	
Malignant	1.24	0.08, 18.72	0.88
Sarcoma classification			
SST	—	—	
DST	2.51	0.85, 7.35	0.09
Bone	4.40	1.29, 15.02	0.02
Bone (versus DST) *	1.75	0.89, 3.47	0.11
Anatomic region			
Appendicular	—	—	
Axial	1.21	0.63, 2.30	0.57
Largest tumor diameter (mm)	1.00	0.99, 1.00	0.24
Grade			
1	—	—	
2	2.89	0.25, 34.07	0.40
3	11.20	1.32, 95.20	0.03
3 (versus 2)	3.87	1.68, 8.94	<0.001

* After releveling, bone was compared to DST, and grade 3 was compared to grade 2.

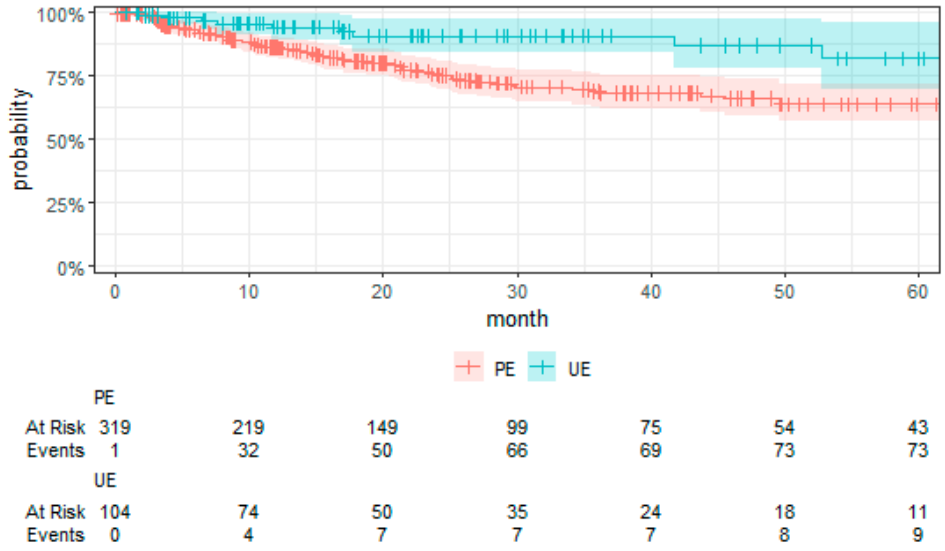


Figure 3. Kaplan–Meier plot of MFS with the 95% confidence interval.

3.3. Impact on Survival

3.3.1. Overall Survival

The hazards of death from any cause were not significantly increased after UE compared to PE (HR 1.47 (0.42, 5.16), $p = 0.55$) (Table 6). Furthermore, the sensitivity analysis (see Appendix A Table A3) did not lead to a substantially different result. The Kaplan–Meier survival curve for OS is displayed in Figure 4. However, the histological grade was an independent prognostic factor, sarcomas with grade 3 versus grade 1 (HR 29.00 (3.34, 251.99), $p = 0.002$) and grade 3 versus grade 2 (HR 12.82 (4.17, 39.36), $p < 0.001$) showing an

increased risk of death. Biological behavior, sarcoma classification, anatomical region, and largest tumor diameter were not significantly associated with OS.

Table 6. Multivariable propensity score weighted Cox regression for OS.

Characteristics	HR	95% CI	*p*-Value
UE	1.47	0.42, 5.16	0.55
Biological Behavior			
Intermediate	—	—	
Malignant	0.77	0.12, 4.91	0.79
Sarcoma classification			
SST	—	—	
DST	2.58	0.58, 11.51	0.21
Bone	2.05	0.35, 11.99	0.43
Bone (versus DST) *	0.79	0.32, 1.98	0.62
Anatomic region			
Appendicular	—	—	
Axial	0.49	0.19, 1.24	0.13
Largest tumor diameter (mm)	1.00	1.00, 1.01	0.24
Grade			
1	—	—	
2	2.26	0.23, 21.90	0.48
3	29.00	3.34, 251.99	0.002
3 (versus 2)	12.82	4.17, 39.36	<0.001

* After releveling, bone was compared to DST, and grade 3 was compared to grade 2.

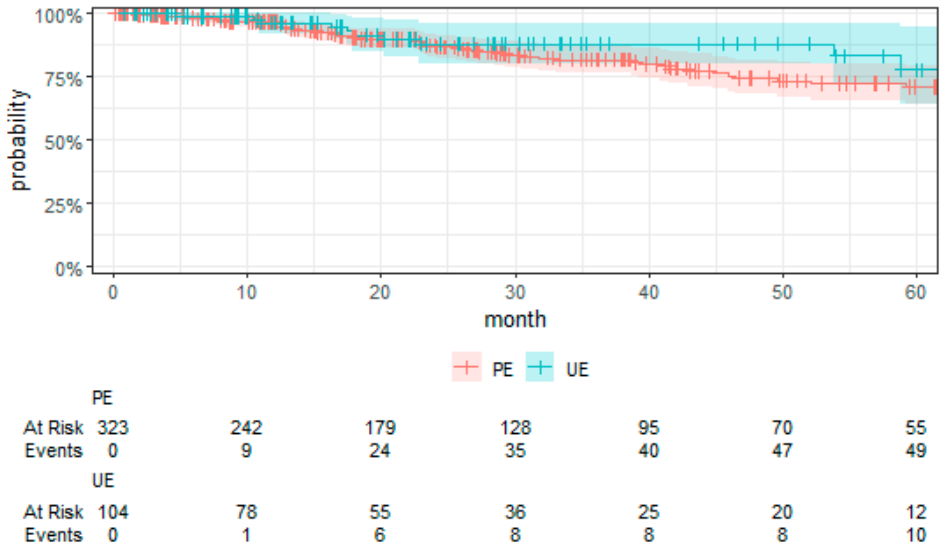


Figure 4. Kaplan–Meier plot of OS with the 95% confidence interval.

3.3.2. Cancer-Specific Survival

The risks of death from sarcomas were not increased after UE compared to PE (HR 1.47 (0.37, 5.94), $p = 0.59$) (Table 7). The sensitivity analysis (see Appendix A Table A4) revealed no impact on the absence of significance. Figure 5 presents the Kaplan–Meier curve for CSS by treatment group. Yet, a higher risk of cancer-specific death was noted with G3 sarcomas compared to G1 (HR 39.94 (2.77, 575.65), $p = 0.01$) or G2 (HR 13.48 (4.15, 43.87), $p < 0.001$). Biological behavior, sarcoma classification, anatomical region, and largest tumor diameter were not significantly associated with CSS outcomes.

Table 7. Multivariable propensity score weighted Cox regression for CSS.

Characteristics	HR	95% CI	*p*-Value
UE	1.47	0.37, 5.94	0.59
Biological Behavior			
Intermediate	—	—	
Malignant	0.80	0.09, 7.01	0.84
Sarcoma classification			
SST	—	—	
DST	2.54	0.49, 13.12	0.27
Bone	2.37	0.35, 16.02	0.38
Bone (versus DST) *	0.93	0.36, 2.39	0.89
Anatomic region			
Appendicular	—	—	
Axial	0.50	0.18, 1.39	0.18
Largest tumor diameter (mm)	1.00	1.00, 1.01	0.22
Grade			
1	—	—	
2	2.96	0.19, 46.56	0.44
3	39.94	2.77, 575.65	0.01
3 (versus 2)	13.48	4.15, 43.87	<0.001

* After releveling, bone was compared to DST, and grade 3 was compared to grade 2.

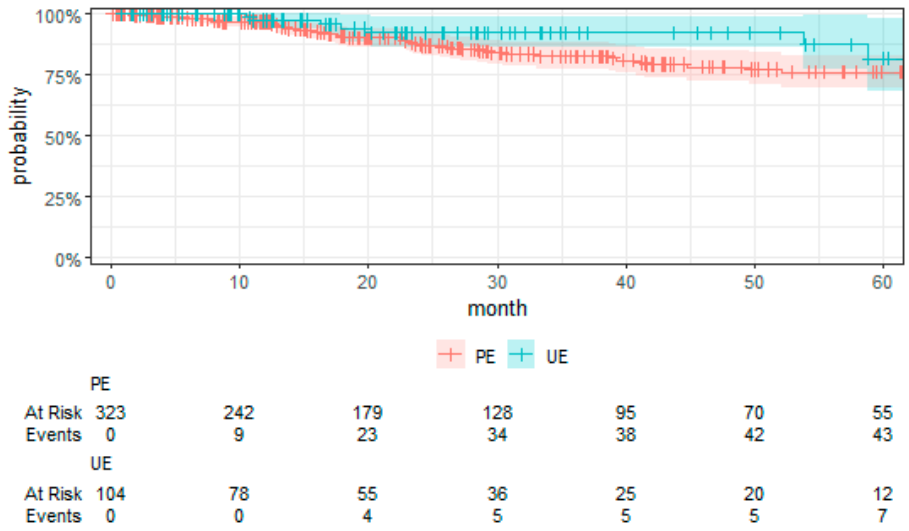


Figure 5. Kaplan–Meier plot of CSS with the 95% confidence interval.

4. Discussion

For the first time, employing TTE to overcome the limitations associated with RCTs, this study presents a comprehensive evaluation of surgical strategies for sarcoma treatment. Our analysis revealed a notably higher risk of local recurrence in patients undergoing UEs compared to those receiving PEs, with a hazard ratio that underscores the significance of the initial surgical management on disease control. We found no significant differences in MFS and OS between the UE and PE groups. These findings suggest that, despite the adverse impact of UEs on local control, subsequent therapeutic interventions might mitigate the short-term risks of metastasis and mortality. Moreover, the tumor grade emerged as a significant prognostic factor, affirming its established role in influencing sarcoma outcomes. High-grade tumors were associated with increased risks of local recurrence, metastasis, and death, highlighting the critical importance of tumor biology in patient prognosis. These key findings contribute to the ongoing discourse on optimal sarcoma management strategies, emphasizing the need for precision in surgical planning and the potential benefits of incorporating TTE into oncological research.

Our study elucidates the complex interplay between surgical strategies and sarcoma outcomes, revealing a notably higher risk of local recurrence for patients undergoing UEs compared to PEs. This finding aligns with the literature but notably is in the upper end of the typical 5-year reported local recurrence rates (8% to 17%), pointing to a potential for non-referral selection bias in our RWT cohort [4,11–13,30–34]. Despite these concerns, our use of TTE effectively navigates these challenges by approximating the rigor of RCTs, providing a robust framework for comparing UE and PE outcomes despite inherent limitations such as selection bias [24,25,35].

Contrary to conventional expectations, our analysis found no significant differences in MFS, CSS, and OS between the UE and PE groups. This deviation from the expected outcomes suggests that subsequent therapeutic interventions may mitigate the adverse impact of UEs on short-term outcomes. The role of tumor grade as a prognostic factor further complicates the relationship between surgical strategy and sarcoma outcomes, with high-grade tumors associated with increased risks irrespective of the initial surgical approach [36–38].

The observed variations in the follow-up treatments for UE patients reflect the individualized nature of sarcoma management post-surgery [8,9,18,20,33]. This diversity in treatment strategies, alongside the differential outcomes reported, underscores the importance of considering both biological aggressiveness and post-surgical care in patient prognosis and treatment planning [36–41].

In light of our findings, the elevated risk of local recurrence post-UE and the nuanced interplay between surgical strategy and tumor biology underscore the need for refined surgical guidelines and patient management strategies in sarcoma care. These insights, alongside the observed disparities in the existing literature, underscore the critical areas for future research, particularly in exploring how individualized treatment strategies post-surgery can influence short-term outcomes. By highlighting these novel aspects, our study points to the significance of integrating the multidisciplinary network approach into the decision-making process, urging a shift towards more personalized and evidence-based approaches in sarcoma treatment planning.

Employing TTE has enabled us to navigate the ethical and logistical hurdles that preclude RCTs in sarcoma research, allowing for a rigorous comparison of UE and PE. This study's insights highlight TTE's utility in generating evidence-based recommendations for sarcoma management, particularly by enhancing our understanding of the differential impacts of surgical strategies [23–25]. Our findings advocate for TTE's broader application, potentially enriching clinical guidelines and decision-making processes in sarcoma care. Using this methodology, we have demonstrated not just a way to address observational studies' methodological challenges in sarcoma research but also a means to propel sarcoma research towards more personalized and evidence-based treatment strategies, aligning with findings from the existing literature [3–6] and setting a precedent for future studies to follow.

While our study leverages the prospective collection of data within the SSN to enhance the robustness of our findings, the retrospective analysis of these data introduces inherent limitations. Notably, including patients diagnosed before 2018 who later presented with recurrences may augment the observed rate of local recurrence, reflecting a form of non-referral selection bias. This aspect necessitates cautious interpretation of our results, particularly concerning the generalizability of our findings across all sarcoma subtypes and treatment modalities. Furthermore, despite the methodological rigor provided by TTE, challenges such as selection bias and the complete balancing of cohort characteristics remain. Additionally, with a median follow-up of 1.9 years, statements about long-term prognoses are hardly possible. These limitations highlight the need for future prospective studies to validate our findings and explore the comprehensive impact of surgical strategies on sarcoma outcomes in a more controlled setting.

The significant risk of local recurrence following UE highlights the critical need for rigorous surgical margin evaluation and, when necessary, individualized re-resection based on

data evidence [18–21,33]. This emphasizes the essential role of a multidisciplinary approach in sarcoma management, where decisions are informed by a comprehensive understanding of tumor biology, potentially enhanced by our application of TTE. TTE's ability to simulate RCT-like conditions provides a robust basis for refining treatment guidelines, facilitating personalized care that integrates tumor-specific biological characteristics [23–25].

Looking forward, it is imperative that future research undertakes prospective studies to validate our findings, with a particular focus on the role of tumor biology in determining treatment efficacy and patient outcomes [36–41]. Additionally, examining how surgical choices affect patient quality of life will be crucial. Such studies should extend beyond traditional survival metrics to capture the broader impact of treatment strategies on the well-being of sarcoma patients, aligning with the shift towards patient-centered care in oncology [8,9,18,33]. This comprehensive approach promises not only to enhance clinical outcomes but also to improve the overall quality of life for individuals facing sarcomas, advocating for treatment plans that are as unique as the patients themselves [20,22].

Ultimately, our study calls for an integration of clinical expertise and multidisciplinary perspectives in developing evidence-based, patient-specific strategies for sarcoma treatment. By embracing the insights provided by TTE and prioritizing the exploration of tumor biology alongside patient-centric considerations, we can advance towards more effective and nuanced care for sarcoma patients.

5. Conclusions

Our application of TTE highlights the significant risk of local recurrence stemming from UE in sarcoma care, illuminating a crucial systemic flaw in the referral to specialized sarcoma networks. This revelation underscores the urgent need for improved collaboration and integration across healthcare systems to ensure that all sarcoma patients receive care coordinated by multidisciplinary teams within specialized networks from the beginning. By fostering stronger links and clearer pathways for referral to sarcoma centers (Hub and Spoke Model), we can move towards a more unified and evidence-based approach to sarcoma management. Future directions must prioritize prospective studies to explore the effectiveness of these integrated care models in reducing the incidence of UE and enhancing overall patient outcomes. This also highlights the need for comprehensive and well-maintained cancer registries.

Author Contributions: Conceptualization, P.H., G.S. (Gabriela Studer), B.B.-L. and B.F.; methodology, P.H. and B.F.; software, T.T.A.F.O., K.N.N. and P.H.; validation, T.T.A.F.O., K.N.N., P.H., G.S. (Georg Schelling) and B.F.; formal analysis, T.T.A.F.O., K.N.N. and P.H.; investigation, T.T.A.F.O., K.N.N. and P.H.; data curation, G.S. (Georg Schelling), T.T.A.F.O., K.N.N. and P.H.; writing—original draft preparation, T.T.A.F.O. and B.F.; writing—review and editing, T.T.A.F.O., K.N.N., P.H., G.S. (Georg Schelling), G.S. (Gabriela Studer), B.B.-L. and B.F.; supervision, G.S. (Gabriela Studer), B.B.-L. and B.F.; project administration, T.T.A.F.O., K.N.N., P.H. and B.F.; funding acquisition, G.S. (Gabriela Studer), B.B.-L. and B.F. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Appendix A

Table A1. Sensitivity analysis: impact of UE on LRFS with additional characteristics and exclusions, respectively.

	HR	95% CI	*p*-Value
Additional Characteristics			
Age *	7.48	2.92, 19.2	<0.001
Resection status (R0, R1/R2) *	2.89	1.05, 7.98	0.04
Tumor volume (cm^3) †	6.51	2.75, 15.42	<0.001
Sex (female, male) *	7.27	2.87, 18.42	<0.001
Chemotherapy with curative intention *	10.68	3.97, 28.73	<0.001
Radiotherapy with curative intention *	6.60	2.71, 16.09	<0.001
Additional exclusion criteria			
ALT and DFSP	7.08	2.67, 18.73	<0.001
Cases with time zero before 1 January 2018	8.11	2.69, 24.41	<0.001

* Instead of the characteristic "biological behavior". † Instead of the characteristic "largest tumor diameter (mm)".

Table A2. Sensitivity analysis: impact of UE on MFS with additional characteristics and exclusions, respectively.

	HR	95% CI	*p*-Value
Additional Characteristics			
Age *	1.38	0.39, 4.93	0.62
Resection status (R0, R1/R2) *	0.79	0.24, 2.62	0.70
Tumor volume (cm^3) †	1.57	0.44, 5.64	0.49
Sex (female, male) *	1.26	0.36, 4.37	0.72
Chemotherapy with curative intention *	1.17	0.35, 3.91	0.79
Radiotherapy with curative intention *	1.32	0.42, 4.16	0.63
Additional exclusion criteria			
ALT and DFSP	1.40	0.40, 4.87	0.60
Cases with time zero before 1 January 2018	1.40	0.30, 6.44	0.67

* Instead of the characteristic "biological behavior". † Instead of the characteristic "largest tumor diameter (mm)".

Table A3. Sensitivity analysis: impact of UE on OS with additional characteristics and exclusions, respectively.

	HR	95% CI	*p*-Value
Additional Characteristics			
Age *	1.32	0.42, 4.20	0.64
Resection status (R0, R1/R2) *	2.19	0.62, 7.72	0.22
Tumor volume (cm^3) †	2.06	0.70, 6.08	0.19
Sex (female, male) *	1.54	0.55, 4.32	0.41
Chemotherapy with curative intention *	1.17	0.28, 4.87	0.83
Radiotherapy with curative intention *	1.49	0.50, 4.38	0.47
Additional exclusion criteria			
ALT and DFSP	1.53	0.47, 4.99	0.48
Cases with time zero before 1 January 2018	1.30	0.26, 6.43	0.74

* Instead of the characteristic "biological behavior". † Instead of the characteristic "largest tumor diameter (mm)".

Table A4. Sensitivity analysis: impact of UE on CSS with additional characteristics and exclusions respectively.

	HR	95% CI	*p*-Value
Additional Characteristics			
Age *	1.36	0.36, 5.15	0.60
Resection status (R0, R1/R2) *	0.92	0.31, 2.75	0.89
Tumor volume (cm^3) †	2.23	0.74, 6.76	0.15
Sex (female, male) *	1.53	0.50, 4.69	0.46
Chemotherapy with curative intention *	1.21	0.27, 5.49	0.81
Radiotherapy with curative intention *	1.57	0.49, 5.06	0.45
Additional exclusion criteria			
ALT and DFSP	1.54	0.42, 5.72	0.52
Cases with time zero before 1 January 2018	1.25	0.21, 7.33	0.81

* Instead of the characteristic "biological behavior". † Instead of the characteristic "largest tumor diameter (mm)".

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Review

From Data Integration to Precision Medicine: A Value-Based Healthcare Approach for Sarcoma Care

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Abstract: The transformation of healthcare from a fee-for-service model to value-based care is particularly crucial in managing complex and rare diseases like sarcoma, where data fragmentation and variability present significant challenges. This manuscript reviews strategies for structured and harmonized data integration—a critical precursor to precision medicine in sarcoma care. We demonstrate how standardizing data formats, ontologies, and coding systems enable seamless integration of clinical, economic, and patient-reported outcomes across institutions, paving the way for comprehensive predictive analytics. By establishing robust value-based healthcare (VBHC) frameworks through digital transformation and predictive models, including digital twins, we create the foundation for personalized sarcoma treatment and real-world-time clinical decision-making. The manuscript also addresses practical challenges, including the need for system standardization, overcoming regulatory and privacy concerns, and managing high costs. We propose actionable strategies to overcome these barriers and discuss the role of advanced analytics and future research directions that further enhance VBHC and precision medicine. This work outlines the necessary steps to build a cohesive, data-driven approach that supports the transition to precision medicine, fundamentally improving outcomes for sarcoma patients.

Keywords: value-based healthcare and sarcoma; data harmonization; interoperability; digital transformation; ontologies and standardized coding systems; predictive analytics

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1. Introduction

1.1. Background and Context

Sarcomas represent a rare and heterogeneous group of malignancies, originating from mesenchymal tissues such as bones, muscles, fat, and connective tissues [1]. Accounting for only about 1% of all adult cancers and approximately 15% of pediatric cancers, sarcomas pose unique challenges in diagnosis, treatment, and research [2]. The complexity of sarcomas is exacerbated by the fact that there are over 70 distinct subtypes, each with its own histological and genetic characteristics [3]. This diversity contributes to fragmented care and a lack of standardized treatment protocols, as the rarity of each subtype often limits the availability of comprehensive data and evidence-based guidelines [4,5].

The fragmentation in sarcoma care is further compounded by the disparate sources of data collected across different institutions and countries. These data sources include clinical records, patient-reported outcomes, imaging studies, genomic data, and economic metrics, all of which are often siloed within specific registries or institutions [6]. The lack of integration among these diverse datasets results in missed opportunities for comprehensive analysis and hinders the development of holistic treatment approaches [7]. Moreover, the

current reliance on retrospective and often incomplete data, which may not fully capture the nuances of individual patient journeys, further limits the ability to deliver personalized and effective care [8].

1.2. Purpose of This Review

This paper seeks to address these challenges by highlighting the critical need for structured and harmonized data integration as a foundational step towards transitioning from a volume-based to a value-based healthcare (VBHC) model in sarcoma care [9]. The aim is to establish a unified framework that allows for the seamless integration of clinical, economic, and patient-reported data, enabling more informed decision-making and thereby improving patient outcomes and decreasing healthcare spending. By building this foundation, the paper also sets the stage for future advancements in precision medicine, where the insights gained from integrated data can be leveraged to develop personalized treatment strategies that are both effective and cost-efficient [9].

1.3. Fragmented Care and Data Approach

The current landscape of sarcoma care is characterized by significant fragmentation, both in terms of care delivery and data management [10,11]. The rarity of sarcomas often necessitates that patients receive care from multiple specialists across different institutions, leading to inconsistencies in treatment approaches and gaps in care coordination [12]. This fragmentation is mirrored in the data management practices within the field, where disparate sources of data are collected and stored in isolation, preventing a comprehensive understanding of patient outcomes [13].

This fragmented approach to data management has significant consequences for clinical research and ultimately treatment outcomes. Without a unified framework for data integration, clinicians are unable to access the full spectrum of information needed to make informed decisions [10,14]. This lack of comprehensive data also impedes the ability to conduct robust clinical research, as the fragmented datasets do not provide a complete picture of patient experiences and outcomes [15]. Moving towards a prospective data assessment model, incorporating real-world-time data collection and integration across all dimensions of sarcoma care is essential [8]. This shift will enable the development of standardized treatment protocols and facilitate the implementation of VBHC principles, ultimately leading to better care coordination and improved patient outcomes.

1.4. The Importance of VBHC

Traditional volume-based care models, which incentivize the provision of more services regardless of their impact on patient outcomes, are increasingly being recognized as unsustainable, particularly in resource-intensive fields such as oncology [16]. In contrast, VBHC emphasizes the importance of achieving the best possible patient outcomes relative to the costs incurred, making it a more sustainable and patient-centered approach to care delivery [17,18].

In sarcoma care, where the costs of treatment can be exceptionally high and the availability of evidence-based guidelines is limited, VBHC offers a framework for optimizing resource allocation and ensuring that care decisions are driven by the goal of maximizing patient value [19,20]. By focusing on quality and outcomes, VBHC encourages the development of more effective and efficient treatment strategies that are tailored to the individual needs of each patient. This approach not only reduces inefficiencies within the healthcare system but also enhances the overall quality of care, leading to better patient outcomes and higher levels of patient satisfaction.

2. Materials and Methods

2.1. Interoperable Digital Platform

The SSN-Sarconnector platform serves as an exemplary model for demonstrating the importance of interoperability in integrating diverse global registries and data sources [6,21].

While the discussion uses Sarconnector as a reference point, the focus remains on the underlying principles that make such platforms effective, emphasizing the need for a universally accessible and interoperable system [8]. This approach allows for the harmonization of structured data from various healthcare systems worldwide, supporting a more comprehensive understanding of patient outcomes, cost-effectiveness, and overall care quality—key components for advancing the VBHC model in sarcoma care [22]. The Sarconnector captures four data dimensions in a fully standardized way, enabling harmonization with other datasets.

2.2. Four Data Dimensions

1. Clinician-Reported Outcome Measures (CROMS):

The structured integration of clinical data through Clinician-Reported Outcome Measures (CROMS) is essential for creating a comprehensive view of patient care [6]. CROMS focus on clinical metrics and outcomes, such as treatment efficacy, safety, and overall patient management, providing insights into the effectiveness of various diagnostic and therapeutic approaches across different sarcoma subtypes. Harmonizing these clinical data points ensures that care is consistently measured and evaluated, fostering improvements in treatment protocols and outcomes.

2. Patient-Reported Outcome Measures (PROMS):

Incorporating Patient-Reported Outcome Measures (PROMS) into the data integration framework provides a holistic view of patient wellbeing, extending beyond clinical metrics to include the patient's perspective on their health and quality of life [6]. PROMS capture patient feedback on their symptoms, physical functioning, and emotional wellbeing, which are vital for understanding the impact of sarcoma treatments from the patient's perspective. This dimension reinforces VBHC's emphasis on patient-centered care by ensuring that the patient's voice is integral to the overall assessment of care quality.

3. Economics-Reported Outcome Measures (ECOMS):

Economic data integration through Economics-Reported Outcome Measures (ECOMS) is crucial for developing the Sarcoma Care Cost Score (SCCS), detailed below [6]. This score provides a standardized metric for evaluating the cost-effectiveness of different treatments, facilitating more informed decision-making and better resource allocation within the VBHC framework. Integrating cost data from multiple sources ensures that the SCCS is comprehensive and reflective of the real-world costs associated with sarcoma treatment.

4. Patient-Centric Omics Measures (PCOMS):

Patient-Centric Omics Measures (PCOMS) focus on integrating molecular and genomic data, providing a personalized understanding of each patient's disease profile [6]. PCOMS enable the identification of specific biomarkers and genetic alterations that can influence diagnosis, treatment response, and prognosis. This dimension is crucial for advancing precision medicine, as it allows for the tailoring of therapies based on individual molecular characteristics, leading to more effective and targeted treatment strategies.

2.3. The Role of AI in Data Structuring

While AI holds significant promise in transforming unstructured data into structured formats, the process is inherently limited by the quality and completeness of the original data input [23,24]. AI can extract patterns and insights from unstructured data, such as free-text clinical notes, but if critical information is absent or inconsistently recorded, the structured output will reflect these deficiencies [25]. This limitation underscores the importance of structured and standardized data entry at the point of care, where clinical, economic, patient-reported, and molecular data must be systematically captured. By ensuring that data are structured from the outset, healthcare systems can minimize post-processing errors, enhance the efficiency and accuracy of AI-driven analyses, and support

the development of robust, interoperable data systems critical for VBHC and future precision medicine applications [26–29]. A minimal dataset incorporated into clinical practice can ensure that critical information is fully captured [8].

2.4. Real-World-Time Data Integration

Integrating both real-world and real-time data is critical for enhancing the relevance and timeliness of clinical decision-making [8]. Real-world data provide insights based on actual patient experiences in diverse settings, while real-time data enable immediate feedback and adjustments in care. Together, these data types ensure that the platform supports dynamic and responsive care strategies tailored to the evolving needs of sarcoma patients. This integration is vital for advancing VBHC and laying the groundwork for future developments in precision medicine.

2.5. Harmonization and Standardization

Data Harmonization:

Harmonizing diverse data types across different healthcare systems is essential for creating an interoperable digital platform [28,30]. Achieving data harmonization involves utilizing standardized data formats, ontologies, and coding systems that enable consistent interpretation and integration of data from multiple sources [31]. For example, standardized clinical terminologies such as SNOMED CT (Systematized Nomenclature of Medicine—Clinical Terms) provide a comprehensive, multilingual clinical healthcare terminology that enables uniform representation of clinical content in electronic health records [32,33]. Disease classifications using ICD-10 (International Classification of Diseases, 10th Revision) and ICD-O (International Classification of Diseases for Oncology) ensure consistent coding of diagnoses and tumor characteristics [33], although these may not sufficiently mirror the sarcoma entities in particular. Laboratory tests and results can be standardized using LOINC (Logical Observation Identifiers Names and Codes), facilitating the comparability of lab data across institutions [34]. For data exchange protocols, the adoption of HL7 FHIR (Fast Healthcare Interoperability Resources) standards is crucial. FHIR defines how healthcare information can be exchanged between different computer systems regardless of how it is stored, allowing for seamless interoperability [34]. Additionally, implementing Common Data Models (CDMs) like the OMOP CDM (Observational Medical Outcomes Partnership Common Data Model) allows disparate data sources to be transformed into a consistent format, enabling large-scale analytics and research [35].

To ensure the quality of data harmonization, specific measurements and indicators are essential [36]. These include the following: Data Completeness: ensuring all required data fields are captured across datasets. Data Accuracy: verifying that the data correctly represents real-world scenarios, which can involve cross-referencing with source documents or validation studies. Data Consistency: maintaining uniform data formats and units across datasets to prevent discrepancies during integration. Data Timeliness: updating data promptly to reflect the most current information, which is critical for real-world-time data integration.

Implementing a Data Quality Assessment Framework can help regularly evaluate these metrics. For instance, the framework may include automated data validation rules, routine data quality reports, and processes for correcting identified errors. Harmonization efforts are critical for overcoming variability in data collection practices and ensuring that all data contribute meaningfully to the overall assessment of care quality [37]. By incorporating these standardized terminologies, coding systems, data models, and quality measurements, robust data harmonization frameworks facilitate effective integration and analysis of information from global networks, ultimately advancing VBHC in sarcoma care.

Standardization of Metrics:

To measure and improve care quality globally, developing standardized metrics that can be applied consistently across different healthcare settings is essential [38–42]. This

section will discuss creating standardized metrics, exemplified using the Sarcoma Clinical Quality Score (SCQS) and the Sarcoma Care Cost Score (SCCS). These metrics provide a common language for evaluating care quality and cost-effectiveness, enabling meaningful comparisons and benchmarking across institutions. Standardization efforts also support transitioning to a VBHC model by ensuring that care is consistently measured and optimized based on universally accepted criteria.

2.6. Practical Challenges in Implementation

Implementing structured and harmonized data integration across diverse healthcare systems presents several practical challenges that must be addressed to realize the full potential of Value-Based Healthcare (VBHC) and precision medicine in sarcoma care.

2.6.1. Standardization Across Systems

Healthcare systems worldwide utilize a variety of electronic health record (EHR) systems with differing data formats, terminologies, and standards, making data interoperability a significant challenge [37,43,44]. Aligning these disparate systems requires adopting common data standards and terminologies, which can be complex and resource-intensive [45]. Efforts to standardize data entry and coding practices must consider variability in clinical workflows and the need for extensive training of healthcare professionals.

2.6.2. Regulatory Hurdles

Data sharing and integration must comply with various regulatory frameworks governing patient privacy and data protection, such as the General Data Protection Regulation (GDPR) in Europe and the Health Insurance Portability and Accountability Act (HIPAA) in the United States [46]. Navigating these regulations can be challenging, especially when collaborating across international borders. Ensuring compliance requires careful planning, legal expertise, and robust data governance policies.

2.6.3. Privacy and Data Security Concerns

Protecting patient privacy and ensuring data security are paramount when integrating sensitive health information [47]. Concerns about data breaches and unauthorized access can hinder data-sharing initiatives. Implementing strong security measures—such as encryption, access controls, and regular security assessments—is essential. Additionally, obtaining informed consent from patients and maintaining transparency about data usage can help build trust and facilitate data sharing.

2.6.4. Limitations of Technologies and Solutions

High Costs

Implementing advanced technologies for structured and harmonized data integration can involve significant financial investment. The costs associated with purchasing hardware and software, upgrading existing systems, and training staff may be prohibitive for some institutions, particularly in resource-limited settings. These expenses can hinder the widespread adoption of such technologies.

Solutions: To mitigate high costs, institutions can explore cost-effective alternatives such as open-source software and cloud-based solutions that reduce upfront investments. Collaborative funding models, partnerships with technology providers, and government grants can also help distribute costs.

Need for Structured Data Input

The effectiveness of data integration relies on the availability of structured data. Transitioning from unstructured to structured data input requires changes in clinical documentation practices, which may increase the workload for healthcare providers and encounter resistance [8].

Solutions: Implementing user-friendly data entry interfaces and integrating structured data-capture seamlessly into existing workflows can minimize disruption. Providing training and support for clinicians is essential to facilitate adoption. Additionally, employing natural language processing (NLP) tools can help extract structured data from unstructured clinical notes, reducing the burden on clinicians.

Potential Accuracy Issues

Technologies like AI and machine learning algorithms are dependent on the quality and quantity of available data. Inaccuracies can arise from biased datasets, insufficient data volume, or errors in data entry, potentially leading to unreliable outputs.

Solutions: Ensuring data quality through validation protocols and using diverse, representative datasets can improve algorithm accuracy. Regularly updating and monitoring algorithms helps maintain their reliability. Involving multidisciplinary teams, including clinicians and data scientists, can enhance oversight and address potential biases or errors.

2.7. Use of AI Language Model Assistance

In the preparation of this manuscript, the authors utilized the AI language model ChatGPT (developed by OpenAI, San Francisco, CA, USA; www.chatgpt.com, accessed 20 October 2024) to assist in drafting and refining the text. The AI tool was employed to generate initial drafts, suggest phrasing, and improve the clarity and flow of the manuscript. All AI-generated content was thoroughly reviewed, edited, and validated by the authors to ensure accuracy and adherence to scientific standards.

3. Advancing VBHC as a Precursor to Precision Medicine

3.1. Establishing VBHC

3.1.1. VBHC as the Foundation

VBHC serves as the essential foundation for the eventual integration of precision medicine in sarcoma care [17,19]. VBHC emphasizes the importance of improving patient outcomes relative to the costs of care, a principle that is particularly critical in rare and complex diseases like sarcoma [16]. Establishing VBHC creates the necessary infrastructure for precision medicine by ensuring that care is consistently measured and optimized based on universally accepted metrics. As healthcare shifts from volume to value, structured data integration becomes a vital tool in laying this foundation [16]. This structured data—comprising clinical, economic, and patient-reported outcomes—serves as the baseline for developing more personalized care strategies, enabling a smoother transition to precision medicine. Furthermore, precision medicine, which optimizes the therapeutic outcome and resource use, enhances VBHC.

3.1.2. Structured Data's Role

The role of structured data in VBHC cannot be overstated [6,48,49]. It provides the benchmarks needed to guide future precision medicine developments by offering a clear, quantifiable understanding of what constitutes effective care. By integrating real-world-time data, clinicians can not only track patient outcomes but also refine treatment protocols based on real-time insights [7,8]. Real-time insights allow for rapid adoption of new clinical protocols and the efficient evaluation of its success. This integration is pivotal in transitioning from traditional, retrospective care models to a dynamic, data-driven approach that continuously evolves with the needs of patients.

3.2. Prospective Data Collection and Its Impact

From Retrospective to Prospective:

The transition from retrospective analysis to a prospective data collection framework marks a significant evolution in sarcoma care [7,50,51]. Retrospective data, while valuable, often reflects past trends that may not fully capture the complexities of current patient populations or the nuances of modern treatments. By moving to prospective data collection,

healthcare providers can gather real-world-time data that more accurately reflects current clinical practices and patient responses [44]. This shift allows for the continuous updating of treatment protocols, leading to more timely and effective interventions. Furthermore, prospective data serves as a more robust foundation for establishing evidence-based guidelines, which are critical for the consistent application of VBHC principles.

Impact of Prospective Data on Treatment Protocols:

The impact of prospective data collection on treatment protocols is profound [8,37,43]. By capturing data in real-time, clinicians can make more informed decisions that are directly aligned with the most current evidence. This approach enhances the precision and personalization of care, enabling the development of guidelines that are not only evidence-based but also adaptable to the individual needs of each patient. Prospective data collection thus plays a crucial role in refining treatment strategies and improving overall patient outcomes within the VBHC framework.

3.3. Linking VBHC to Future Precision Medicine

Building Blocks:

Structured and harmonized data collected under the VBHC framework serves as the building blocks for future innovations in precision medicine, including AI integration, digital twinning, benefit-harm modeling, and other advanced technologies [52,53]. As these technologies evolve, the groundwork laid by VBHC ensures that their implementation is both effective and equitable, with a clear focus on improving patient outcomes while managing costs.

The Role of VBHC in Future Precision Medicine:

VBHC's role in facilitating the transition to precision medicine is multifaceted [27]. By establishing a care model that prioritizes outcomes and efficiency, VBHC ensures that new technologies are integrated into clinical practice in a way that maximizes their potential benefits. This includes ensuring that AI-driven insights and digital twin simulations are grounded in real-world-time data and are applicable across diverse patient populations [53]. The VBHC model also promotes equity in the adoption of precision medicine, ensuring that all patients, regardless of their location or socioeconomic status, have access to the latest advancements in care. This equitable approach is essential for realizing the full potential of precision medicine in sarcoma treatment.

3.4. Measuring the Impact of Initiatives Through Outcomes and Benchmarks

Evaluating these initiatives is crucial for demonstrating their value in advancing Value-Based Healthcare (VBHC) and preparing for precision medicine. To this end, we propose specific outcomes and benchmarks that reflect improvements in patient care and system efficiency, primarily through the Sarcoma Clinical Quality Score (SCQS) and the Sarcoma Care Cost Score (SCCS) [6].

The SCQS is a composite metric quantifying sarcoma care quality across multiple dimensions of clinical performance. It evaluates adherence to evidence-based protocols, monitors patient survival rates (overall and progression-free), tracks complication and recurrence rates, and incorporates patient-reported outcome measures (PROMs) regarding functional status and quality of life. By aggregating these factors, the SCQS provides a comprehensive assessment of clinical effectiveness, enabling benchmarking across institutions and over time.

The SCCS assesses the economic aspect of sarcoma care by analyzing direct medical costs (surgeries, medications, hospital stays, outpatient services), indirect costs (lost productivity, long-term care needs), and resource utilization efficiency (operating room time, diagnostic procedures). This score helps identify cost-saving opportunities without compromising quality, aligning with VBHC's goal of maximizing patient value.

Implementing the SCQS and SCCS enables healthcare providers to benchmark performance against national and international standards, identify areas for improvement, track

progress over time, and inform decision-making through data-driven insights that refine treatment protocols and resource allocation.

Additional metrics include interoperability scores assessing a system's ability to exchange and interpret shared data; data quality indicators monitoring completeness, accuracy, consistency, and timeliness; and patient satisfaction scores capturing patient experiences to provide a holistic view of care quality.

By incorporating these outcomes and benchmarks, we establish a clear framework for measuring the effectiveness of structured and harmonized data integration in advancing VBHC. This approach ensures tangible improvements in patient outcomes, care quality, and cost-efficiency, ultimately paving the way for precision medicine in sarcoma care.

4. Expanding the Framework Globally

4.1. Digital Platforms as Enablers

4.1.1. Global Integration Through Digital Platforms

Digital platforms, such as Sarconnector, serve as critical models for integrating and connecting international centers focused on sarcoma care [14,21]. These platforms are designed to foster global collaboration by providing a centralized, interoperable system that harmonizes data across diverse regions and healthcare systems. By enabling seamless data exchange and communication between institutions, these platforms break down geographical barriers, allowing for the sharing of best practices, research findings, and patient outcomes. This global integration is essential for addressing the challenges posed by rare diseases like sarcoma, where patient populations are dispersed and data fragmentation hinders progress.

Sarconnector, for example, is not just a tool but a blueprint for how such platforms can be developed and deployed on a global scale. It exemplifies how interoperability can be achieved through standardized data inputs and harmonized metrics, ensuring that data collected from different parts of the world is consistent and comparable. This level of integration is crucial for building a global network of sarcoma care centers that can work together to improve patient outcomes and advance research.

4.1.2. Hub-And-Spoke Model

The implementation of the hub-and-spoke model through digital platforms represents a strategic approach to the regional and global coordination of sarcoma care [54]. In this model, specialized centers of excellence (hubs) provide advanced care and expertise, while regional hospitals and clinics (spokes) offer more localized services. Digital platforms facilitate this model by enabling real-time communication, data sharing, and coordinated care across the network.

In Switzerland, for example, this model has been effectively used to connect different regions and hospitals, ensuring that patients have access to the highest levels of care regardless of their location [55]. Through Sarconnector and similar platforms, Swiss sarcoma centers can collaborate on complex cases, share diagnostic and treatment data, and ensure that all patients receive care that is consistent with the latest evidence-based guidelines. This model not only improves the quality of care but also makes it more efficient and accessible, serving as a template for global expansion.

4.2. Global Collaboration and Standardization

4.2.1. International Partnerships

Building international partnerships is a cornerstone of expanding the VBHC framework globally. Collaborating with global sarcoma organizations such as the Connective Tissue Oncology Society (CTOS), EURACAN, SELNET, Sarcoma Patients EuroNet (SPAEN), and the European Musculo-Skeletal Oncology Society (EMSOS) is essential for standardizing care practices and sharing expertise [10,56–59]. These partnerships enable the development of globally recognized guidelines and best practices, ensuring that all patients receive the highest standard of care, regardless of where they are treated.

Through these collaborations, data from different countries can be pooled, providing a richer dataset for research and the development of new treatments with increased chances of good generalizability. Moreover, a diverse dataset allows for the evaluation of heterogeneous treatment effects and subsequently individualized treatment effects. This global pooling of data also facilitates the benchmarking of outcomes and the identification of best practices, which can then be disseminated across the network to improve care quality worldwide.

4.2.2. Personalized Guidelines Development

Leveraging global data to create personalized, evidence-based guidelines marks a significant advancement over traditional evidence-based guidelines, which are often based on expert opinion rather than empirical data [24,60,61]. By moving towards guidelines informed by prospective, real-world-time data, the sarcoma care community can develop more accurate and applicable treatment protocols tailored to individual patient needs.

These personalized guidelines are particularly important in rare diseases like sarcoma, where variability in patient responses to treatment is high [45,62]. By using data collected through interoperable digital platforms, clinicians can develop guidelines that are not only evidence-based but also highly specific to the diverse patient populations they serve. This approach ensures that treatment recommendations are grounded in real-world outcomes, making them more effective and relevant to clinical practice.

The shift towards prospective, real-world-time data also allows for the continuous updating of guidelines as new data become available, ensuring that they remain current and reflective of the latest scientific advancements. This dynamic approach to guideline development is a key component of VBHC and a precursor to the broader adoption of precision medicine in sarcoma care.

4.2.3. Challenges in Global Adoption of VBHC

Implementing Value-Based Healthcare (VBHC) globally faces challenges due to cultural differences, economic disparities, and variations in healthcare systems [16,18,63,64]. Cultural beliefs and practices influence patient expectations and acceptance of VBHC principles, potentially hindering adoption in certain regions. Economic constraints, especially in low-resource settings, can limit the availability of the infrastructure and technology necessary for VBHC implementation. Additionally, differing healthcare policies and organizational structures across countries complicate standardization efforts.

To overcome these challenges, it is essential to tailor VBHC models to local contexts by considering cultural sensitivities and resource availability [18]. Capacity building through training and education can empower local healthcare professionals. Engaging stakeholders from diverse regions promotes inclusive collaboration, ensuring that VBHC initiatives address specific local needs. Leveraging cost-effective technologies and advocating for supportive policies can further facilitate global adoption.

4.3. Future Directions Enhancing Value-Based Healthcare

4.3.1. Practical Enhancements to VBHC

Looking ahead, several emerging trends have the potential to further enhance Value-Based Healthcare (VBHC) in sarcoma care. Emphasizing cost efficiency over mere cost reduction is essential, focusing on optimizing health outcomes relative to the costs incurred. The integration of advanced analytics and predictive modeling, including artificial intelligence and machine learning, can support personalized treatment plans and improve clinical decision-making. Incorporating personalized medicine and genomics allows for tailored therapies that increase effectiveness and avoid unnecessary costs. Expanding digital health technologies, such as telemedicine and remote monitoring, can improve patient engagement, access, and care efficiency. Enhancing interoperability and data sharing facilitates comprehensive data integration and collaboration across systems. Patient engagement and shared decision-making empower patients, improving adherence, satisfaction, and

outcomes. Lastly, developing value-based payment models aligns financial incentives with VBHC goals, encouraging providers to deliver high-quality, efficient care. By embracing these future directions, the healthcare community can build upon the foundation established through structured and harmonized data integration, further advancing VBHC and paving the way for precision medicine in sarcoma care.

4.3.2. Future Research Directions

Advancing VBHC and precision medicine in sarcoma care presents several opportunities for future research:

Empirical Evaluation of VBHC Implementation

Conducting multicenter studies to assess the impact of VBHC frameworks on patient outcomes, cost-efficiency, and care quality in sarcoma treatment. Evaluating the effectiveness of standardized metrics like the Sarcoma Clinical Quality Score (SCQS) and the Sarcoma Care Cost Score (SCCS) across diverse healthcare settings will provide valuable insights into their applicability and utility.

Addressing Implementation Challenges

Investigating strategies to overcome practical challenges such as standardization across different systems, regulatory hurdles, and privacy concerns. Research into cost-effective solutions and technological innovations can facilitate structured data input and integration, particularly in resource-limited settings.

Global Adaptation of VBHC Models

Studying the adaptation of VBHC principles to different cultural, economic, and healthcare contexts. Exploring how VBHC can be tailored to local needs will enhance its universal applicability. Assessing the effectiveness of capacity-building initiatives and inclusive collaboration can promote global adoption.

Integration of Advanced Technologies

Researching the integration of artificial intelligence, machine learning, and digital health technologies into VBHC frameworks. Evaluating the impact of these technologies on data analysis, predictive modeling, and personalized care can enhance clinical decision-making and patient outcomes in sarcoma care.

By pursuing these research directions, the healthcare community can build upon the foundations established in this review, further advancing VBHC and precision medicine in sarcoma care globally.

5. Conclusions

This review has highlighted the critical importance of structured and harmonized data integration as the cornerstone for establishing Value-Based Healthcare (VBHC) in sarcoma care [28]. Transitioning from fragmented, retrospective data approaches to a cohesive, prospective data integration framework is a transformative step toward more effective, efficient, and patient-centered care [6,8,21]. By harmonizing clinical, economic, and patient-reported outcome data across global networks, we create a unified foundation that supports the accurate measurement of care quality and costs, as exemplified by metrics like the SCQS and the SCCS [6].

Establishing this VBHC foundation is essential for preparing the ground for the next leap in sarcoma care—precision medicine [9,30]. Robust data systems and metrics enable the integration of advanced technologies such as artificial intelligence (AI), digital twinning, and real-world-time data analytics [52], facilitating the development of personalized treatment guidelines based on evidence rather than tradition. Looking ahead and embracing emerging trends will further enhance VBHC and pave the way for precision medicine. Focusing on cost efficiency, integrating advanced analytics and predictive modeling, expanding digital health technologies, enhancing interoperability, and promoting patient

engagement and shared decision-making are vital steps forward. Aligning financial incentives with VBHC goals through value-based payment models will encourage providers to deliver high-quality, efficient care (Figure 1).

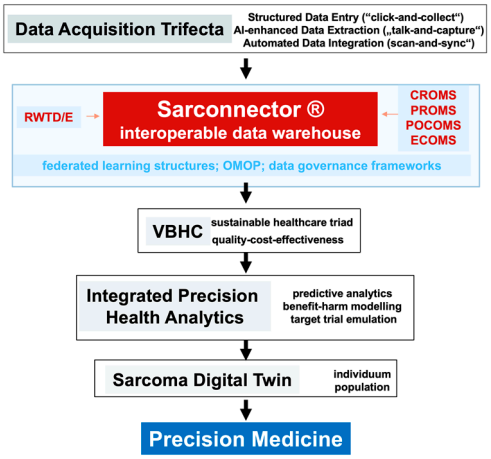


Figure 1. The graphical abstract illustrates the integration of structured and harmonized data into the Sarconnector Interoperable Data Warehouse, which supports value-based healthcare (VBHC) in sarcoma care. Real-world-time data acquisition, including clinician-reported outcomes (CROMS), patient-reported outcomes (PROMS), economic measures (ECOMS), and omics data (PCOMS), feeds into predictive analytics and the Sarcoma Digital Twin. This system facilitates precision medicine by enabling individualized, evidence-based care while optimizing clinical outcomes and cost-effectiveness.

The journey toward achieving VBHC in sarcoma care and laying the groundwork for precision medicine requires the concerted effort of global stakeholders. We call upon healthcare providers, researchers, policymakers, and international sarcoma organizations to collaborate in implementing structured and harmonized data integration systems and to embrace emerging innovations that enhance VBHC. This collaboration is essential to ensure that all patients, regardless of their geographic location, have access to high-quality, evidence-based care.

By prioritizing the development of interoperable digital platforms, standardized metrics, and forward-looking strategies, we can pave the way for a new era in sarcoma care—one where treatment decisions are guided by real-world-time data, personalized to each patient, and grounded in the principles of value-based care. This is a feasible, actionable path forward, provided that the global sarcoma community unites in this common goal.

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information of all their consecutive patients with suspicion/confirmation of sarcoma at the weekly MDT/SB and to prospectively register the patients in a common real-world-time database. This database is designed for quality assessment of sarcoma care, predictive modeling, and the creation of the sarcoma digital twin to realize predictive and value-based precision sarcoma care. We would like to thank all representatives and members of the SSN: Silke Gillessen-Sommer, Barbara Kopf, Glauco Martinetti (Ente Ospedaliero Cantonale, Bellinzona, Locarno, Lugano), Christian Michelitsch, Hugo Keune (Kantonsspitäler Graubünden KSGR), Paul Magnus Schneider, Marco Gugolz (Hirslanden Zürich), Markus Weber, Marc Widmer (Stadtspital Zürich), Beata Bode (Patho Enge, Zurich), Stefan Breitenstein, Guido Speck (Kantonsspital Winterthur), Gabriela Studer, Benno Fuchs (LUKS Teaching University Hospital Luzern), and the Faculty of Medicine and Health Sciences, University of Lucerne, Switzerland (Reto Babst, Stefan Boes). The authors acknowledge the use of ChatGPT (developed by OpenAI, San Francisco, CA, USA) for assistance in the preparation of this manuscript.

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Real-time interaktive Analyse der Behandlungs-Qualität von Sarkom-Patienten



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Sarkome sind bösartige Tumore des Binde- und Stützgewebes, machen lediglich ca. 1% aller Krebsformen aus, und gehören so zu den seltenen Erkrankungen. Molekular werden fast 200 verschiedene biologische Entitäten unterschieden, und die Behandlung erfolgt ausgesprochen transdisziplinär. Die Weiterentwicklung von neuen Therapieformen für Sarkom Patienten gestaltet sich als sehr schwierig, da es einerseits keine prospektiven, longitudinalen Datenerfassungen -und schon gar nicht in Echtzeit und durch den Patienten definierte Parameter- gibt, und weil diese in der Regel auch nicht transdisziplinär erfasst werden. Zudem müssen immer neue Herausforderungen gemeistert werden.

Abstract: Sarcomas are malignant tumors of the connective and supporting tissues, account for only about 1% of all cancers, and thus belong to the rare diseases. Molecularly, nearly 200 different biological entities are distinguished, and treatment is distinctly transdisciplinary. The further development of new forms of therapy for sarcoma patients is very difficult, because on the one hand there is no prospective, longitudinal data collection – and certainly not in real time and patient-defined parameters – and because these are usually not collected in a transdisciplinary manner. In addition, new challenges must always be mastered.

Key Words: Sarcoma, MDT, real-time/real-world data, predictive outcome analysis

Seit Januar 2020 müssen alle Krebsdiagnosen per Gesetz gemeldet werden, wofür aber keine einheitliche digitalisierte Lösung zur Erfassung von strukturierten Daten besteht. Zudem führte die Schweiz im April 2021 ein Gesetz zur Qualität und Wirtschaftlichkeit in der Medizin ein, obwohl die eigentliche Qualität noch nicht wirklich definiert ist. Darüber hinaus müssen wir uns immer grösseren Herausforderungen in unserem Gesundheitswesen stellen, wo die Kostenexplosion ungebremst zunimmt, und immer neue Sparmassnahmen definiert werden, ohne aber die effektiven Kosten abbilden zu können und dadurch der Spielraum der Akteure an der Front immer weiter eingeengt wird («Silo-Mentalität»).

Swiss Sarcoma Network (SSN)

Das SSN wurde vor 3 Jahren als Verein gegründet. Mitglieder sind die Institutionen, welche sich verpflichten, alle transdisziplinären Patienten prospektiv im wöchentlichen multidisziplinären Sarkom-Tumorboard (MDT-SB) vorzustellen und die Daten im Register zu teilen. Das definierte Ziel beabsichtigt die transparente Erfassung der Qualität der Behandlung von Sarkom Patienten. Grundsätzlich steht das SSN allen Institutionen offen, die zu dieser transparenten Qualitätserfassung bereit sind.

Um dies zu erreichen, werden die Prinzipien der value-based health care (VBHC) verfolgt. Strukturierte, klinisch-metrische Daten werden longitudinal über den gesamten Behandlungsablauf für jeden einzelnen Patienten erfasst.

Zur Beschreibung des Aufbaus sowie der Zielsetzung des SSN können die Qualitätsdimensionen nach Donabedian angewandt werden: Prozessqualität, Strukturqualität und Ergebnisqualität. Prozessqualität erfasst das SSN zum Beispiel dadurch, dass der Zeitpunkt dokumentiert wird, an welchem diagnostische Untersuchungen und therapeutische Schritte durchgeführt werden, um so zeitliche Prozesse abzubilden. Weitere Parameter der Prozessqualität, wie z.B. das Einhalten der Leitlinien während Sarkomboard Entscheiden, werden ebenfalls dokumentiert. Strukturqualität stellt das SSN allein schon durch seinen Aufbau sicher:

Das SSN besteht organisatorisch aus drei Hauptpfeilern: nebst dem wöchentlich stattfindenden MDT-SB ist das SwissSarcoma-Registry zu erwähnen, sowie die Forschung und Fort- und Weiterbildung. Letztere wird unter www.sarcoma.academy zusammengefasst. Hierbei werden monatlich internationale Webinars organisiert, in denen abwechslungsweise ein Hauptthema durch einen weltweit anerkannten Sarkomexperten vorgestellt wird, und Fallbesprechungen stattfinden mit einem internationalen Expertenpanel. Mittlerweile loggen sich jeweils Teilnehmer aus allen fünf Kontinenten ein.

Das SSN ist international eingebettet, einerseits durch das International Advisory Board bestehend aus 4 Exponenten, die das Netzwerk im Aufbau direkt beraten und für konkrete Patientenfragen aus dem MDT-SB direkt zur Verfügung stehen. Andererseits ist das SSN Mitglied von SELNET, einem Horizon2020 geförderten internationalen Sarkom-Netzwerk Programm. Dies integriert das SSN in die international vernetzte Grundlagen- und translationale Forschung. Im SwissSarcomaRegistry sind aktuell die Daten von knapp 4000 Patienten erfasst, was mit dem erwähnten Set-up exzellente Möglichkeiten für die Versorgungsforschung erlaubt.

Ergebnisqualität als letzte Kategorie der Donabedian Kriterien wird durch regelmässige systematische Erhebungen von Patienten berichteten Ergebnissen (PROMs) sowie Patienten berichteten Erfahrungen (PREMs) direkt vom Patienten, sowie durch Bestimmung von «harten» Qualitsindikatoren, wie z.B. Rezidivrate oder Überleben, sichergestellt. Da strukturierte Daten erfasst werden, wird es ebenfalls möglich sein, jedem diagnostischen und thera-

German Medical Award 2021 für das SwissSarcomaNetwork

Der German Medical Award wird seit 2015 jährlich vergeben und steht für die Medizin der Zukunft mit Schwerpunkt auf Qualität, Transparenz von optimalen Versorgungsleistungen sowie Digitalisierung im Gesundheitswesen. Das SwissSarcomaNetwork (www.swiss-sarcoma.net) wurde im Jahr 2021 mit diesem prestigeträchtigen Preis in der Kategorie «Medical Research» ausgezeichnet, in der das Projekt der real-time interaktiven Analyse der Behandlungs-Qualität von Sarkom Patienten vorgestellt wurde.

peutischen Schritt ein entsprechendes «Preisschild« zuzuordnen, wodurch die effektiven Kosten einer Sarkombehandlung ermittelt werden können.

Definition von Qualitätsindikatoren (QI) der Sarkombehandlung

Um die Qualität der Sarkom Behandlung überhaupt erfassen zu können, muss diese zuerst definiert werden. Das Internationale Advisory Board des SSN mit vier weltweit anerkannten Sarkomexperten (Jean-Yves Blay, Lyon; Axel LeCesne, Paris; Javier Martin-Broto, Madrid; Alessandro Gronchi, Milan) definierte zu diesem Zweck Qualitätsindikatoren für die Abklärung und Behandlung von Patienten mit Sarkom. Diese können in 6 Kategorien eingeteilt werden (Tab. 1):

TAB. 1 **Kategorien von Qualitätsindikatoren**

• Abklärung von Patienten mit Sarkomverdacht
• Management des MDT-SB
• Therapie (inkl. Chirurgie, Strahlentherapie, Chemotherapie)
• Komplexität der Sarkomtherapie
• Outcome (definiert durch den Arzt)
• PROMS / PREMS (definiert durch den Patienten)
Jede einzelne dieser Kategorien erhält bis zu 10 Subparameter, welche die Kategorie weiter definieren. Natürlich können diese Kategorien bei Bedarf flexibel erweitert und ergänzt werden.

Real-time and real-world (RTWD) Datenerfassung

Selbstverständlich kann eine solche Fülle von klinischen Parametern und komplexen Daten nicht mit herkömmlichen Methoden abgebildet und erfasst werden. Zudem stellt die «Datenexplosion» in der Medizin ein zunehmend ernstes Problem dar, dem wir uns stellen müssen. Die Herausforderung kann zusammengefasst werden mit den 5V's of big data, nämlich: Geschwindigkeit, Volumen, Variabilität, Korrektheit und Wertigkeit. Die zukünftige Herausforderung besteht darin, Daten nicht nur zu berichten, sondern durch analytische Verfahren neues Wissen zu generieren, welches in Zukunft einen Krankheitsverlauf oder sinnvolle Therapieentscheidungen für jeden einzelnen Patienten voraussagen kann. Dadurch kann eine deskriptive Analyse in eine prädiktive und präskriptive Analyse weiterentwickelt werden. Die Möglichkeiten der digitalen Transformation werden uns dies ermöglichen. Um in einem ersten Schritt RTWD zu generieren, entschloss sich das SSN, das SwissSarcomaRegistry mit dem MDT-SB zu koppeln. Somit kann der Moment, an dem sich alle Vertreter der Fachdisziplinen einmal wöchentlich austauschen und offene Fragen zur Abklärung und Behandlung der Sarkompatienten diskutieren, im Register festgehalten werden. Weiterhin erfolgt die Eingabe von Daten somit zeitgleich zum klinischen Ablauf und interdisziplinär.

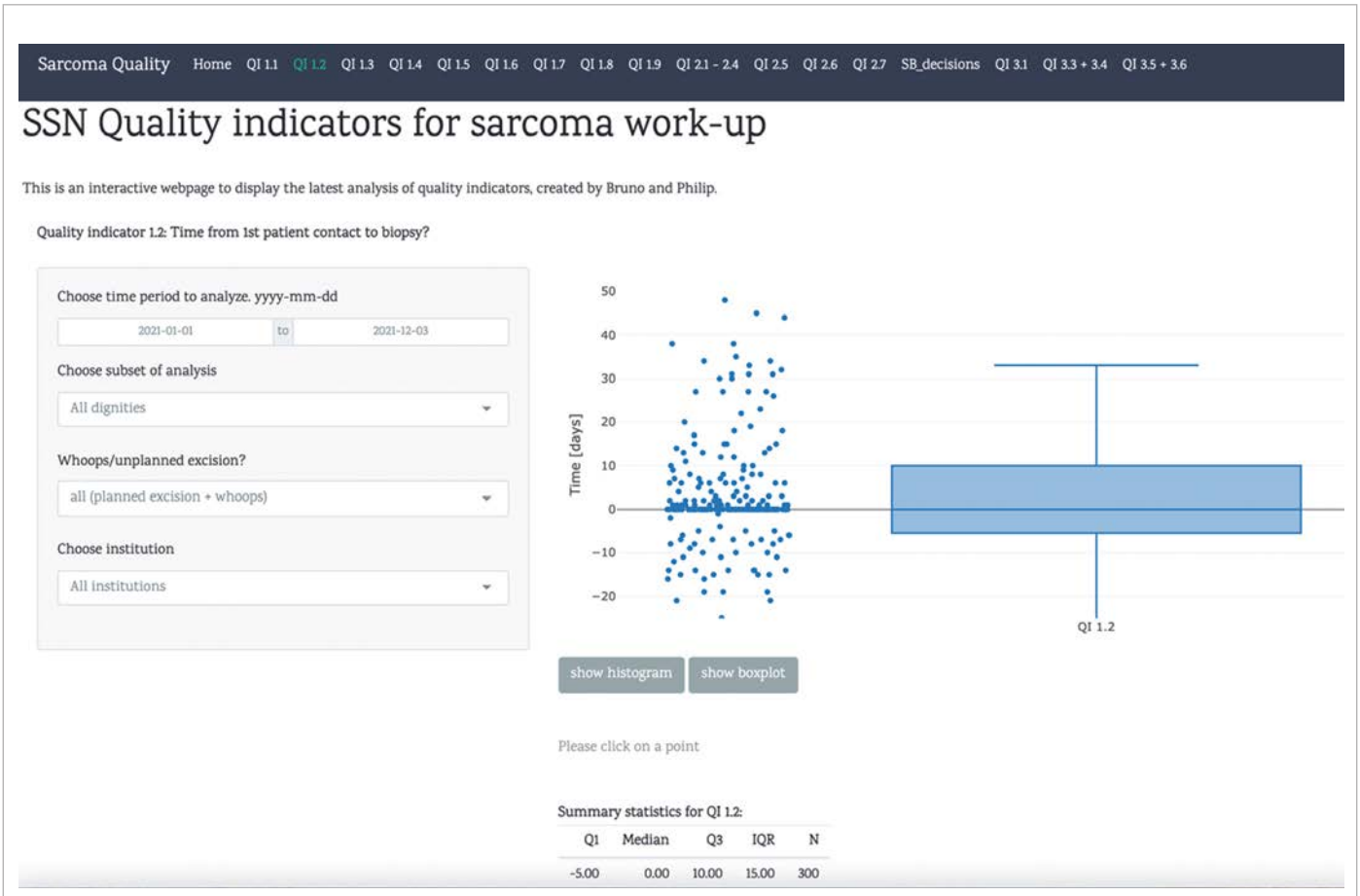


Abb. 1: Ein Auszug der IAW, auf der der QI Work-up «Zeit vom ersten Patienten Kontakt bis zur Biopsie?» dargestellt wird. Im Cockpit links können spezifische Parameter bestimmt werden, woraufhin sich rechts zeitgleich die Diagramm Analyse zeigt.

IT Platform und interaktive Frontside-Website

Eine integrierte IT-Plattform zur Erfassung von strukturierten Daten bildet die Grundvoraussetzung, um RTWD unabhängig von der Geografie und gleichzeitig aus mehreren Institutionen abzubilden. Das SSN kooperiert mit Adjumed Services Zurich, ein digitaler Anbieter mit jahrzehntelanger Erfahrung, der die Standards der Datensicherheit erfüllen und verantworten kann. Das AdjumedCollect bildet die Basis, aufgrund derer die Analysen auf einer interaktiven Website (IAW) abgebildet werden können. Unter einer IAW verstehen wir eine Website, auf der der Sarkom Experte eine Auswahl von definierten Parametern betreffend eines spezifischen Kollektivs frei wählen kann und sich die entsprechende Grafik der korrespondierenden Datenanalyse im Form eines Diagrammes sofort darstellt, mit direktem Zugang zu den Rohdaten zur Kontrolle und Überprüfung (Abb. 1).

Um die Korrektheit der Daten zu überprüfen, wurde eine IAW für fehlende Daten konstruiert. Damit können potentiell fehlende Daten sofort identifiziert und komplettiert werden. Das Herzstück bildet die IAW für die oben aufgeführten Qualitätsindikatoren. Hierbei können auf Knopfdruck deskriptive Analysen von Qualitätsindikatoren eines Kollektivs nach Zeitperiode, nach Dignität, Diagnose, anatomische Lokalisation, Erst- und follow-up Vorstellung, geplante versus ungeplante Resektionen sowie nach Institutionen dargestellt werden. Eine weitere IAW wird für die Kostenerfassung erstellt. Hierbei kann für jede Intervention und z.B. MDT-SB Vorstellung ein «Kostenschild» zugeordnet werden, wodurch die effektiven Kosten für die medizinische Leistung für jeden einzelnen Patienten über den gesamten Behandlungszyklus ermittelt werden können. Zudem wurde eine IAW für PROMS/PREMS erstellt, auf der aktuell insgesamt 9 Fragebogen digital erfasst sind und welche die Patienten z.B. vorgängig zu einer Konsultation auf einem iPad ausfüllen können. Mittlerweile verwenden wir diese routinemässig im Alltag und erfassen alle konsekutiven Patienten. Eine weitere IAW wurde aufgebaut, auf der ein Cockpit erlaubt, eine RTWD Darstellung der PROMS z.B. in Form eines Radar charts direkt zu visualisieren. Selbstverständlich sind alle diese Information mit den Daten des SwissSarcoma-Registry verknüpft, sodass eine holistische Analyse mit allen klinischen metrischen Parametern verknüpft erfolgen kann.

Erwartungen

Die konsekutive, transparente Erfassung eines kompletten Kollektivs von Sarkom Patienten in Form von strukturierten Daten von Qualitätsindikatoren longitudinal über den gesamten Behandlungsverlauf in Echtzeit eröffnet bisher unvorstellbare Möglichkeiten. Diese erlauben, die verschiedenen Abklärungs- und Behandlungsarten in absoluter Zahl zu erfassen, wodurch die Wertigkeit einer Therapie bezogen auf den einzelnen Patienten erstmals definiert und zudem finanziell in Relation zur Behandlungsqualität ausgewiesen werden kann. Dies wird nicht-optimale oder unnötige Behandlungen eliminieren und die Qualität der Behandlung zu definierten Kosten verbessern.

Strukturierte Daten der Behandlung von Sarkompatienten bilden die Grundlage für eine prädiktive Analyse. Mit Hilfe von Machine Learning Algorithmen sowie statistischen Methoden erlauben sie im Kollektiv grundsätzlich eine Aussage betreffend Prognose für einen einzelnen Patienten. Darüber hinaus wird es möglich sein, für jeden Einzelfall Analysen einzelner Therapieschritte zu generieren und aufgrund derer den bestmöglichen Therapieweg für den einzelnen Patienten gezielt auszuwählen. Darauf wird schlussendlich die personalisierte Medizin begründet werden können.

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Take-Home Message

- Eine RTWD-interaktive Analyse und Monitoring der Qualität der Behandlung von Sarkompatienten ist für alle zugänglich, die bereit sind, Daten zu teilen. Eine solche Datengrundlage bildet die Basis für prognostische und prädiktive Outcome Analysen, welche in naher Zukunft für Sarkompatienten die «precision medicine» Realität werden lässt.

Anmerkung des Chefredaktors

Im auch für seltene Tumorentitäten föderalen Schweizer Gesundheitssystem muss erwähnt werden, dass angestrebte nationale Zusammenschlüsse nicht immer vollständig gelingen. Im hier vorliegenden Fall ist es leider so. Dies erschwert gerade repräsentative Datenerfassungen. Der Vollständigkeit halber seien weitere überregionale Sarkom-Netzwerke für mögliche fachliche Vernetzungen erwähnt:

- Sarcoma Medical Exchange (wöchentlicher Austausch von medizinischen Onkologen und Onkologinnen)
- University Sarcoma Network
- SAKK Sarcoma Working Group

POLITICS 15-12-2023

The SwissSarcomaNetwork

Pioneering Precision Medicine: Benchmarking RWT-Evidence-Based Insights to Revolutionize Sarcoma Care – the SwissSarcomaNetwork (SSN)

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Precision medicine offers personalized and targeted treatment strategies in healthcare. However, the roadmap to realizing precision medicine remains largely unclear. There are multiple challenges in today's healthcare environment, such as optimal collaboration among various disciplines, organizations in networks versus centralization efforts, digital transformation, process efficiency, quality issues and costs.

Implementing precision medicine requires a systematic approach and the integration of various components. By following the roadmap as presented herein, healthcare professionals can enhance care quality, optimize patient outcomes, and provide personalized treatment plans. The integration of data-driven methodologies and the development of the patient digital twin hold great promise for improved patient experiences and better long-term outcomes in medical care.

Surgeons historically played a pivotal role in driving medical innovations, with their advancements subsequently being adopted across the field of medicine. In case of sarcoma surgery, a multidisciplinary and intricate approach is essential to achieve optimal outcomes. The collaboration and coordination of various disciplines are crucial not only for surgical procedures but for all aspects of sarcoma care. This integrated approach holds immense significance in defining precision medicine. By embracing a comprehensive team-based approach, the transdisciplinary sarcoma surgery-based philosophy can pave the way for advancements in the overall care and treatment of sarcoma patients, pushing the boundaries of what is currently possible. The innovations and breakthroughs emerging from sarcoma surgery may set the stage for the next level of development in sarcoma care, benefiting patients by providing more precise and effective interventions and care. The SwissSarcomaNetwork (SSN) focuses on the sustainable health care triad and specifically on the quality of sarcoma care. This article aims to provide a concise roadmap for implementing precision medicine, addressing the main goal of providing personalized treatment. For each step of the roadmap, a brief note is included on the current SSN achievements.

1. Start of the process

The journey to enhance sarcoma care begins by recognizing the importance of data-driven approaches and adopting a systematic methodology. Multidisciplinary teams comprising healthcare professionals, data scientists, and technology experts collaborate to develop a comprehensive framework that encompasses the entire care process, from data collection to personalized treatment planning. This framework integrates data collection, storage, interoperability, analysis, benchmarking, assessment, value-based evaluation, and iterative improvement. It aligns the goals of sarcoma patients and healthcare providers. The framework outlines strategies for collecting real-world-time data, including measures and quality indicators from various sources. Thereby, the roadmap optimizes sarcoma care through data-driven approaches, collaboration, and iterative improvement (Figure 1).

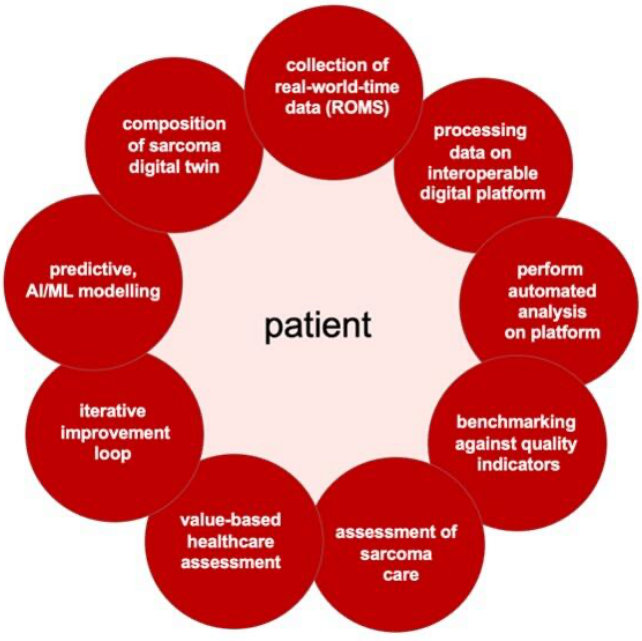


Figure 1: The roadmap to realize precision medicine: Real-world-time data, value-based benchmarking and digital twinning represent the key driver to realize precision medicine in sarcoma care.

2. Collection of Real-World-Time Data

Data collection in sarcoma care involves gathering real-world-time data from multiple sources to gain a comprehensive understanding of the longitudinal care journey. This process encompasses Clinical-Reported Outcome Measures (CROMS), which provide objective clinical indicators recorded by healthcare professionally, such as patients' medical condition, treatment progress, and health outcomes. Patient-Reported Outcome Measures (PROMS) and Patient-Reported Experience (PREMS) capture subjective experiences, including quality of life, symptoms, functional abilities, and satisfaction with care. Holistically, it also involves DROMS (Diagnostic-Reported Outcome Measures), IROMS (Imaging-Reported Outcome Measures), FROMS (Functional-Reported Outcome Measures), SROMS (Safety-Reported Outcome Measures), and EROMS (Economic-Reported Outcome Measures).

Various sources are utilized to collect this diverse data, including electronic health records (EHR), surveys, interviews and focus groups. EHR provide comprehensive information on patients' medical history, treatments, and outcomes. Surveys enable the gathering of additional patient-reported data, focusing on specific aspects of sarcoma care. Interviews and focus groups allow for in-depth qualitative data collection, providing with an opportunity to express their experiences and perspectives. By incorporating data from these different sources, the data collection process ensures a holistic representation of the sarcoma care journey. Such comprehensive evaluation approach allows healthcare professionals to assess both the medical outcomes and the patients' experiences, needs, and satisfaction.

SSN has defined a set of some 500 parameters designed to assess the quality of sarcoma care. These include physician- as well as patient-based information and are collected from daily routine processes. Specifically, SSN published on the Sarcoma-specific instrument to longitudinally assess health-related outcomes of the routine care cycle.

3. Processing Data on an Interoperable Digital Platform (such as Sarconnector)

The use of an interoperable digital platform is crucial for securely storing and managing data in sarcoma care. This platform offers advantages in terms of data integration, accessibility, and analysis. It enables seamless integration of data from various sources, ensuring compatibility across different systems. Healthcare professionals can easily access and retrieve relevant data, promoting collaboration and evidence-based decision-making. The platform also supports effective data management, facilitating the processing of large and complex datasets. It provides tools for efficient data storage, organization, and retrieval, allowing healthcare professionals to navigate and analyze effectively (within a so-called data management ecosystem including data registry, data warehouse and data lake). Additionally, the platform serves as a foundation for subsequent analyses, incorporating advanced analytics techniques to uncover patterns and correlations within the data management ecosystem. Data security is prioritized through encryption, access controls, and adherence to privacy regulations. By leveraging an interoperable digital platform, healthcare professionals can efficiently access, manage, and analyze data, leading to improved decision-making and advancements in sarcoma care.

SSN has introduced the Sarconnector, an interoperable digital platform which allows harmonized data assessment from various sources to include all data dimensions.

4. Performing Automated Analysis on the Interoperable Digital Platform

Once sarcoma care data is securely stored on the interoperable digital platform, automated analysis becomes crucial. It utilizes tools and algorithms for statistical analysis, data mining, and machine learning. Statistical analysis uncovers patterns and trends, summarizing data characteristics and making predictions. Data mining techniques extract valuable insights from large data sets, revealing hidden patterns and anomalies. Machine learning algorithms learn from data to make predictions and optimize treatment decisions. Automated analysis empowers data-driven decisions, improving care strategies and patient outcomes. It uncovers associations between treatments and outcomes, identifies non-adherence factors, and enhances patient experiences. By continuously evaluating and refining practices, healthcare professionals deliver effective and patient-centered care. Therefore, automated analysis reveals insights, supports decision-making, and improves sarcoma care outcomes.

SSN's Sarconnector is designed to synthesize meta-level data to integrate both descriptive, inferential, non-/parametric and Bayesian statistics, with its main focus on exploratory data analysis and its visualization.

5. Benchmarking against quality indicators

Benchmarking against quality indicators is essential for evaluating the effectiveness of sarcoma care. It involves comparing analyzed data against predefined standards specific to sarcoma care. These indicators provide measurable criteria for assessing healthcare performance and identifying areas of improvements.

Survival rates are crucial metrics that reflect treatment effectiveness and patient outcomes, recurrence rates indicate treatment success and the likelihood of cancer returning. Adherence to treatment guidelines evaluates the consistency of care delivery. Patient satisfaction scores capture subjective experiences and preferences, guiding improvements in care. Additional quality indicators include evidence-based practices, safety protocols, multidisciplinary care teams, follow-up care, and patient-centered principles. The choice depends on organizational goals and priorities.

Benchmarking allows healthcare professionals to assess their performance objectively and identify areas for improvement. It provides a quantitative assessment, highlighting specific aspects where standards may not be met. Furthermore, benchmarking facilitates learning from high-performing professionals and organizations. Analyzing their data reveals effective strategies and interventions, enabling others to enhance their care processes and outcomes. Benchmarking therefore is critically important for sarcoma care as it promotes continuous quality improvement. It empowers professionals to evaluate performance, implement interventions, and optimizes care delivery. By striving for excellence, sarcoma patients receive the highest quality care available.

SSN has introduced benchmarking by assessing a multilayer outcome to compare results from one's own practices, processes, or outcomes to those of other organizations or practices in the same field, both nationally and internationally.

6. Assessment of Sarcoma Care

The assessment of sarcoma quality care involves evaluating various dimensions of care, including clinical outcomes, patient experiences, adherence to quality indicators, and relevant parameters. Clinical outcomes, such as survival rates and treatment responses, assess the effectiveness of interventions. Patient experiences, captured through PROMs and PREMs, provide insights into care satisfactions and patient centeredness. Adherence to quality indicators ensures evidence-based practices are followed. Safety measures, coordination of care, and communication are additional considerations. This assessment helps identify areas of improvement and strengths, guiding interventions and resource allocation. It promotes continuous learning and collaboration among healthcare professionals, facilitating knowledge exchange and improvement in sarcoma care. By prioritizing interventions based on assessment findings, healthcare professionals can enhance patient outcomes and experiences. The assessment contributes to overall knowledge and the development of best practices within the field. We expect from the assessment of sarcoma quality care to evaluate clinical outcomes, patient experiences, adherence to quality indicators, and relevant parameters. It guides improvement initiatives, fosters collaboration, and drives continuous enhancement in sarcoma care.

SSN introduced the quality indicators of sarcoma care together with an international advisory board of world-renowned sarcoma experts.



Figure 2: Gelebte Interdisziplinarität: Sarkomchirurge, Thoraxchirurge, Wirbelsäulenchirurge und intraoperative Navigation arbeiten Hand in Hand.

7. Value-based Healthcare Assessment

Value-based healthcare assessment evaluates sarcoma care by considering effectiveness, efficiency, and patient-centeredness. Metrics like cost-effectiveness, patient-reported value, and quality-adjusted life years (QALYs) are used to optimize value. Effectiveness measures outcomes achieved, such as survival rates and patient well-being, to identify best interventions. Efficiency assesses resource utilization in relation to outcomes, using cost-effectiveness analysis to guide resource allocation. Patient centeredness tailors care to individual needs, with patient-reported value capturing satisfaction and quality of life. QALYs measure quantity and quality of life gained through interventions, aiding decision-making. Other metrics like patient-reported outcomes and satisfaction scores provide additional insights. Value-based healthcare assessment aims to optimize value in sarcoma care, ensuring resources are allocated for maximum effectiveness, efficiency, and patient-centeredness. By integrating this assessment, healthcare professionals prioritize interventions that deliver the greatest value, leading to improved patient outcomes and experiences.

SSN has defined a value-based healthcare delivery model for sarcoma patients, and is able to correlate the clinical care efforts with financial expenses by use of the interoperable digital platform, the so-called Sarconnector.

8. Iterative Improvement Loop

The iterative improvements loop is crucial of enhancing sarcoma care based on assessment findings. It involves analyzing assessment results, identifying areas for improvement, and implementing targeted interventions to drive ongoing improvements in clinical outcomes, patient experience, and value delivered. After conducting the assessment, the healthcare team carefully reviews the findings and identifies opportunities for enhancement. Targeted interventions are then developed and implemented within the care process, such as changes to protocols, treatment pathways, patient education, coordination of care, or the adoption of new technologies. Feedback loops are established to monitor the impact of interventions, allowing healthcare professionals to assess effectiveness and make data-driven decisions, adjustments and refinements in sarcoma care, adapting to changing needs and best practices. By continuously refining the care process, healthcare professionals strive to provide the best possible care for sarcoma patients, enhancing outcomes and patient experience while optimizing value delivered.

SSN has established the Sarcoma Academy (www.sarcoma.academy), an international webinar forum for global exchange. This enables an up-to-date input from world-renowned experts of sarcoma care, and the potential to harmonize and share data on the global stage.

9. Predictive AI/ML Modelling

Predictive artificial intelligence (AI) and machine learning (ML) modeling techniques offer valuable insights and decision-making support. These techniques use real-world-time data to develop predictive models that forecast outcomes, identify high-risk patients, and guide treatment decisions.

Predictive AI/ML modeling involves training algorithms on historical data to identify patterns and make predictions or classifications. In sarcoma care, various techniques like decision trees, logistic regression, support vector machines, and deep learning algorithms can be employed.

-*Forecasting future outcomes:* by analyzing collected data, models can identify patterns contributing to disease progression, treatment response, or survival rates. This enables healthcare professionals to anticipate outcomes and plan interventions accordingly. For instance, predicting sarcoma recurrence allows monitoring high-risk patients closely and adjusting treatment plans.

-*identifying high-risk patients:* Models analyze data to pinpoint patients at greater risk of poor outcomes or complications. Healthcare professionals can prioritize resources and intervention for these patients, providing targeted care. Models can predict treatment-related side effects, allowing tailored supportive care.

-*enhancing personalized treatment decisions:* Analyzing patient-specific data like clinical characteristics and genetic profiles enables the identification of suitable treatment options. Tailoring interventions to individual patients improves effectiveness.

-*uncovering hidden patterns:* Insights on risk factors and treatment modalities associated with better outcomes inform care plans and resource allocation, thereby empowering healthcare professionals to optimize care delivery.

SSN's Sarconnector includes currently a 5-year follow-up of patients, which paves the way for outcome studies. A current project for example identifies risk factors to develop Clavien-Dindo complications after sarcoma surgery.

10. Composing sarcoma Digital Twin

Over time, as more data is collected and analyzed, a digital twin of sarcoma care is created. This digital twin is a virtual replica of an individual patient that simulates the behavior of the care process. It incorporates the insights gained from predictive modeling and integrates patient-specific data, enabling the generation of personalized treatment plans. The digital twin serves as a powerful tool to optimize care, providing a platform for experimentation, scenario analysis, and continuous learning. It allows healthcare professionals to simulate the impact of different interventions, refine treatment strategies, and ultimately improve patient outcomes.

The digital twin allows physicians to simulate the impact of interventions, test various treatment options, and refine strategies to achieve optimal patient outcomes. It facilitates evidence-based decision-making and continuous learning, leading to improved care delivery. For patients, the digital twin offers personalized treatment based on individual characteristics and preferences. By incorporating patient-specific data such as treatment response, the digital twin tailors interventions to meet specific needs, enhancing precision and effectiveness of care. Patients thereby actively participate in decision-making, explore different treatment options, and understand potential outcomes. The digital twin empowers patients, improves treatment outcomes, and increases engagement in the care process.

Conclusions

The integration of real-world-time data, interoperable digital platforms, automated analysis, benchmarking, assessment, value-based healthcare evaluation, iterative improvement loops, predictive AI/ML modeling, and the creation of a sarcoma digital twin offer tremendous opportunities to advance sarcoma care. By embracing these steps, healthcare professionals can enhance the quality and effectiveness of care, optimize patient outcomes, and provide personalized treatment plans. Through continuous refinements and the application of data-driven methodologies, the future of sarcoma care holds great promise for improved patient experiences and ultimately better long-term outcomes.

SSN has established the basic requirements to realize precision care for sarcoma patients.

Further reading:

Heesen *et al.*
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Diagnostic and Prognostic Research

REVIEW

Open Access

Clinical prognostic models for sarcomas: a systematic review and critical appraisal of development and validation studies

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Abstract

Background Current clinical guidelines recommend the use of clinical prognostic models (CPMs) for therapeutic decision-making in sarcoma patients. However, the number and quality of developed and externally validated CPMs is unknown. Therefore, we aimed to describe and critically assess CPMs for sarcomas.

Methods We performed a systematic review including all studies describing the development and/or external validation of a CPM for sarcomas. We searched the databases MEDLINE, EMBASE, Cochrane Central, and Scopus from inception until June 7th, 2022. The risk of bias was assessed using the prediction model risk of bias assessment tool (PROBAST).

Results Seven thousand six hundred fifty-six records were screened, of which 145 studies were eventually included, developing 182 and externally validating 59 CPMs. The most frequently modeled type of sarcoma was osteosarcoma (43/182; 23.6%), and the most frequently predicted outcome was overall survival (81/182; 44.5%). The most used predictors were the patient's age (133/182; 73.1%) and tumor size (116/182; 63.7%). Univariable screening was used in 137 (75.3%) CPMs, and only 7 (3.9%) CPMs were developed using pre-specified predictors based on clinical knowledge or literature. The median c-statistic on the development dataset was 0.74 (interquartile range [IQR] 0.71, 0.78). Calibration was reported for 142 CPMs (142/182; 78.0%). The median c-statistic of external validations was 0.72 (IQR 0.68–0.75). Calibration was reported for 46 out of 59 (78.0%) externally validated CPMs. We found 169 out of 241 (70.1%) CPMs to be at high risk of bias, mostly due to the high risk of bias in the analysis domain.

Discussion While various CPMs for sarcomas have been developed, the clinical utility of most of them is hindered by a high risk of bias and limited external validation. Future research should prioritise validating and updating existing well-developed CPMs over developing new ones to ensure reliable prognostic tools.

Trial registration PROSPERO CRD42022335222.

Keywords Sarcoma, Bone neoplasms, Soft tissue neoplasms, Prognosis, Nomograms

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Background

Sarcomas are a diverse group of malignant soft-tissue or bone tumors arising from mesenchymal tissue, classified as a rare disease with an estimated incidence of 5 cases per 100,000 [1, 2]. While sarcomas only make up 0.9% of adult cancers, they account for 15–20% of childhood cancers diagnosed in the USA [2, 3]. The 5-year survival rate is about 70%, but greatly depends on patient-specific and tumor-specific factors and can be as low as 16.7% in patients with metastasis [3, 4]. The Surveillance, Epidemiology, and End Result Program (SEER) estimates 13,590 new cases in the USA in 2024 with 5200 estimated deaths [3]. Due to their rarity, heterogeneous nature, and poorly predictable clinical course, the clinical management of sarcomas remains challenging. Notably, the survival probabilities of sarcoma patients vary between and within different sarcoma subtypes. For example, it has been shown that the 5-year overall survival (OS) rate of synovial sarcoma patients differs between genders, with a rate of 35.6% for males and a rate of 68.7% for females [5].

Clinical prognostic models (CPMs) may enable more precise outcome prediction and allow for risk-stratified clinical decision-making in patients with sarcomas [6, 7]. The current ESMO-EURACAN-GENTURIS clinical practice guideline published by the European Society of Medical Oncology (ESMO) states that risk-predicting tools have identified a threshold of risk (< 60% 10-year OS) above which the administration of chemotherapy may provide statistically and clinically significant benefits and thereby recommend the use of such prediction models [7].

While the high predictive performance of a CPM does not necessarily improve therapeutic decision-making, the accuracy and performance of a CPM are essential when considering implementing a CPM in routine clinical practice. To ensure that CMPs are transportable from the development cohort to a different cohort of patients, e.g. in a different country, the use of high methodological standards for development and rigorous external validation are essential. However, a systematic review assessing the risk of bias in prediction models developed using supervised machine learning showed that most included studies used poor methodology and are at high risk of bias [8, 9]. A major contributing factor to the high risk of bias was a small sample size and too few events during the development phase [9]. Complexities of the collected data such as censoring were rarely accounted for in those models [9]. Moreover, more than half of the included models were not adequately reported and are therefore not available for independent validation [9]. These results were corroborated by a systematic review of prediction models for patients with chronic lymphocytic leukemia in which poor reporting standards and a high risk of bias were found for all included CPMs [10].

While various CPMs for sarcomas have been published over the past years, only a minority (e.g. "Sarculator" and "PERSARC") are used in clinical practice. This may be largely due to a lack of knowledge of the performance of developed CPMs and the number of external validations of these CPMs.

Therefore, the aims of this systematic review were to systematically review and critically assess the CPM landscape in the field of sarcomas.

Methods

This systematic review reported the following aspects of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11]. This study was registered in PROSPERO on August 12th, 2022 (CRD42022335222).

Information sources and search strategy

We performed a literature search in Medline, EMBASE, Cochrane Central and Scopus on June 7th, 2022. No filters, date or language restrictions were applied. The search strategy was developed and conducted by an information specialist and details about the literature search are presented in the Supplementary Table S1.

Eligibility criteria

We included CPM studies for any kind of sarcoma that were developed or validated on cohort studies, randomised controlled trials, nested case–control studies, case-cohort studies, databases, or registries [12]. A CPM was defined as a prognostic model that includes only predictors readily available in clinical practice (e.g. patient's sex, patient's age, tumor size, tumor grade). Therefore, studies that developed or validated prognostic models that included pathological, biological or radiological variables not commonly used in clinical practice were excluded. The decision about which predictors are commonly available in clinical practice was independently made by two reviewers and the discrepancy was resolved by discussion or involvement of a third reviewer. According to Riley et al., a random split of the development dataset is not considered a true external validation [13]. Therefore, we defined that models whose performance was evaluated using a random split technique were only internally validated. Table 1 presents the PICOTS format used for eligibility assessment.

Study selection, data collection process and analysis

After the literature search, studies were de-duplicated using Endnote 20 and then imported into Rayyan [14]. The abstract screening was conducted on Rayyan [14],

Table 1 PICOTS format used for eligibility assessment

PICOTS framework	Eligibility criteria for this systematic review
P—Participants	Patients with a histological diagnosis of soft tissue or bone sarcoma
I—Index models	All clinical prognostic models predict overall survival, event-free survival, progression-free survival, disease-specific survival/sarcoma-specific survival, progression of disease, local recurrence rate, systemic recurrence rate and development of metastasis
C—Comparator	Not applicable because we aim to identify all models that were developed and/or validated for sarcomas
O—Outcome	Overall survival, event-free survival, progression-free survival, disease-specific survival/sarcoma-specific survival, progression of the disease, local recurrence rate, systemic recurrence rate and development of metastasis
T—Timing	Any timing starting with the date of pathologically established diagnosis
S—Setting	Any setting

subsequently followed by full-text screening. Data were extracted using Microsoft Excel. Title screening, data extraction and risk of bias assessment were done independently and in duplicate (PH, SMC). Discrepancies were resolved by discussion or by consultation of a third reviewer (BF, OCC). The collected variables are presented in Supplementary Table S5. For discrimination, the c-index and area under the receiver operating characteristic curve (AUC) were combined and are jointly referred to as AUC in this manuscript. The risk of bias of each developed and/or validated CPM was assessed using the prediction model risk of bias assessment tool (PROBAST) [15]. PROBAST assesses the risk of bias over four domains: participant selection, predictors, outcomes, and analysis. If at least two questions of one domain were rated as "probably no" or "no", the whole domain was rated to be at high risk of bias. If at least two questions of one domain were rated as "No information", the whole domain was rated to be of unclear risk of bias. Each domain is rated to be of low, high or unclear risk of bias. When investigators assessed more than one domain to be of high risk of bias, the whole study was ranked to be of high risk of bias, irrespective of the other two domains being of unclear or low risk of bias. At the time of writing this review, no complete guidance on the application of the GRADE system for CPM development/validation studies was published. Therefore, no GRADE assessment was conducted for this review. We qualitatively summarised the results of this review using descriptive statistics. Data were analyzed using R Statistical Software (version 4.3.1) [16].

Results

After deduplication, we retrieved 7656 records. After the abstract screening, 181 full-text articles were assessed for eligibility. Of those, 31 were excluded because the study population included non-sarcoma patients. Five studies were excluded since some of the variables that were included in the CPM were judged to not be available in routine clinical practice. A total of 145 studies developing 182 CPMs and externally validating 59 CPMs were included. Figure 1 presents the flow diagram for study selection.

Datasets for CPM development

One hundred seventy models (170/182; 93.4%) were developed using retrospective data, 10 models (10/182; 5.5%) were developed on prospectively collected data and 2 models (2/182; 1.1%) were developed using a combination of retrospectively and prospectively collected data. Most models (109/182, 59.9%) were developed using the Surveillance, Epidemiology, and End Results Program (SEER) dataset. Of the models not developed on the SEER dataset, single-institution datasets were used in the development of 50 models (50/182; 27.5%), multi-institutional datasets in 22 models (22/182; 12.1%), and one model (1/182; 0.5%) utilised data from the National Cancer Database. Only 15 (15/182; 8.2%) CPMs were developed on a multi-national dataset. None of the models developed on multi-institutional datasets accounted for clustering between institutions.

The median sample size was 635 (IQR 317.0–1110.5), but no study provided justification for the sample size. The median number of events was 201.5 (IQR 119.2–316.8), however, the number of events was not provided for 102 CPMs (102/182; 56.0%).

CPM development

In the development process of 135 models (135/182; 74.2%), continuous variables were categorised, with data-driven methods being the most common approach (47/182, 25.8%). Twelve models (12/182; 6.6%) included continuous predictors using restricted cubic splines as a method of modelling non-linear relationships between continuous variables and the outcome, while 28 models (28/182; 15.4%) included continuous predictors as linear

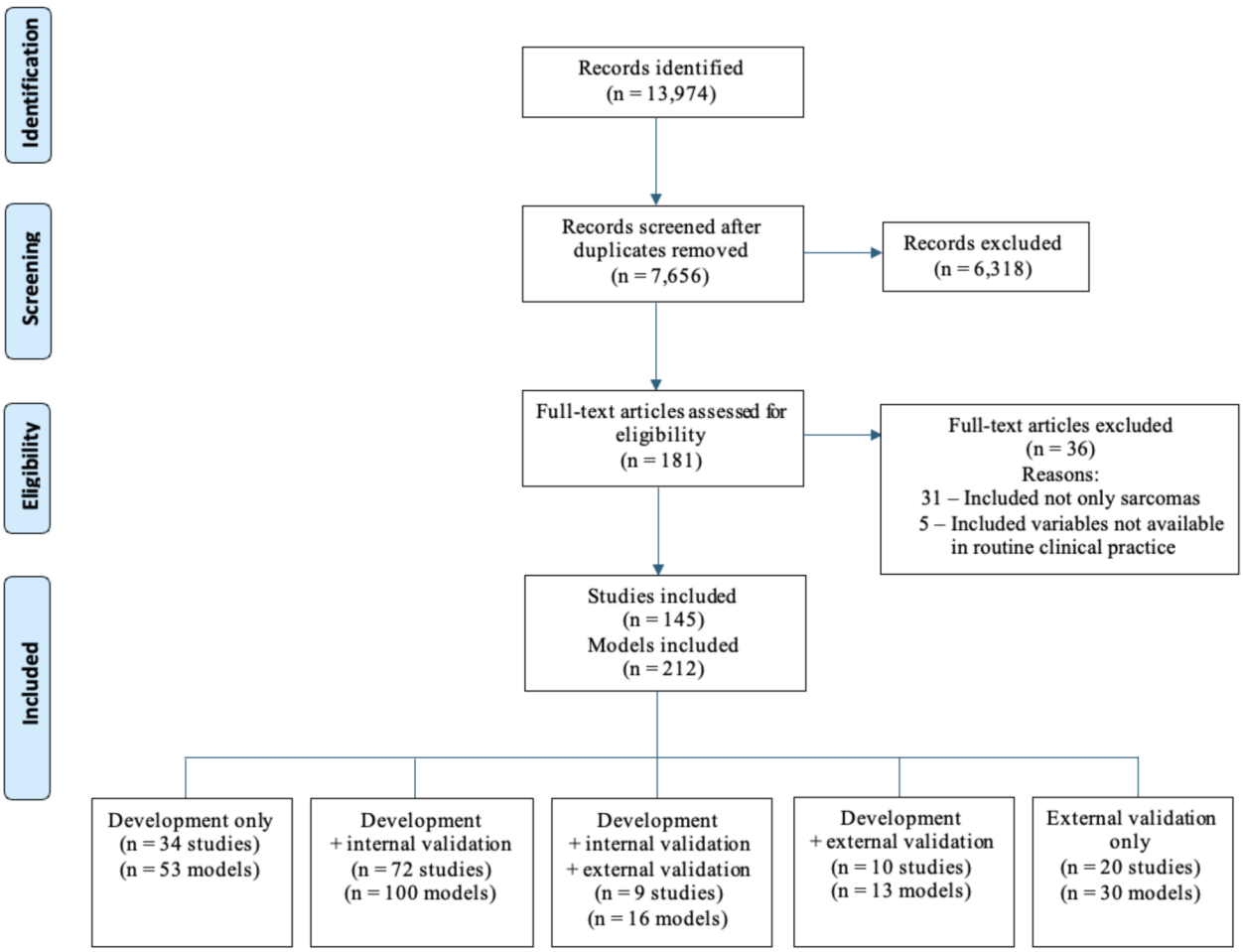


Fig. 1 Flow diagram of selected articles

variables. Table 2 describes the handling of missing data during the development and external validation of the included CPMs.

Table 3 describes the histological entities that CPMs were developed for, the predicted outcomes and included predictors. The median number of candidate predictors was 10.5 (IQR 8.8–13.0), though the number of candidate predictors was not available for 18 models (9.9%). The median number of events per variable was 20.0 (IQR 11.4–39.9), and the median number of predictors included in the final model was 5.0 (IQR 4.0–6.0). Supplementary Figure S1 presents a bar chart of the 10 most frequently considered and included predictors.

Cox proportional hazards regression (146/182, 80.2%) was the most widely used statistical model, followed by logistic regression (14/182, 7.7%) and the Fine and Gray competing risks model (12/182, 6.6%). Univariable selection of predictors was performed in 137 of 182 models (75.3%), multivariable selection without prior univariable selection in 11 models (11/182; 6.0%), and predictors

Table 2 Missing data handling during development and external validation

	Overall *N* = 241	Development only *n* = 182	External validation only *n* = 59
Missing data reporting			
None	178 (74.2%)	138 (75.8%)	40 (67.8%)
Overall	40 (16.7%)	32 (17.6%)	8 (13.6%)
Detail[a]	23 (9.6%)	12 (6.6%)	11 (18.6%)
Missing data method			
Complete case	161 (67.1%)	129 (70.9%)	32 (54.2%)
Multiple imputation	6 (2.5%)	6 (3.3%)	0
Unclear	73 (30.4%)	47 (25.8%)	27 (45.8%)
Assumed mechanism of missingness reported	1 (0.4%)	1 (0.5%)	0

[a] Missing data was provided for each variable

Table 3 Outcomes and predictors of included CPMs

	Overall $N = 241$	Development $n = 182$	External validation $n = 59$
Sarcoma entity			
Osteosarcoma	54 (22.4%)	46 (25.3%)	8 (13.6%)
Ewing sarcoma	29 (12.0%)	25 (13.7%)	4 (6.8%)
Soft-tissue sarcoma	61 (25.3%)	21 (11.5%)	40 (67.8%)
Chondrosarcoma	26 (10.8%)	19 (10.4%)	7 (11.9%)
Leiomyosarcoma	13 (5.4%)	13 (7.1%)	0 (0.0%)
Angiosarcoma	10 (4.1%)	10 (5.5%)	0 (0.0%)
Liposarcoma	8 (3.3%)	8 (4.4%)	0 (0.0%)
Rhabdomyosarcoma	7 (2.9%)	7 (3.8%)	0 (0.0%)
Outcomes			
Overall survival	101 (41.9%)	81 (44.5%)	20 (33.9%)
Cancer-specific survival	70 (29.0%)	56 (30.7%)	14 (23.7%)
Distant metastasis	14 (5.8%)	10 (5.5%)	4 (6.8%)
Local recurrence	10 (4.1%)	8 (4.4%)	2 (3.4%)
Disease-free survival	9 (3.7%)	4 (2.2%)	5 (8.5%)
Lung metastasis	3 (1.2%)	3 (1.6%)	0 (0.0%)
Metastasis-free survival	3 (1.2%)	3 (1.6%)	0 (0.0%)
Progression-free survival	3 (1.2%)	3 (1.6%)	0 (0.0%)
Other	28 (11.6%)	14 (7.7%)	14 (23.7%)
Ten most included predictors			
Age	179 (74.3%)	133 (73.1%)	46 (78.0%)
Size	149 (61.8%)	116 (63.7%)	36 (61.0%)
Grade	103 (42.7%)	71 (39.0%)	32 (54.2%)
Surgery	77 (32.0%)	69 (37.9%)	8 (13.6%)
Site	71 (29.5%)	58 (31.9%)	13 (22.0%)
Stage	61 (25.3%)	56 (30.8%)	5 (8.5%)
Sex	41 (17.0%)	34 (18.7%)	7 (11.9%)
Chemotherapy	39 (16.2%)	33 (18.1%)	6 (10.2%)
Histological type	63 (26.1%)	29 (15.9%)	34 (57.6%)
Race	24 (9.9%)	21 (11.5%)	3 (5.1%)

were pre-specified using expert opinion or literature in only 7 models (7/182; 3.9%).

No performance measure was reported for 9 (9/182; 5.0%) CPMs. A measure of discrimination was reported for 89.6% (163/182) of developed CPMs. The median reported AUC was 0.74 (IQR 0.71–0.78). Calibration was reported for 142 (142/182; 78.0%) CPMs and the only reported measure of the calibration was the calibration plot (142/142; 100%). DCA was only rarely reported (41/182; 22.5%).

CPM validation

Of 182 developed models, internal validation was performed for 116 models (63.7%). The most common form of internal validation was split sample (67/116; 57.8%), followed by bootstrapping (30/116; 25.9%), cross-validation (10/116; 8.6%) and a combined approach of split sample and bootstrapping (13/116; 11.2%). Forty-two (62.7%) of the 67 CPMs that were internally validated using a random split sample were classified as external validation by the authors of the respective studies.

Fifty-nine models (59/182; 32.4%) were externally validated, of which 29 models (29/59; 49.2%) were developed in the same study. Thirty models (30/59; 50.8%) were externally validated after their development was described in a previously published paper. Nine models (9/59; 15.3%) were externally validated based on prospectively collected data. Only 8 CPMS (8/59; 13.6%) were validated on a multi-national dataset. The median sample size was 307.0 (IQR 115.5–631.0).

Fifty-six out of 59 external validations (94.9%) reported at least one measure of discrimination. The median AUC of all external validations was 0.72 (IQR 0.68–0.75). Calibration was only reported for 46 out of 59 (78.0%)

externally validated CPMs. A DCA was only provided for 7 out of 59 (11.9%) external validations.

Risk of bias

Of the 241 evaluated models, 169 (70.1%) were at high risk of bias, 45 (18.7%) were at unclear risk of bias and only 27 models (11.2%) were at low risk of bias. A summary of the risk of bias for each dimension is presented in Fig. 2 and Supplementary Table S7.

Discussion

In this systematic review of CPMs for sarcomas, we identified 182 CPMs. Despite the abundance of available CPMs in the current literature, a considerably high proportion suffered from poor methodological conduct (70.8% had a high risk of bias), lack of independent external validation (67.6% of developed CPMs were not externally validated), inadequate reporting of performance and in particular calibration metrics (22.0% reported no calibration metric), lack of sample size calculation (none presented a sample size calculation) and inefficient handling of missing data (70.9% applied complete case analysis). The most common dataset was the SEER cancer dataset which hosts freely available cancer data maintained by the National Cancer Institute in the USA. This dataset encompasses roughly 48% of the total cancer population in the USA [17]. While this dataset contains a large number of observations, certain predictors are not reported in enough detail (such as pathological information or type of chemotherapy).

We found that only 32.4% of identified CPMs were externally validated. This is largely in line with a previous review of prognostic prediction models using machine learning in oncology where a proportion of 24% was found [9]. Furthermore, 62.7% of internal validations that used the random split-sample approach, were wrongly classified as external validations. However, external validations are a prerequisite for the use of a CPM in clinical practice [18]. As a CPM cannot be validated on every patient population (e.g. each individual geographical region), it has been argued that a validated CPM may not exist [19]. Nevertheless, external validations are indispensable to assess the transportability of a CPM [18, 20]. As we found that only a minority of CPMs were externally validated, future research should prioritise external validation over the development of CPMs. Published recommendations for the validation of CPMs should be followed [13, 18, 20–25].

Since prediction models are used to guide physicians and patients in making a joint decision about future therapy, the performance of a CPM needs to be rigorously evaluated [26]. However, we found that 5% of included CPMs did not report any performance measures. In 22% of the

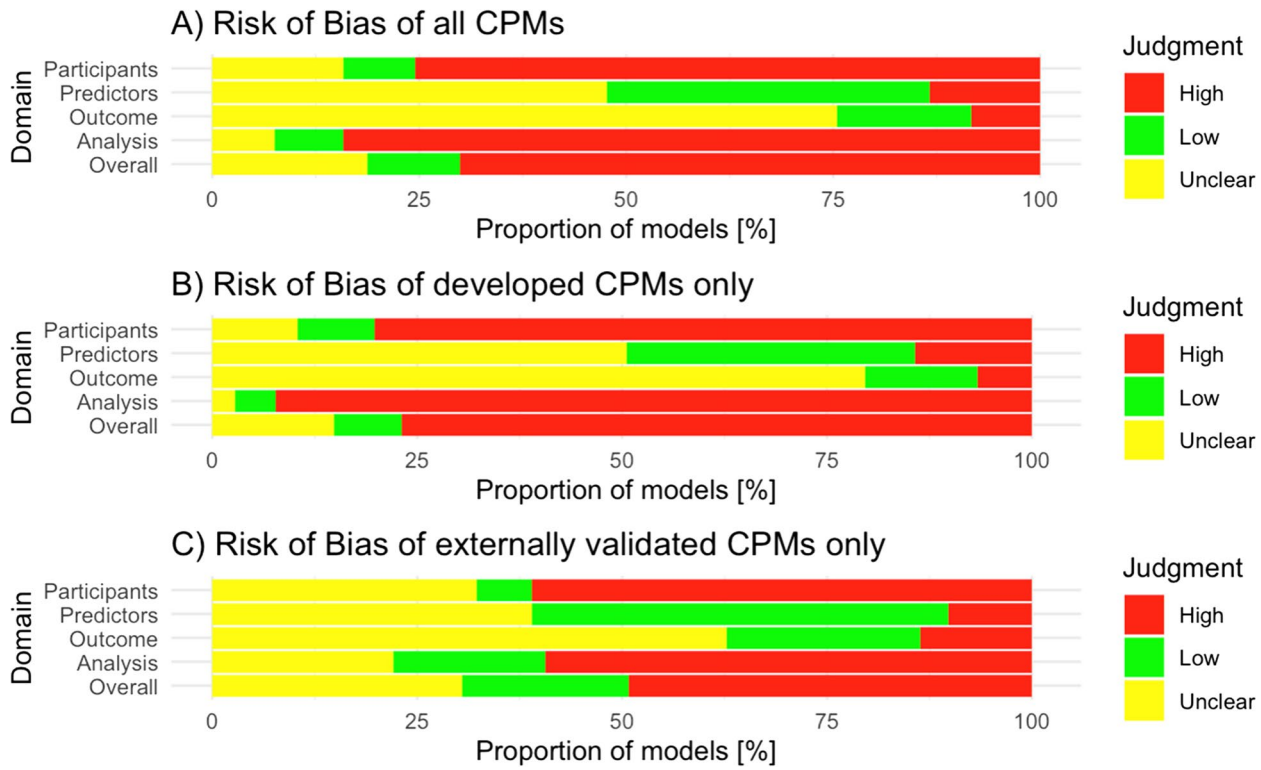


Fig. 2 Risk of Bias of all included CPMs (**A**), of all developed CPMs only (**B**), of all externally validated CPMs only (**C**)

included models, no metric of calibration was reported. This figure is higher than the number that has been reported in a systematic review of prognostic prediction models in oncology (7%) published in 2022 [9]. A potential explanation is that studies included in this systematic review might have adhered more closely to reporting guidelines. However, neither this study nor the study by Dhiman et al. assessed the adherence to a reporting guideline [9]. The reporting of calibration measures is important as the accuracy of the point-estimate of the predicted risk may have significant implications for treatment decisions and ultimately impact patient outcomes [27, 28].

None of the studies included in this review described an adequate sample size calculation prior to the development or external validation of their CPM. This finding is in line with the results from other systematic reviews that critically assessed the methodological conduct of prognostic modelling studies [29]. However, an adequate sample size during model development determines the stability of a CPM, while during model validation it influences the precision of estimates and width of confidence intervals of performance statistics [30]. Extensive guidance on sample size considerations for CPM development (Riley et al., 2019 [31, 32]) and external validation (Collins et al., 2015 [33]) has been published.

We found that the most frequently (70.9%) used method for handling missing data was complete case analysis. This is higher than reported in the previous systematic review of prognostic models for sarcomas [9]. The complete case approach is only valid when data can be assumed to be missing completely at random [34]. However, in the majority of cases, it is questionable whether this assumption is correct. Only one of the studies included in this review described the assumed mechanism of data missingness. The problem of poor handling of missing data in prediction modelling research has been described previously [35]. Missing data can lead to biased estimates of model parameters, resulting in inaccurate predictions, overfitting and eventually a low generalisability of the CPM [36]. Modern imputation methods may be used to mitigate the issue of missing data [37]. Sensitivity analyses should be conducted to quantify the effect of missing data and different imputation methods on predicted risks and performance of the CPM.

A model that was developed and subsequently validated on a multi-institutional and multi-national dataset will likely be more generalisable than a model developed on a dataset from a single institution [38]. In this systematic review, we found that 27.5% of CPMs were developed on a dataset from a single institution, only 8.2% were developed on a multi-national dataset, and only 13.6% were validated on a multi-national dataset.

To mitigate this issue, data harmonisation on an international level is necessary to be able to merge data from multiple institutions and multiple countries. The development of a unified dataset is also necessary as the rapid changes in the histopathological classification of sarcomas due to advances in molecular tumor research pose a particular challenge for data harmonisation. The use of different hospital information systems, storage of data in different databases and ultimately the big quest for data privacy further complicate international data sharing and migration.(38) In this respect, the use of federated learning may represent a viable solution that allows to development of a machine learning or classical statistical model without sharing patient data beyond their respective institution [38, 39]. Federated learning could thereby enable multi-institutional collaborations to develop and validate CPMs [38].

This systematic review has several limitations. Our literature search might have missed studies that did not mention the development or external validation of a CPM in the title or abstract of their manuscript. Furthermore, the literature search focused on the term "survival", "progression" and "recurrence". Therefore, studies of CPMs predicting other outcomes might have been missed. A scoping review during the specification of the literature search has shown that the vast majority of studies developing or validating a CPM for sarcomas focused on such an outcome which is the reason that the final literature search only included these search terms. As sarcomas are a group of cancers with an expected life expectancy of several years, short-term outcomes (such as time until discharge from hospital) might be less reported [40]. Moreover, some studies used a CPM to stratify patients into risk categories and reported the predicted as well as observed risk in their study group, thereby unintentionally performing an external validation of the respective CPM [41]. These studies are inherently difficult to identify because the use of a CPM for stratification might not have been mentioned in the title or abstract. Our search strategy was performed nearly 2 years ago and more CPMs for sarcomas have been published in the meantime. However, given the large amount of CPMs included in our review, including studies published after June 7, 2022 would likely not change our conclusions or recommendations.

In conclusion, we found that the majority (70.8%) of included models were at high risk of bias and suffered from poor methodological conduct. Therefore, use in routine clinical practice may not be recommended for most published CPMs of sarcomas. As most risk of bias stemmed from the analysis domain, researchers should consider published guidance on the development and external validation of CPMs. As only 32.4% of CPMs were externally validated, future research efforts should concentrate on the external validation of existing CPMs rather than on the development of new ones.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41512-025-00186-8.

Supplementary Material 1: Table S1. Search strategy in Cochrane Central.

Supplementary Material 2: Table S2. Search strategy in Embase.

Supplementary Material 3: Table S3. Search strategy in Medline.

Supplementary Material 4: Table S4. Search strategy in Scopus.

Supplementary Material 5: Table S5. Table of extracted variables.

Supplementary Material 6: Table S6. Table of included studies.

Supplementary Material 7: Table S7. Risk of Bias using the Prediction model Risk Of Bias Assessment Tool (PROBAST).

Supplementary Material 8: Figure S1. Bar chart of the (a) most considered and (b) included predictor variables.

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Authors' contributions
PH and BF conceptualised the study. PH, SMC, OCC and BF curated the data. PH and OCC did the formal analysis. PH, OCC and BF wrote the first draft of the manuscript and all authors were involved in the writing, reviewing, and editing of the manuscript. PH, OCC and BF accessed and verified the data. All authors had access to the data and had final responsibility for the decision to submit for publication.

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Competing interests
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Perspective

The Next Frontier in Sarcoma Care: Digital Health, AI, and the Quest for Precision Medicine

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Abstract: The landscape of sarcoma care is on the cusp of a transformative era, spurred by the convergence of digital health and artificial intelligence (AI). This perspectives article explores the multifaceted opportunities and challenges in leveraging these technologies for value-based, precision sarcoma care. We delineate the current state-of-the-art methodologies and technologies in sarcoma care and outline their practical implications for healthcare providers, administrators, and policymakers. The article also addresses the limitations of AI and digital health platforms, emphasizing the need for high-quality data and ethical considerations. We delineate the promise held by the synergy of digital health platforms and AI algorithms in enhancing data-driven decision-making, outcome analytics, and personalized treatment planning. The concept of a sarcoma digital twin serves as an illustrative paradigm for this integration, offering a comprehensive, patient-centric view of the healthcare journey. The paper concludes with proposals for future research aimed at advancing the field, including the need for randomized controlled trials or target trial emulations and studies focusing on ethical and economic aspects. While the road to this transformative care is laden with ethical, regulatory, and practical challenges, we believe that the potential benefits far outweigh the obstacles. We conclude with a call to action for multidisciplinary collaboration and systemic adoption of these technologies, underscoring the urgency to act now for the future betterment of sarcoma care and healthcare at large.

Keywords: digital health; artificial intelligence; value-based healthcare; sarcoma; precision medicine; benchmarking; interoperable platforms; quality indicators

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1. Introduction

Sarcoma, a rare and heterogenous group of malignant tumors originating from mesenchymal tissues, poses unique challenges for healthcare providers and patients alike. With over 100 subtypes and often complex clinical presentations, treating sarcoma requires a multidisciplinary, data-driven approach—an approach that modern healthcare is progressively leaning towards but has not yet fully realized [1–5]. In terms of the state of the art, recent advancements in genomics, targeted therapies, and immunotherapy have begun to reshape the landscape of sarcoma treatment. However, these advancements are often isolated in their impact, lacking a cohesive, data-driven strategy for implementation across healthcare systems. The integration of artificial intelligence (AI) and digital health platforms represents the next frontier in this context. These technologies have the potential to synthesize large and complex datasets, from genomic information to real-world-time patient outcomes, thereby enabling more precise and personalized care. This is particularly crucial for sarcoma, given its heterogeneity and the consequent need for highly individualized treatment plans. The dawn of precision medicine has ushered in an era

where treatment is personalized, not just to the disease but to the individual [6]. Yet, while the promise of precision medicine is substantial, its full realization is intricately tied to the evolution of healthcare systems towards value-based models, especially for complex conditions like sarcoma [7,8].

The notion of value-based healthcare (VBHC) emphasizes patient-centricity, focusing on metrics that matter most to the patient's well-being. This patient-centricity must be supported by robust, real-world-time data analytics that not only gauge the quality of care but also its cost-effectiveness [9,10]. Recent advancements in digital health technologies and AI have demonstrated unprecedented potential to empower this transition, offering an innovative toolkit for data collection, management, and predictive analytics [11–13].

However, the intersection of digital health and AI remains an underexplored terrain, especially in the context of sarcoma care [14]. This article aims to go beyond a mere review of existing technologies and methodologies. Instead, it seeks to offer a forward-looking perspective on how the confluence of these technologies could redefine the very essence of sarcoma care, contributing to a future where diagnosis is precise, treatment is personalized, and outcomes are continually optimized [15] (Figure 1).

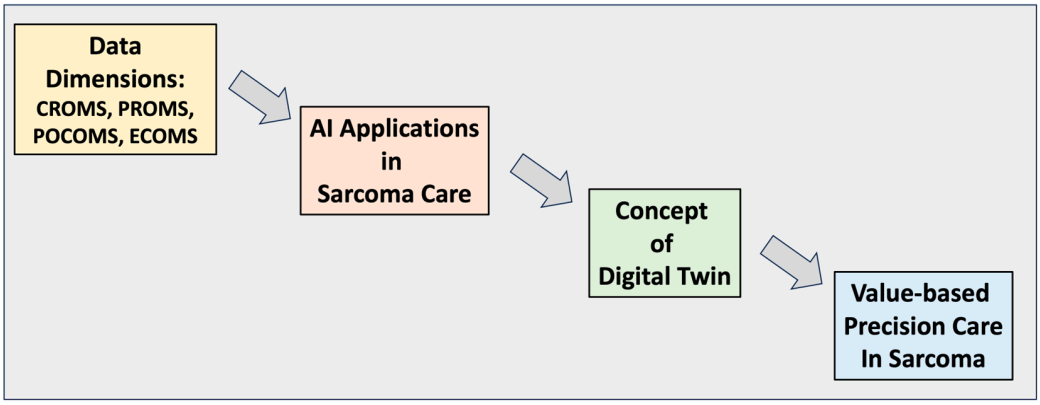


Figure 1. The figure depicts the evolution of sarcoma care, emphasizing patient-centricity and a data-driven approach. Digital health technologies, like Sarconector, form the foundation, streamlining patient data integration. Building on this, AI employs advanced algorithms to precisely characterize sarcoma subtypes and predict treatment outcomes. The pinnacle is the 'digital twin', a virtual patient profile that harnesses AI for predictive modeling and treatment optimization. CROMS = clinician-reported outcome measures; PROMS = patient-reported outcomes measures; POCOMS = patient-omics-centric outcome measures; ECOMS = economic measures.

In doing so, this article embarks on a visionary journey to explore the untapped potential of digital health and AI. It aims to serve as a catalyst for multidisciplinary dialogue and research, encouraging healthcare professionals, policymakers, and technologists to collaborate in transforming the future of sarcoma care—making it more precise, sustainable, and, above all, value-based.

2. The Vision for Value-Based Precision Care in Sarcoma

The pursuit of value-based healthcare is not merely a trend but a paradigm shift—one that brings the patient to the center of the healthcare universe [16]. In the context of sarcoma, a complex and rare malignancy, this transformation is not just aspirational but essential [15]. The heterogeneity of sarcoma, spanning multiple subtypes and clinical complexities, demands an individualized, outcomes-focused approach [17,18]. Traditional healthcare systems, largely built on a volume-based model, often fall short in providing the comprehensive, personalized care that sarcoma patients require. Value-based care in sarcoma envisions a healthcare ecosystem where every stakeholder, from surgeons and oncologists to data scientists and policymakers, collaborates to enhance the patient experience—from diagnosis to treatment and follow-up. It is an approach that goes beyond

the immediate clinical outcomes to consider the patient's quality of life, long-term well-being, and the economic sustainability of the care provided. In this envisioned ecosystem, treatment protocols are not rigid pathways but dynamic algorithms, constantly updated with real-world-time data and adapted to each patient's unique medical history, genomic profile, and even psychosocial needs [19–21].

This vision is not utopian; it is attainable. Emerging technologies in digital health, coupled with advances in artificial intelligence and machine learning, offer the tools needed to actualize this vision. Imagine a future where an interoperable digital platform integrates multi-dimensional data, from medical imaging to genomic sequencing and patient-reported outcomes. These data are then processed by sophisticated AI algorithms to provide actionable insights, ranging from predicting treatment responses to estimating healthcare costs [19,22]. Moreover, the continuous benchmarking against quality indicators ensures that the care provided is not just effective but continually optimized [22].

However, the transition from vision to reality entails overcoming significant barriers—technological, ethical, and institutional. The subsequent sections of this article delve into these challenges, offering a multi-faceted perspective on how the confluence of digital health and AI can serve as the linchpin in materializing the vision for value-based care in sarcoma.

3. Potential of Digital Health

Digital health stands as a cornerstone in the realization of value-based care, especially in the intricate landscape of sarcoma [23,24]. The advent of technologies such as interoperable Electronic Health Records (EHRs), telemedicine, and real-world-time data platforms has enabled healthcare systems to move beyond the siloed structures of the past [19,22]. These technologies permit the seamless integration of multi-dimensional patient data—from diagnostic imaging and laboratory results to patient-reported outcomes and follow-up care metrics [25]. The role of digital health in sarcoma care is not merely auxiliary; it is transformative. For instance, telemedicine has proven to be invaluable in providing specialized sarcoma care to patients in remote locations, breaking down geographical barriers to quality healthcare. This is particularly crucial for a rare and complex disease like sarcoma, where specialized expertise may not be readily available in all regions. Interoperable EHRs, on the other hand, facilitate multi-disciplinary collaboration by allowing seamless data sharing between oncologists, radiologists, pathologists, and even primary care physicians. This is vital in sarcoma care, which often requires a multi-disciplinary approach for optimal outcomes. The EHRs can also be integrated with AI algorithms to flag potential issues or suggest alternative treatment pathways based on historical data and predictive analytics. Moreover, real-world-time data platforms can serve as a tool for continuous quality improvement. By tracking key performance indicators in real-time, healthcare providers can identify areas for improvement almost instantaneously, allowing for rapid intervention and adaptation of care protocols [19].

But the potential of digital health is not just in data collection; it is in data utilization. Advanced digital platforms can streamline the diagnostic journey, enhance treatment personalization, and even predict clinical outcomes, thereby offering a more holistic, patient-centric model of care. For example, digital platforms can automate the pre-diagnostic phase by gathering and analyzing patient history, symptoms, and preliminary test results, thereby aiding clinicians in making more accurate initial assessments. These platforms can also integrate with wearable devices that monitor patient vitals and other health metrics, providing a continuous stream of data that can be invaluable for ongoing care and monitoring. Furthermore, digital health technologies can facilitate patient engagement by providing platforms for virtual consultations, remote monitoring, and even digital therapeutics. These technologies empower patients to take an active role in their healthcare journey, thereby aligning with the principles of value-based care.

In essence, digital health technologies serve as the scaffolding upon which value-based care in sarcoma can be constructed, offering the dual advantages of operational efficiency and clinical efficacy.

4. Future Applications of AI in Sarcoma Care

As we look toward the horizon of sarcoma care, artificial intelligence (AI) emerges as a highly promising tool for advancing the field [26,27]. While current applications have been instrumental in diagnosis and treatment planning, the future holds even greater promise. Advanced machine learning algorithms are poised to delve into multi-omics data, offering unprecedented levels of precision in characterizing sarcoma subtypes and predicting treatment responses. The application of machine learning in sarcoma research extends beyond clinical data and can incorporate environmental, genetic, and lifestyle factors. By creating more comprehensive models that consider these variables, AI has the potential to identify new risk factors and even suggest preventative measures for at-risk populations. Deep learning techniques, a subset of machine learning, could be particularly impactful in image analysis. These algorithms can analyze complex patterns in radiological images that may be too subtle for the human eye, thereby aiding in early diagnosis and more accurate staging of the disease. This is crucial for sarcoma, where early diagnosis can significantly improve prognosis.

These algorithms could also integrate radiomic features with pathological and clinical data, refining prognostic accuracy [28]. Moreover, AI has the potential to support real-time decision making during surgeries through augmented reality interfaces, allowing for more precise surgical interventions. The introduction of natural language processing (NLP) can further enhance patient engagement by automating the analysis of patient-reported outcomes, thereby incorporating the patient's voice directly into the care continuum. NLP's real strength lies in its ability to convert unstructured data, such as patient narratives or free-text clinical notes, into structured data that can be easily analyzed. This is particularly valuable in sarcoma care, where patient experiences and symptoms can be highly variable and complex. By applying NLP algorithms to these unstructured data sources, healthcare providers can gain insights into patient well-being, treatment side effects, and even early indicators of complications that may not be readily apparent through traditional structured data. These structured data can then be integrated into machine learning models to improve predictive accuracy, thereby contributing to more personalized and effective treatment plans.

In a value-based healthcare framework, AI can enable more personalized, efficient, and outcome-oriented care, serving as a catalyst for transforming the ideal of precision sarcoma care into a tangible reality.

5. The Concept of Sarcoma Digital Twin

The notion of a "Digital Twin" in sarcoma care is a groundbreaking concept that aligns closely with the goals of precision medicine and value-based healthcare [29]. Drawing inspiration from the Swiss Sarcoma Network's robust digital platform, the Sarconector, a sarcoma digital twin serves as a virtual replica of an individual patient's medical profile, integrating real-world-time data including Clinical-Reported Outcome Measures (CROMS), Patient-Reported Outcome Measures (PROMS), POCOMS (patient-omics-centric outcome measures), ECOMS (economic measures), and other metrics from multiple sources like Electronic Health Records (EHR), surveys, and interviews [22,30].

The concept of a digital twin goes beyond merely storing or aggregating data; it serves as a dynamic, interactive model that evolves in real-world-time. As new clinical data become available, whether they are from imaging studies, laboratory tests, or patient-reported symptoms, the digital twin updates accordingly. This dynamic nature allows for a more nuanced understanding of the patient's condition, thereby facilitating more informed clinical decisions. Moreover, the digital twin concept is not limited to the individual patient level. When aggregated across a population of sarcoma patients, these digital

twins can serve as a rich data repository for observational studies, clinical trials, and even epidemiological research. This collective data pool can be invaluable for identifying patterns or trends in sarcoma treatment and outcomes, thereby contributing to evidence-based medicine.

By leveraging AI-driven analytical tools, the digital twin can assist in predictive modeling, optimizing treatment plans, and even simulating potential outcomes of various therapeutic strategies. This creates an innovative ecosystem for quality-centric, value-based sarcoma care, enabling iterative improvement based on ongoing assessments and benchmarking. The utility of AI in this context is multifold. For instance, machine learning algorithms can analyze the digital twin data to predict patient responses to different treatment modalities, thereby aiding in personalized treatment planning. Furthermore, natural language processing (NLP) algorithms can sift through clinical notes and patient interviews to extract valuable insights that may not be readily apparent through quantitative data alone. These AI-driven analyses can be integrated into the digital twin, providing a comprehensive, 360-degree view of the patient's health status and treatment options. The concept of a sarcoma digital twin also has implications for healthcare economics. By providing a more accurate and personalized treatment plan, it has the potential to reduce unnecessary tests and treatments, thereby contributing to cost-effectiveness and sustainability in healthcare systems. In doing so, the concept of a sarcoma digital twin pushes the frontier of what is possible in delivering personalized, effective, and efficient care to sarcoma patients.

6. Roadmap to the Future

The Swiss Sarcoma Network's comprehensive roadmap to sarcoma care offers a visionary blueprint for the future, highlighting the synergy between AI and digital health in achieving a sustainable healthcare system. From a practical standpoint, this roadmap serves as a guide for healthcare providers, administrators and policymakers. It outlines actionable steps such as the adoption of interoperable digital platforms, the integration of AI in diagnostic and treatment protocols, and the establishment of quality indicators for continuous improvement. These practical measures aim to facilitate the transition from traditional, volume-based healthcare models to a more dynamic, value-based approach. The roadmap also suggests the use of real-world-time data to validate and refine AI algorithms, thereby ensuring that technological advancements are rooted in tangible clinical benefits. The roadmap outlines a multi-faceted approach that includes real-world-time data collection, interoperable digital platforms for data management, automated analysis employing AI algorithms, and benchmarking against quality indicators specific to sarcoma care [19,26]. These elements come together to assess various dimensions of care, including clinical outcomes and patient experiences. The ultimate aim is to continuously refine sarcoma care through iterative improvements, bringing the healthcare system closer to realizing value-based precision care. Adding another layer of innovation, the roadmap aims to incorporate the concept of a sarcoma digital twin, a virtual replica of an individual patient's medical condition that integrates seamlessly with AI-driven predictive modeling. As the roadmap evolves, there will be an increasing focus on aligning costs with value, thereby contributing to a more sustainable, efficient, and patient-centric healthcare system. Thus, the roadmap represents not just a pathway for sarcoma care but also serves as a model for the broader application of precision medicine and value-based healthcare.

While the Swiss Sarcoma Network provides a innovative model, its potential is not confined to Switzerland alone. By fostering international collaborations and partnerships, this roadmap can be scaled globally, adapted to diverse healthcare infrastructures and socio-cultural contexts. Key to this expansion is the network's emphasis on interoperability and standardization, facilitating seamless data exchange across borders. The establishment of international sarcoma care consortiums, working cohesively within the potential of such platform, can harmonize methodologies, share best practices, and collectively advance the vision of precision medicine. As more regions adopt this model, there is an opportunity for global real-world-time data aggregation, enhancing AI's predictive capabilities and refining

treatment strategies. Thus, the roadmap represents not just a pathway for sarcoma care but also serves as a model for the broader application of precision medicine and value-based healthcare on a global scale.

7. Ethical and Regulatory Forethought

As we advance toward a new paradigm of value-based precision care in sarcoma, underpinned by digital health and AI, ethical and regulatory considerations must be addressed with the same vigor as technological innovations [31,32]. The collection, storage, and analysis of patient data pose questions about data security, privacy, and informed consent. Ensuring equitable access to advanced sarcoma treatments catalyzed by AI and digital tools is paramount to preventing disparities in care. However, it is important to acknowledge the limitations of our approach. While AI and digital health platforms offer transformative potential, they are no without their drawbacks. The quality of AI algorithms is highly dependent on the quality and quantity of the data fed into them. Incomplete or biased data can lead to inaccurate or even harmful clinical decisions. Additionally, the ethical implications of AI decision making in healthcare are still not fully understood and require further study. There is also the risk of over-reliance on technology, which could potentially undermine the role of medical professionals in patient care. Furthermore, the cost of implementing advanced digital solutions may be prohibitive for smaller healthcare facilities, potentially widening the gap in the quality of care. Regulatory bodies and ethical committees must work in concert with healthcare providers, technology developers, and policymakers to standardize protocols, ensuring that they are universally applicable and ethically sound. These protocols must also be flexible enough to adapt to rapid technological advancements without compromising patient safety or data integrity. As real-world data platforms become more integrated into the healthcare system, legal frameworks will play a critical role in shaping the ethical landscape of digital health and AI in sarcoma care. Thus, ethical and regulatory forethought is not a mere afterthought but an integral component of the roadmap to value-based precision care.

8. Challenges and Barriers: A Call to Action

While the horizon is bright with the promise of digital health and AI ushering in a new era of value-based precision care in sarcoma, the path is fraught with challenges that require immediate attention. Practically speaking, the implementation of this roadmap will necessitate substantial investments in technology and human resources. Hospitals and healthcare providers will need to upgrade their existing infrastructures to support data-intensive AI algorithms. Training programs will be essential for clinicians to effectively interpret and act upon AI-generated insights. Moreover, the roadmap calls for a collaborative effort involving not just the medical community but also regulatory bodies and insurance providers. This multi-stakeholder approach is crucial for overcoming the financial, ethical, and logistical barriers to implementing a value-based healthcare model in sarcoma care. Resource constraints, a lack of standardized data protocols, and resistance to change within medical institutions all pose significant barriers. The dearth of expertise in data science within the medical community adds another layer of complexity. Furthermore, data privacy concerns and regulatory hurdles can slow down the pace of innovation. However, these challenges should not deter us; rather, they should serve as a clarion call to action. This involves not only healthcare professionals and technologists but also policymakers, patient advocacy groups, and regulatory bodies. A collective, multidisciplinary effort is crucial to overcome these barriers. Funding must be allocated for research and development, educational initiatives must be put in place, and policy frameworks need to be developed to encourage data sharing and interoperability. By acknowledging and addressing these challenges head-on, we can accelerate the journey toward realizing the full potential of digital health and AI in transforming sarcoma care.

9. Conclusions and Proposals for Future Research

In the evolving landscape of sarcoma care, the convergence of digital health and artificial intelligence offers a beacon of hope for personalized, efficient, and value-based treatment options. We have explored the promise this union holds—from the integration of real-world-time data and interoperable digital platforms to the application of AI for predictive analytics, all the way to the conceptualization of the sarcoma digital twin, thereby enabling predictive and value-based precision sarcoma care. As we look to the future, several avenues for research emerge. First, there is a need for randomized controlled trials (or, alternatively, target trial emulations) to validate the efficacy of AI algorithms in sarcoma diagnosis and treatment planning. Second, research should focus on the ethical implications of AI in healthcare, particularly in the context of data privacy and informed consent. Third, the economic aspects of implementing digital health platforms and AI in sarcoma care warrant in-depth study, including cost–benefit analyses and long-term sustainability assessments. Lastly, future work could explore the integration of other emerging technologies, such as blockchain for secure data sharing or augmented reality for enhanced surgical planning, into the existing digital health ecosystem. These research proposals aim to fill the existing gaps in our understanding and provide a comprehensive framework for the adoption of digital health and AI in sarcoma care. While the challenges are significant, they are not insurmountable. We stand at the cusp of a transformative era in healthcare, one where the systematic adoption of these technologies could revolutionize the way we approach not just sarcoma, but complex diseases at large. However, to realize this vision, a coordinated, multidisciplinary effort is essential. The time for action is now; let us seize this moment to propel sarcoma care into a future replete with the benefits of digital health and AI, ultimately improving outcomes and quality of life for patients around the globe.

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Review

Real-World-Time Data and RCT Synergy: Advancing Personalized Medicine and Sarcoma Care through Digital Innovation

Philip Heesen [1,2,3], Georg Schelling [2], Mirko Birbaumer [4], Ruben Jäger [5], Beata Bode [3], Gabriela Studer [1,2] and Bruno Fuchs [1,2,5,*,†] on behalf of the Swiss Sarcoma Network

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Simple Summary: This study looks at how combining real-world/time data/evidence (RWTD/E) with traditional clinical studies (known as randomized controlled trials) can improve healthcare research and ultimately patient care. Unlike past methods that often rely on outdated information, RWTD/E provides up-to-the-minute data on patient health, making it a powerful tool for doctors and researchers. This approach is especially useful in areas like sarcoma, a type of cancer, where understanding each patient's unique situation can lead to improved treatment plans. We discuss how this mix of real-world/time data and traditional research can lead to more personalized medicine, helping to create treatments tailored to individual patient needs. It also aids in managing health at a community level by spotting trends and improving health policies, making care more efficient and focused on what patients truly benefit from. Furthermore, we explore how applying new methods, like creating digital twins of patients' health profiles to RWTD/E can help in predicting individualized treatment effects. This study aims to elaborate that using prospective RWTD/E alongside traditional clinical trials can make healthcare more effective, patient-focused, and ready to adapt to new discoveries and technologies.

Abstract: This manuscript examines the synergistic potential of prospective real-world/time data/evidence (RWTD/E) and randomized controlled trials (RCTs) to enrich healthcare research and operational insights, with a particular focus on its impact within the sarcoma field. Through exploring RWTD/E's capability to provide real-world/time, granular patient data, it offers an enriched perspective on healthcare outcomes and delivery, notably in the complex arena of sarcoma care. Highlighting the complementarity between RWTD/E's expansive real-world/time scope and the structured environment of RCTs, this paper showcases their combined strength, which can help to foster advancements in personalized medicine and population health management, exemplified through the lens of sarcoma treatment. The manuscript further outlines methodological innovations such as target trial emulation and their significance in enhancing the precision and applicability of RWTD/E, underscoring the transformative potential of these advancements in sarcoma care and beyond. By advocating for the strategic incorporation of prospective RWTD/E into healthcare frameworks, it aims to create an evidence-driven ecosystem that significantly improves patient outcomes and healthcare efficiency, with sarcoma care serving as a pivotal domain for these developments.

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Keywords: real-world/time data/evidence (RWTD/E); randomized controlled trials (RCTs); healthcare research; personalized medicine; population health management; sarcoma care; digital twin; target trial emulation; value-based healthcare (VBHC); patient outcome optimization

1. Introduction

In the dynamic context of evidence-based healthcare, real-world/time data/evidence (RWTD/E) assumes a critical role, extending past the limitations of randomized controlled trials (RCTs) that might arise when randomization would be unethical or when an RCT would be too costly to undertake [1–5]. The progression towards a joint use of RCTs and RWTD/E signifies a fundamental paradigmatic transition towards the incorporation of exhaustive, contemporaneous patient data, augmenting the depth and breadth of healthcare research and decision-making mechanisms [6–8]. Emphasizing this evolution, the first part traces the trajectory from an exclusive reliance on conventional RCT methodologies to a comprehensive, data-informed strategy. The integration of RWTD/E with RCTs represents a significant advancement in evidence-based healthcare [1]. RWTD/E's unique ability to provide real-world/time, contextual data offers a complementary perspective to the controlled environments of RCTs. This synthesis enhances our understanding of healthcare interventions by bridging the gap between clinical trial settings and real-world/time patient experiences, thereby enriching the evidence base for more informed healthcare decisions and policies [9].

RWTD/E is not only an important complimentary part to RCTs, but also contrasts sharply with traditional retrospective analyses of health data (Table 1). RWTD/E enhances the granularity and relevance of healthcare data, providing immediate insights into treatments and outcomes prospectively. This evolution not only captures the fluidity of healthcare interactions but also offers substantial advantages over retrospective data by enabling timely, informed decision-making and a deeper understanding of patient care processes [10].

Table 1. Overview of data types in healthcare research: definitions, sources, and contexts of use.

Term	Definition	Source of Data	Timing of Data Collection	Usage Context
Retrospective data	Data collected from past events, often through examination of existing records such as medical charts and billing information	Historical records, medical charts, insurance claims	Collected after all events have occurred, looking back in time	Analyzing past events, to understand outcomes, trends, and areas for future research. Subject to selection biases
Prospective data	Data collected from the initiation of the study forward, with specific research questions and data collection processes in mind	Direct observations, surveys, clinical assessments.	Collected moving forward from the start of the study	Observing and assessing outcomes following specific exposures or interventions, minimizing recall biases and clarifying temporal relationships
Randomized controlled trials (RCTs)	Health-related data derived from sources outside traditional clinical trials, including EHRs, registries, and patient generated data	Controlled experimental settings	Prospective, starting at the time of the trial	Establishing causality between interventions and outcomes, minimizing bias through randomization and control

Table 1. *Cont.*

Term	Definition	Source of Data	Timing of Data Collection	Usage Context
Real-world data (RWD)	Health-related data derived from sources outside traditional clinical trials, including EHRs, registries, and patient generated data	EHRs, claims, registries, patient devices	Not specific to real time; collected during routine clinical practice	Capturing patient experiences in routine practice to understand healthcare delivery and outcomes in natural settings
Real-world evidence (RWE)	Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analyzing RWD	Derived from RWD	Analysis occurs at any time post data collection	Supporting clinical decision-making and health policy by providing evidence from real-life setting beyond controlled trials
Real-time data (RTD)	Information that is collected and immediately available for use or analysis as events occur, without significant delay	Monitoring devices, clinical care systems	Immediate, as events occur	Required in scenarios requiring immediate action, like critical care monitoring.
Real-world/time data and evidence (RWTD/E)	Conceptualized as combining real-world context with the immediacy of real-time data collection and analysis	EHRs, patient devices, and real-time monitoring systems	Real-time, as events occur in real-world settings	Enhancing understanding of healthcare interventions in real-world settings with the immediacy of real-time data capture

This study's strategic importance lies in its potential to significantly influence the ongoing evolution of healthcare research, quality, and policy [11]. By integrating prospective RWTD/E with RCTs, it aims to bridge the gap between clinical evidence and practical application, thus enhancing patient outcomes and informing evidence-based policy decisions. This manuscript contributes to critical debates on optimizing healthcare delivery through a nuanced understanding of real-world/time patient experiences and outcomes, positioning itself at the forefront of advancing healthcare effectiveness and efficiency [12–14]. Therefore, we herein explore the potential and synergistic value of prospective RWTD/E alongside RCTs in enriching healthcare research and decision-making processes.

2. Real-World/Time Data/Evidence: Foundations and Future

RWTD/E encompasses the prospective collection and analysis of healthcare data as it occurs, capturing the continuum of patient care also known as the patient pathway, in real-world and real-time [1,3]. A patient pathway delineates the comprehensive journey of a patient through the healthcare system for specific conditions or treatments, highlighting the sequence of care events and interactions with healthcare providers. This concept is paramount for the future as it underscores the importance of understanding and optimizing the entire spectrum of patient care, from initial consultation through treatment and follow-up, thereby enhancing patient outcomes and potentially aligning with value-based healthcare (VBHC) principles by enabling the accurate assessment of care cycle costs [15]. This approach includes data from electronic health records, patient-generated data, and other healthcare interactions, providing a comprehensive view that reflects the temporal and contextual realities patients face across various settings [16]. RWTD/E's defining feature is its ability to offer a dynamic, ongoing snapshot of healthcare processes, setting a foundation for evidence that is both immediate and reflective of the complexities of real-world patient experiences.

Prospective RWTD/E and RCTs serve distinct, complementary roles in evidence generation [17]. RCTs, with their structured and controlled setup, are designed to minimize bias and establish causality under specific conditions. In contrast, RWTD/E offers a broader, more inclusive approach by capturing data in real-life settings, reflecting the complexity and diversity of patient experiences. This expansive nature of RWTD/E complements the precision of RCTs, providing a more holistic understanding of healthcare interventions across different populations and settings.

The scope of RWTD/E spans from electronic health records to patient-generated data, encompassing a wide array of healthcare interactions. This breadth allows RWTD/E to provide invaluable insights across diverse healthcare scenarios, reflecting the real-life complexity and variability of patient care. Through the aggregation and analysis of this extensive data, RWTD/E enhances our understanding of healthcare outcomes, treatment effectiveness, and patient experiences in various settings, underscoring its critical role in advancing evidence-based medicine.

Prospective RWTD/E provides distinct advantages over retrospective data by dynamically capturing and analyzing healthcare events as they occur. This immediacy equips RWTD/E to mirror the current state of patient care accurately, yielding real-world/time insights into treatment outcomes and healthcare delivery effectiveness. The inherent dynamism of RWTD/E supports a healthcare system that is both responsive and adaptable, swiftly integrating the latest evidence into patient care pathways. Conversely, retrospective data, while offering historical insights, is static and grounded in past healthcare practices. It is subject to significant selection biases, as it often relies on pre-existing records that may not represent the full spectrum of patient experiences. Such biases limit the ability to generalize findings to broader patient populations. The temporal aspect of RWTD/E signifies its unique advantage, offering continuous data collection that provides a dynamic, evolving picture of patient care and outcomes. This continuous timeline of data captures the nuances of healthcare processes in real time, enabling a deeper, more accurate understanding of treatments, patient responses, and the effectiveness of healthcare interventions as they unfold.

RWTD/E demonstrates remarkable adaptability and relevance across diverse healthcare settings, from hospitals and clinics to remote patient monitoring and home care. Its application spans the healthcare continuum ("patient pathway"), offering insights into patient care processes and system efficiencies in real-world/time. This versatility supports personalized patient care strategies, public health initiatives, and health policy development, showcasing RWTD/E's essential role in advancing healthcare delivery and outcomes across various environments.

RWTD/E enhances the insights gained from RCTs by providing a broader understanding of treatment effectiveness and patient experiences in real-time settings. This complementary relationship allows for a more comprehensive evaluation of healthcare interventions, filling gaps in knowledge about their real-world applicability and impact on patient-centered outcomes.

The future of RWTD/E looks promising, with anticipated technological innovations and advancements in data analytics expected to significantly enhance its utility and impact. These developments promise to deepen our understanding of healthcare processes, improve patient outcomes, and drive more informed decision-making across the healthcare spectrum.

3. Enhancing Healthcare Insights through Prospective RWTD/E

RWTD/E offers a nuanced perspective on patient outcomes, capturing the diverse experiences and journeys of patients ("patient pathways") across healthcare settings. This approach is vital for benchmarking between institutions, both nationally and internationally, especially using quality indicators for specific care areas like sarcoma. By examining data from varied healthcare experiences, RWTD/E enables a broader understanding of patient outcomes, supporting the development of more effective healthcare strategies and policies

through benchmarking efforts [18,19]. This enhanced view is essential for advancing patient care and ensuring high-quality healthcare delivery across different regions and populations.

RWTD/E captures a wide spectrum of patient demographics, including those often underrepresented in traditional healthcare research. This comprehensive data collection enables a deeper understanding of treatment effects across diverse populations [20,21]. Sarcoma care guidelines, for instance, show a variety of treatment pathways, indicating that patient care can significantly vary not only within a single country but also across different geographical regions. RWTD/E's expansive dataset offers critical insights into these variations, emphasizing the need for personalized treatment strategies that consider the unique contexts of different patient groups [22,23].

RWTD/E can offer valuable insights beyond what is typically captured in RCTs, especially regarding drug effectiveness and patient adherence [2]. For sarcoma, where individual patient responses can vary widely due to the heterogeneity of the disease, RWTD/E can highlight how treatments perform in a broader, more diverse population, potentially revealing variations in effectiveness and adherence not apparent in the controlled conditions of RCTs. This underscores the importance of integrating RWTD/E for a more nuanced understanding of treatment outcomes in sarcoma care.

RWTD/E embraces the intricacies of healthcare in real-world/time settings, recognizing factors like comorbidities and diverse healthcare practices that RCTs often overlook. This comprehensive approach allows for a more authentic understanding of how treatments work in the complex web of patient care, highlighting the need for flexible, adaptable healthcare strategies that can accommodate the full spectrum of patient experiences.

Among the illustrative case studies demonstrating RWTD/E's substantial contributions to healthcare insights, a notable example is the benchmarking study comparing two multidisciplinary teams (MDTs) in sarcoma treatment [18]. Utilizing the interoperable digital platform Sarconnector® for real-world/time data assessment (which is currently accessible through www.adjumed.net), this study unveiled significant variations in treatment approaches, particularly in chemotherapy indications, but also in indications for biopsies or surgeries, among other areas [18]. Such discrepancies underscore the critical importance of RWTD/E in identifying and addressing gaps in care delivery. This benchmarking effort not only highlights RWTD/E's capability to standardize and evaluate quality and cost metrics across different healthcare settings, but also emphasizes its potential to drive data-driven optimizations in patient care strategies. Through the harmonized data approach facilitated by Sarconnector® (assessing, for example, a minimal data set (Appendix A), healthcare providers can pinpoint areas for improvement, leading to enhanced patient outcomes and more efficient healthcare delivery. This case exemplifies RWTD/E's power in advancing a value-based care model by providing actionable insights that are pivotal for improving healthcare quality, efficiency, and patient satisfaction across diverse medical disciplines beyond sarcoma care [24].

Additionally, the application of RWTD/E can lead to more cost-efficient healthcare delivery by identifying the most effective treatments and avoiding unnecessary or less effective interventions [25].

Emulating target trials with RWTD/E represents a pivotal advancement in harmonizing the rigorous methodologies of RCTs with the intricate realities of real-world/time healthcare [26–28]. This sophisticated approach capitalizes on the comprehensive datasets afforded by RWTD/E to approximate the conditions and controls of RCTs, thereby offering a refined method for assessing intervention outcomes among diverse patient populations. Such an emulation not only corroborates and broadens the applicability of clinical trial findings, but also fosters the tailoring of treatment strategies to meet the individual needs and circumstances of patients. Consequently, it plays a vital role in the evolution of personalized medicine, enabling healthcare providers to devise more effective and flexible care plans that reflect the genuine complexities of patient experiences. In doing so, target trial emulation underscores the transformative potential of RWTD/E in elevating healthcare quality,

efficiency, and patient satisfaction, thereby reinforcing its indispensable contribution to advancing a value-based care paradigm.

4. Methodological Advancements in RWTD/E

Advancements in data capture technologies, such as wearable devices and mobile health applications, have significantly propelled the capabilities of RWTD/E [29–31]. These innovations allow for the continuous, real-world/time monitoring of patient health metrics and behaviors, providing a wealth of data that are both granular and expansive. This evolution in data collection not only enriches the depth of RWTD/E but also broadens its applicability across healthcare research, enhancing our understanding of patient experiences and outcomes in everyday life.

The integration of advanced analytical techniques, such as machine learning and artificial intelligence (AI), has been transformative in processing complex RWTD/E datasets [32–35] and might enable the accurate prediction of outcomes or individualized treatment effects and eventually the optimal choice of a therapy sequence for an individual patient.

The interpretation of RWTD/E is being significantly enhanced through the use of sophisticated visualization tools and the fostering of cross-disciplinary collaborations. These strategies improve the comprehensibility and actionable nature of complex datasets, allowing for a more nuanced understanding across various healthcare domains.

Digital health platforms play a crucial role in prospective RWTD/E by aggregating data from diverse sources, ensuring consistency, and enabling comprehensive analyses [36]. These platforms, enhanced by AI, improve data collection, analysis, and interpretation, which are pivotal for patient-centered models like the 'Sarcoma Digital Twin' [31,37,38]. This concept represents an innovative approach to sarcoma care, creating detailed, personalized models that reflect individual patient conditions and treatment responses, facilitating better healthcare decisions.

Efforts to enhance the quality and reliability of RWTD/E are further complemented by implementing standardization initiatives and conducting validation studies, ensuring that data collected from diverse sources remain consistent and accurate. Alongside these critical efforts, the emulation of target trials emerges as a pivotal strategy, bolstering the credibility and applicability of RWTD/E findings. This approach meticulously simulates the controlled conditions of RCTs within the RWTD/E framework, employing rigorous analytical methods to ensure that real-world/time evidence maintains a high level of precision and relevance. By integrating emulated target trials into the standardization and validation process, RWTD/E not only adheres to the highest standards of data integrity but also significantly advances the utility of real-world/time insights in clinical research and healthcare decision-making. Such methodological sophistication highlights the transformative potential of RWTD/E, positioning it as an indispensable resource in the evolution towards more evidence-driven, patient-centered healthcare models.

Methodological advancements in RWTD/E, notably through the integration of target trial emulation, have significantly transformed the landscape of real-time patient monitoring and intervention. This methodology enhances the capacity for immediate and impactful healthcare interventions, directly contributing to the optimization of patient care practices and the achievement of superior health outcomes. The implementation of RWTD/E, enriched by the principles of target trial emulation, heralds a new era in patient care—one that is deeply rooted in evidence-based, personalized treatment paradigms and geared towards maximizing patient well-being and satisfaction. Through this innovative lens, RWTD/E is set to redefine expectations for treatment efficacy and patient care standards, demonstrating a commitment to advancing healthcare through methodological excellence and technological integration.

5. RWTD/E in Informing Healthcare Policy and Practice

In the context of modern healthcare policy development, real-world/time data/evidence (RWTD/E) is instrumental in underpinning the creation and refinement of evidence-based

guidelines and protocols. RWTD/E facilitates a data-driven policymaking process by providing empirical insights into the effectiveness, safety, and patient satisfaction of healthcare interventions. Such evidence ensures that healthcare policies are reflective of the current clinical practices and patient needs, enabling policy frameworks to be dynamically adjusted in response to the evolving healthcare landscape. Consequently, RWTD/E serves as a critical resource for policymakers, guiding the establishment of healthcare standards that are both efficacious and patient-centric. This approach not only optimizes healthcare delivery but also ensures that policy adaptations are continuously informed by comprehensive, real-world/time evidence, thereby promoting better health outcomes and system efficiency.

RWTD/E may exert a profound impact on the formulation of clinical guidelines by furnishing a rich tapestry of data that encapsulate patient outcomes and the efficacy of treatments within real-world contexts. The analytic process of dissecting RWTD/E to unveil underlying patterns and trends offers a comprehensive perspective that transcends the confines of traditional controlled trials. Such a breadth of evidence empowers guideline developers to integrate a more diverse and representative array of findings, ensuring that clinical guidelines are not only grounded in empirical reality but are also finely tuned to the multifaceted nature of patient care. Consequently, the incorporation of RWTD/E into guideline development translates to protocols that are inherently aligned with actual clinical practices and patient experiences, fostering enhancements in health outcomes and elevating patient satisfaction through guidelines that are both responsive and reflective of real-world/time healthcare dynamics.

RWTD/E critically elevates healthcare decision-making by supplying real-time, evidence-based insights crucial for shaping both institutional strategies and national healthcare policies. This data-driven paradigm enables healthcare executives and policymakers to enact decisions deeply attuned to the evolving needs of patients and the prevailing healthcare environment. By integrating RWTD/E, decision-makers are equipped with a dynamic toolset to navigate and respond to the complexities of healthcare delivery, ensuring that interventions and policies are not only informed by the latest evidence but are also precisely targeted to enhance efficiency and effectiveness within the healthcare system. Thus, RWTD/E stands as a pivotal asset in the advancement of healthcare strategies, promoting a more informed, agile, and patient-centric approach to healthcare governance.

RWTD/E fundamentally undergirds the tenets of value-based healthcare by furnishing granular insights into the efficacy and economic efficiency of healthcare interventions from a real-world/time perspective. This methodology facilitates a nuanced evaluation of interventions, emphasizing their tangible impact on patient health outcomes alongside their cost implications. By leveraging RWTD/E, healthcare decision-makers are empowered to conduct comprehensive assessments that foreground the value delivered to patients and the system at large, enabling a judicious allocation of resources towards interventions that demonstrably maximize clinical benefit while optimizing economic utilization [25]. Consequently, RWTD/E serves as an essential instrument in the operationalization of VBHC, driving the transition towards healthcare models that prioritize measurable improvements in patient outcomes and sustainability of healthcare provisioning.

RWTD/E plays a critical role in augmenting healthcare quality and patient safety by facilitating the identification of improvement opportunities via the analysis of real-world/time data. This analytical exploration into RWTD/E uncovers actionable insights into patient care dynamics, revealing efficacy gaps and safety concerns that might not be apparent within the confines of controlled research environments. Such revelations often catalyze significant policy reformulations, ensuring that clinical practices and protocols are meticulously aligned with contemporary evidence delineating optimal care strategies. Consequently, the iterative refinement of healthcare delivery, informed by RWTD/E, underscores a commitment to elevating the standards of patient care, enhancing safety protocols, and fostering a healthcare ecosystem where quality and safety are perpetually optimized based on real-world patient outcomes and experiences.

The effective utilization of real-world/time data/evidence necessitates the active engagement of a diverse consortium of stakeholders, encompassing healthcare providers, patients, policymakers, and researchers [11]. This multidisciplinary collaboration is pivotal for the holistic integration of RWTD/E into healthcare policy and practice, ensuring that derived insights are comprehensively leveraged to inform and enhance healthcare delivery systems. The synergistic involvement of these stakeholders facilitates a multifaceted perspective in the analysis and application of RWTD/E, fostering policies and practices that are not only evidence-based but also reflect the collective expertise and experiences of the entire healthcare ecosystem. Consequently, this collaborative model amplifies the impact of RWTD/E on healthcare outcomes, driving forward improvements that are both informed by robust data and aligned with the nuanced needs and expectations of all parties involved. Such concerted efforts underscore the importance of stakeholder engagement in maximizing the potential of RWTD/E for substantial and sustainable healthcare advancements.

The advent of digital health and artificial intelligence (AI) marks a fundamental transformation in healthcare, steering it towards more value-based models [18,37]. This shift, catalyzed by the strategic integration of real-world/time data/evidence, is fundamentally altering the landscape of healthcare policy, the development of clinical guidelines, and the dynamics of stakeholder engagement. Recent studies elucidate the transformative potential of digital health and AI in crafting a healthcare ecosystem that is not only more efficient and equitable but also deeply rooted in patient-centric care. For instance, digital health tools and AI have been shown to shift healthcare from reactive to proactive by predicting and preventing diseases, as demonstrated in the transformation of health systems in low- and middle-income countries [39]. For example, in Kenya, the Leap platform uses AI-powered mobile health solutions to train community health workers to manage chronic diseases, leading to early interventions and improved health outcomes [39]. Additionally, AI enhances diagnostic accuracy, personalized treatment plans, and proactive disease prevention, further emphasizing its role in improving patient outcomes and operational efficiency [40,41]. By harnessing RWTD/E, this paradigmatic shift in healthcare is underscored, showcasing a move towards policy formulations and clinical practices informed by real-world/time, granular insights and outcomes. This evolution reflects a commitment to leveraging cutting-edge technology and comprehensive data analytics to refine healthcare outcomes and operational efficiency, ultimately guiding the transition towards a healthcare system that prioritizes value-based models. In this context, RWTD/E emerges as a pivotal force in driving informed decision-making and fostering an environment where healthcare delivery is continuously optimized to meet the intricate needs of patients, thereby reinforcing the strategic importance of digital health and AI in realizing a future characterized by informed, efficient, and patient-centered healthcare.

6. Case Studies and Practical Applications of RWTD/E

Diverse case studies from the Swiss Sarcoma Network (SSN), such as leveraging the Sarconnector® platform, have illuminated the potential transformative impact of real-world/time data/evidence (RWTD/E) on patient outcomes in sarcoma care [18,19,37]. For example, these studies show that the use of real-world/time data analysis for benchmarking of the diagnostic pathway analysis has led to improved adherence to clinical guidelines, optimized treatment protocols, and enhanced patient outcomes, demonstrating the critical role of continuous quality improvement in sarcoma treatment [20]. These initiatives facilitate multidisciplinary team decision-making processes for complex sarcoma cases, enabling the exploration of integrating patient-specific data, real-world/time analysis, and predictive modeling. Such efforts lay the groundwork for personalized treatment plans that promise to markedly improve patient outcomes, highlighting RWTD/E's broader application in tailoring treatments across various healthcare settings.

In advancing toward personalized medicine, the SSN is exploring the potential of prospective RWTD/E through initiatives like Digital Twinning and Predictive Analyt-

ics (DTPA), aiming to stand at the forefront of this innovation [31,37,38]. By laying the foundation for creating digital twins of patients' medical profiles, the SSN envisions enabling tailored treatment strategies that account for the individual variability in disease progression and response to therapy. This forward-looking approach, intended to leverage RWTD/E to analyze patient outcomes and genetic information, underscores the envisioned pivotal role of RWTD/E in optimizing patient care and improving outcomes, embodying the future of personalized treatment plans.

The Swiss Sarcoma Network's prospective RWTD/E Data Warehouse/-Lake exemplifies the strategic vision for utilization in population health management by offering a proposed comprehensive view of health trends and patient outcomes for sarcoma [18]. This vision aims to support the identification and analysis of health trends, facilitating the development of targeted preventive strategies and effective resource allocation. By planning to harness RWTD/E, stakeholders anticipate enhancing public health responses and tailoring health initiatives to diverse community needs, showcasing RWTD/E's potential revolutionary impact on population health management [25].

The planned integration of RWTD/E into the SSN's clinical workflows, particularly through initiatives like the weekly MDT/SB Tumor Conference, aims to demonstrate the practical benefits of real-world/time data in clinical decision-making. This collaborative enhancement of patient care pathways reflects RWTD/E's wider potential for integration across healthcare settings, with ambitions to identify effective treatments, reduce hospital readmission rates, and enhance patient management practices, significantly contributing to healthcare delivery optimization and patient care across disciplines.

The SSN's envisioned Quality Metrics and Outcome Measures initiative is anticipated to underscore RWTD/E's impact in driving measurable improvements in healthcare quality and patient safety (Appendix A). Through the future systematic evaluation of sarcoma care effectiveness and efficiency, informed by real-world/time data, the SSN aims to implement policy adjustments and practice enhancements. These projected data-driven advancements reflect RWTD/E's transformative potential in optimizing healthcare delivery and improving patient outcomes, demonstrating its wide-ranging impact across multiple healthcare domains.

7. Future Directions

As we navigate the evolving landscape of healthcare, the anticipatory advancements in RWTD/E herald a new era of precision and personalization in patient care. Emerging technologies, notably AI-driven analytics and blockchain for secure, ethical data sharing, are set to further refine RWTD/E's capabilities [33,35,42]. These innovations promise to enrich healthcare insights, offering unprecedented accuracy and predictability in treatment outcomes and healthcare strategies. Such technological progress underscores RWTD/E's pivotal role, as demonstrated by the Swiss Sarcoma Network (SSN) initiatives, in bridging the gap between clinical evidence and its practical application, enhancing patient outcomes, and informing policy with the depth of real-world/time insights.

The integration of prospective RWTD/E with diverse data sources, including IoT devices and genomics, represents a comprehensive approach to patient health analysis [42]. This multidimensional perspective—encompassing medical, lifestyle, and environmental factors—will advance the precision medicine frontier, tailoring healthcare delivery to individual needs while facilitating broader, population-wide health evaluations. This envisioned integration aligns with the SSN's prospective strategies, aiming to leverage RWTD/E for a holistic understanding and management of sarcoma care, reflecting a broader applicability across healthcare disciplines.

Addressing future challenges, particularly around data privacy, standardization, and interoperability, remains paramount as RWTD/E expands. Ensuring the ethical use of patient data, while promoting research collaboration, echoes the discussions in previous chapters on the necessity for a balanced approach to data sharing that respects privacy and maximizes healthcare innovation [43–45]. Efforts towards developing universal data

standards and employing interoperable platforms will be critical in realizing the full potential of RWTD/E, enabling seamless integration and efficient data utilization across the healthcare continuum [46–48].

Furthermore, enhancing patient engagement through prospective RWTD/E, as envisioned by initiatives like Sarconnector®, presents an opportunity to revolutionize the patient-provider dynamic. Enabling real-world/time access to health data and care plans empowers patients to actively participate in their healthcare journey, contributing to research and shared decision-making processes [35,49]. This direct involvement is poised to foster a more collaborative, informed, and patient-centered healthcare experience, highlighting the importance of RWTD/E in facilitating meaningful patient engagement and personalized care.

8. Conclusions

In conclusion, the strategic importance of prospective RWTD/E in advancing healthcare research, practice, and policy is undeniable. It stands as a testament to the power of integrating comprehensive, real-world/time data into healthcare decision-making, offering a path to more effective, efficient, and patient-centered care. As we reflect on the insights and advancements discussed throughout this manuscript, it is clear that the journey of RWTD/E is only beginning. Its continued evolution will require not only technological innovation but also a commitment to ethical practices and multidisciplinary collaboration. The Swiss Sarcoma Network's ongoing efforts exemplify this journey, charting a course toward a future where healthcare is transformed by the depth and dynamism of real-world/time data/evidence.

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Appendix A. The SSN-Minimal Data Set (SSN-MDS) Includes the Basic Parameters of Sarcoma Patient Care, Which Allow Data Harmonization over the Geography and Across Institutions

Institution	free field
Pat ID	number
Gender (M/F)	[0] male [1] female
Date of birth	DD/MM/YY
Affected tissue	[0] Superficial Soft Tissue [1] Deep Soft Tissue (according to the investing fascia; note that a tumor located superficially but invading the investing fascia should be recorded as deep) [2] Bone
Site of lesion	[0] Foot [1] Distal lower limb below knee—anterior compartment [2] Distal lower limb below knee—lateral compartment [3] Distal lower limb below knee—posterior compartment [4] Distal lower limb below knee—more than one compartment [5] Popliteal fossa/knee [6] Proximal lower limb at or above knee—anterior compartment [7] Proximal lower limb at or above knee—posterior compartment [8] Proximal lower limb at or above knee—more than one compartment [9] Buttocks and inguinal region [10] Hand [11] Distal upper limb below elbow—ventral compartment [12] Distal upper limb below elbow—dorsal compartment [13] Distal upper limb below elbow—more than one compartment [14] Elbow [15] Proximal upper limb at or above the elbow—ventral compartment [16] Proximal upper limb at or above the elbow—dorsal compartment [17] Proximal upper limb at or above the elbow—more than one compartment [18] Axilla/scapula [19] Head and neck [20] Chest wall [21] Abdominal wall [22] Paraspinal [23] Retroperitoneal [24] Uterus [25] Other visceral [26] Intrathoracic [0] C-spine [27] T-spine [28] L-spine [29] Sacrum [30] Scapula [31] Prox humerus [32] Mid humerus [33] Dist humerus [34] Prox forearm [35] Mid forearm [36] Dist forearm [37] Carpus [38] Hand [39] Clavicle [40] Post pelvis [41] Acetabulum [42] Ant pelvis

Site of lesion	[43] Prox femur [44] Mid femur [45] Dist femur [46] Prox tibia [47] Mid tibia [48] Dist tibia [49] Fibula [50] Foot
Disease Status @ diagnosis	[0] Localized disease [1] Oligometastatic disease (5 or less lesions) [2] Polymetastatic disease (6 and more lesions)
Date of index surgery	DD/MM/YY
Type of index surgery	[0] Previous inadvertent excision; no re-excision [1] Re-excision after previous primary inadequate resection [2] Primary surgery without soft tissue reconstruction [3] Primary surgery with soft tissue reconstruction [4] Primary surgery without bone reconstruction [5] Primary surgery with bone reconstruction [6] Primary surgery with bone and soft tissue reconstruction
Margin status	[0] R0 [1] R1 [2] R2 [3] unknown
Tumor maximal size (cm)	If patients has undergone preoperative Tx, please record the largest diameter either pre or post the preop therapy
Date of histological diagnosis	DD/MM/YY
Histological diagnosis	[0] Angiosarcoma of soft tissues [1] Atypical chondromatous tumor [2] Atypical lipomatous tumor/well differentiated liposarcoma [3] Chondrosarcoma [4] Conventional osteosarcoma [5] Dedifferentiated liposarcoma [6] Desmoid-type fibromatosis [7] Ewing sarcoma [8] Giant cell tumor of bone [9] GIST [10] Intramuscular myxoma [incl. variants] [11] Leiomyosarcoma [excluding skin] [12] Myxofibrosarcoma [13] Myxoid liposarcoma [14] Pleomorphic liposarcoma [15] Solitary fibrous tumor [16] Synovial sarcoma [17] Tenosynovial giant cell tumor [18] Undifferentiated/unclassified sarcoma
If other, please specify	Free text
Grading (FNCLCC)	[0] Grade 1 (Low grade): Total score 3–5 [1] Grade 2 (Intermediate grade): Total score 6–7 [2] Grade 3 (High grade): Total score 8–9 [3] Unknown [4] None available

Chemotherapy (index)	[0] No therapy [1] Neoadjuvant (localized disease) [2] Preoperative (metastatic) [3] Adjuvant (localized) [4] Postoperative (metastatic) [5] Palliative intent: treatment pressure
Radiotherapy (index; type of administration)	[0] Preoperative [1] Postoperative [2] Pre- and postoperative [3] IORT [4] Brachytherapy [5] Preoperative + IORT [6] Preoperative + brachytherapy [7] IORT + postoperative [8] Brachytherapy + postoperative [9] IORT + postoperative [10] Brachytherapy + postoperative operative [11] In combination with hyperthermia [12] None
Radiotherapy (index; schedule)	[0] Normofractionated 25 × 2 Gy [1] Hypofractionated 15 × 3 Gy [2] Ultrahypofractionated 5 × 5 Gy [3] Other
Date of 1st local recurrence	DD/MM/YY; otherwise “none”
Treatment of 1st LR	[0] Surgery [1] Chemotherapty [2] Radiotherapy [3] Surgery + Radiotherapy [4] Surgery + Chemotherapty [5] Surgery + Chemotherapty + Radiotherapy [7] Radiotherapy + Chemotherapty [6] Best supportive care
Date of 1st LR surgery	DD/MM/YY
Date of 2nd LR	DD/MM/YY
Treatment of 2nd LR	[0] Surgery [1] Chemotherapty [2] Radiotherapy [3] Surgery + Radiotherapy [4] Surgery + Chemotherapty [5] Surgery + Chemotherapty + Radiotherapy [7] Radiotherapy + Chemotherapty [6] Best supportive care
Date of 2nd LR surgery	DD/MM/YY
Date of pulmonary metastasis	DD/MM/YY; otherwise “none”
Date of extrapulmonary metastasis	DD/MM/YY; otherwise “none”
Site of extrapulmonary metastasis	free field

Treatment of metastasis	[0] Surgery [1] Chemotherapty [2] Radiotherapy [3] Surgery + Radiotherapy [4] Surgery + Chemotherapty [5] Surgery + Chemotherapty + Radiotherapy [7] Radiotherapy + Chemotherapty [6] Best supportive care
Date of last follow-up	DD/MM/YY
Status	[0] NED (no evidence of disease) [1] AWD (alive with disease) [2] DOD (dead of disease) [3] DOC (dead of other causes)

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Systematic Review

Reporting Matters: Severe Adverse Events in Soft Tissue Sarcoma Therapy—A 30-Year Systematic Review of Placebo- and Non-Systemic-Controlled Randomized Trials

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Simple Summary

Chemotherapy and newer targeted drugs are often used to treat soft tissue sarcoma, a rare malignant tumour of mesenchymal origin. We looked at every randomized clinical trial of systemic therapy for soft tissue sarcoma published in the past 30 years and re-analyzed the safety information. After standardizing the data, we found that about 1 in 6 patients developed severe drops in white-blood-cell counts and 1 in 10 suffered severe stomach- or bowel-related problems. Life-threatening side effects occurred in fewer than 1 in 20 patients. Newer drugs were no safer than traditional chemotherapy. However, only 50% of the selected studies reported side effects extensively and 3/8 used different grading systems, so today's risk estimates are still uncertain. Our findings show that serious but manageable side effects are common, and they highlight the urgent need for future sarcoma trials to report safety data consistently and transparently. Clearer reporting will help patients make better-informed treatment choices and allow doctors to prepare more effective supportive care.

Abstract

Background: Systemic therapy for soft tissue sarcoma (STS) provides modest survival benefit but carries clinically relevant toxicity. Published trials report adverse events (AEs) of varying quality and extension. Poor toxicity reporting hampers balanced risk–benefit appraisal. **Methods:** A PRISMA-2020 systematic review was registered in PROSPERO CRD420251087366. PubMed, CENTRAL, and Google Scholar were searched from 16 December 2024 to 16 April 2025 for randomized controlled trials (RCTs) evaluating chemotherapy, kinase inhibitors, or immune checkpoint inhibitors in STS. AE terms were harmonized to CTCAE v5.0; event rates were normalized to patients evaluable for safety. Pooled proportions used DerSimonian–Laird random-effects models; between-group comparisons employed unpaired *t*-tests. Risk of bias (RoB 2) was assessed with the Cochrane RoB 2 tool. **Results:** Ten RCTs (1079 treated, 979 control patients; 1994–2024) met the inclusion criteria, although two lacked sufficient presentation of toxicity data and seven failed to report parallel control-arm AEs. Pooled normalized incidences for treated patients were as follows: grade ≥ 3 hematological AEs, 17% (95% CI 14–20); severe gastrointestinal AEs, 9% (8–11); and grade 4 AEs, $\leq$6%. Anthracycline-based and kinase-inhibitor regimens displayed comparable composite grade ≥ 3 burdens (58% vs. 84%, $p = 0.64$). Between-study

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heterogeneity was considerable for gastrointestinal and hematological events ($I^2 > 60\%$), driven by differing AE scales and denominators. Late-effect toxicities (cardiac, hepatic, neurological, and nephrological) were rarely reported, occurring in <1% of the patients. Across the three RCTs with control-arm data, experimental therapy increased common grade 3 AEs by 4–12 percentage points ($p = 0.001$). RoB 2 flagged serious concerns in 4/10 trials. **Conclusions:** Severe AEs in STS systemic therapy are moderately frequent; while the toxicity spectrum differs across drug classes (e.g., hematological for anthracyclines vs. neuropathic or fatigue-related for agents such as eribulin), the aggregate burden of severe AEs has not been lower for newer agents. Confidence in these estimates is limited by incomplete and non-standardized AE reporting. Future sarcoma trials must adopt CTCAE v5.0, specify explicit safety denominators, and publish full AE matrices to enable high-certainty risk–benefit assessment.

Keywords: soft-tissue sarcoma; systemic therapy; chemotherapy; adverse events; toxicity; CTCAE; randomized controlled trials; meta-analysis; reporting standards

1. Introduction

Soft tissue sarcomas (STS) encompass more than 70 mesenchymal malignancies yet constitute less than 1% of adult cancers [1]; their crude incidence is 3.3 per 100,000 in the United States [2], 3.3–4.7 per 100,000 across Europe [3], and yields roughly 330 new cases annually in Switzerland (https://www.krebsliga.ch/ueber-krebs/krebsarten/weichteilkrebs-weichteilsarkome#:~:text=Weichteilkrebs%20(Weichteilsarkome),knapp%207%25%20aller%20Krebserkrankungen%20aus (accessed on 17 September 2025)) Despite multimodal advances, 5-year overall survival (OS) remains 55–65%, underscoring a persistent mortality burden that is disproportionate to their rarity [4].

Definitive treatment of localized STS rests on limb-sparing surgery plus radiotherapy [5]; systemic chemotherapy is optional in high-risk patients, and its peri-operative utility remains contentious [6]. Because these medicines can cause serious side effects, patients and doctors need reliable numbers to weigh the risks against the limited benefits they usually provide [7]. Proponents argue that anthracycline-based regimens may eradicate occult micro metastases [8], whereas sceptics underscore that no randomized trial has demonstrated a convincing overall survival advantage for localized disease and that, in the metastatic setting, chemotherapy yields no clinically meaningful benefit beyond brief tumour control [9]. When used, doxorubicin—often paired with ifosfamide—remains the reference backbone [10], and newer targeted or immune agents (pazopanib, regorafenib, pembrolizumab) extend progression-free survival by only weeks to months without improving overall survival or patient-reported outcomes [1,8,11]. Given these modest efficacy signals, rigorous quantification of treatment-related early/transient and late/persistent toxicity becomes paramount to inform risk–benefit discussions and trial design [12–14].

Systemic therapy is frequently limited by—usually transient and reversible—hematological and gastrointestinal toxicities, which trigger dose reductions, delays, and early discontinuation [15]; reported grade ≥ 3 AE frequencies vary widely because trials employ disparate grading scales, selective event reporting, and inconsistent denominators, complicating efforts to balance these toxicities against the modest efficacy benefits observed.

No up-to-date synthesis rigorously harmonizes AE definitions, normalizes event rates to cohort size, and interrogates reporting quality across both historical and contemporary RCTs, leaving clinicians without reliable toxicity benchmarks [16] and hindering the design of future trials that can meaningfully weigh risk against benefit in this rare cancer.

This systematic review seeks to resolve the uncertainty around chemotherapy-related toxicity in STS by answering a single overarching question: "What is the nature, frequency, and treatment attribution of adverse events in systemic therapy for soft tissue sarcoma, and how consistently are these events reported across randomized controlled trials?" To this end, we will (i) pool and normalize the incidence of CTCAE grade ≥ 3 and grade 4 toxicities across all eligible RCTs; (ii) compare composite toxicity burdens between conventional anthracycline-based regimens and newer targeted or immune therapies; (iii) calculate treatment-versus-control risk differentials where parallel safety data exist; and (iv) critically appraise AE reporting practices to identify methodological deficits and propose harmonized, CTCAE v5.0-driven standards for future sarcoma trials.

2. Materials and Methods

This systematic review and meta-analysis was conducted in accordance with PRISMA 2020. The protocol was registered prospectively in PROSPERO (CRD420251087366); any deviations are noted below.

The selection process followed predefined PICO criteria:

Patient/Population: patients with histologically confirmed soft tissue sarcoma (STS) of any subtype or age.
Intervention: systemic therapy (e.g., cytotoxic chemotherapy, kinase inhibitors, or immune checkpoint inhibitors) administered in the adjuvant, neoadjuvant, or palliative setting.
Comparison: no systemic therapy, i.e., surgery $\pm$ radiotherapy, best supportive care, or placebo.
Outcome: incidences of grade ≥ 3 adverse events (AEs); secondary outcomes: overall survival and treatment-related mortality.
Study type: randomized controlled trials.

Exclusion criteria were duplicate publications, non-English language, and absence of extractable AE data.

A professional librarian designed comprehensive search strings (Supplementary Table S1). PubMed, CENTRAL, and Google Scholar were queried from inception to 8 January 2025. Searches were updated on 16 April 2025.

Two reviewers (RA, PH) independently screened titles and abstracts, assessed full texts, and resolved discrepancies by consensus with a third reviewer (BF). Reasons for exclusion at the full-text stage are detailed in Supplementary Table S2. The selection process is illustrated in a PRISMA 2020 flow diagram (Figure 1).

Using a piloted electronic form, two reviewers extracted study characteristics (author, year, design, setting, drugs, dosing, sample size, follow-up) and outcome data (numerators and denominators for AEs by grade, survival estimates). Disagreements were resolved by a third reviewer. The screening tool Rayyan (Rayyan: AI-Powered Systematic Review Management Platform) was used to screen for duplicates and detection of wrong study types.

Study characteristics are summarized in Table 1.

AE terms reported as WHO grades or narrative descriptors were recoded to CTCAE v5.0 organ classes using a predefined mapping key (https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v5-5x7.pdf (accessed on 17 September 2025)) For each study, we identified the denominator used for toxicity reporting; frequencies were normalized to "patients evaluable for safety". Trials lacking an explicit denominator were excluded from quantitative synthesis but retained for qualitative comment.

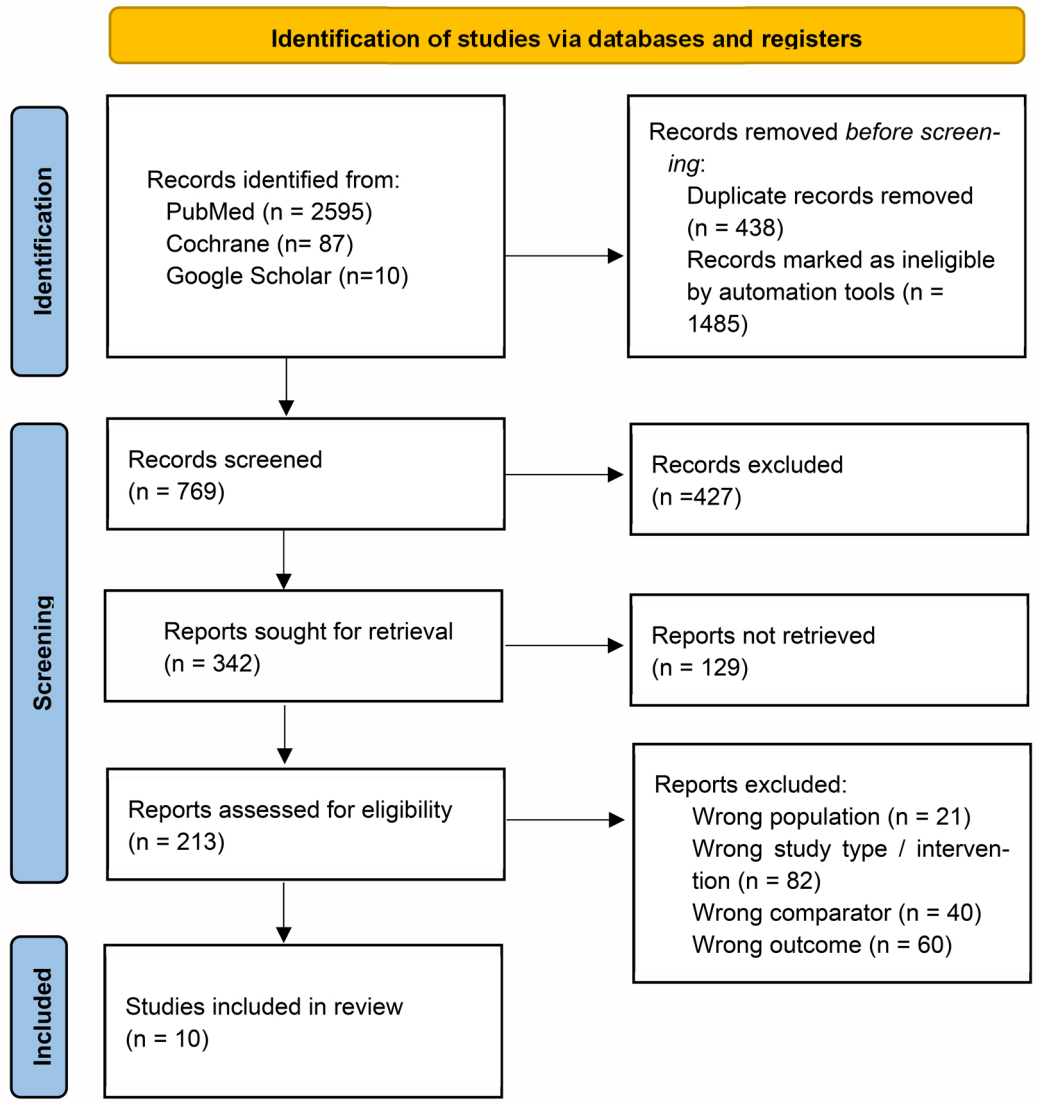


Figure 1. PRISMA 2020 flow diagram.

Randomized trials were appraised with the Cochrane RoB 2 tool. Appraisal was performed by one reviewer (RA) and the support of ChatGPT v.4. Detailed judgements are provided in Supplementary Table S3 and Figure S1.

The primary endpoint was the pooled incidence of CTCAE grade $\geq$ 3 AEs. Further measures included grade 4 AE incidence, normalized AE burden (events per 100 treated patients), and treatment-versus-control risk ratios (RRs) in selected toxicity classes.

Pooled proportions were computed on logit-transformed data using a DerSimonian–Laird random-effects model when $\geq$3 studies were available; otherwise, results are presented descriptively. Special attention was also given to late-effect toxicities under the supervision of a fourth reviewer (GS). Normalized AE burden was calculated as (events $\div$ patients evaluable for safety) $\times$ 100. Between-group comparisons (anthracycline vs. kinase inhibitor regimens) employed unpaired two-tailed *t*-tests (α = 0.05). Treatment effect RRs were calculated when both arms reported events. Statistical heterogeneity was quantified with I^2 and τ^2 in the DerSimonian–Laird random-effects model analyses, and 95% CIs were calculated using the Hartung–Knapp method. Analyses were performed in R 4.3.2 using the meta and metafor packages; figures were drafted in Excel 365.

Table 1. Study characteristics.

Study Title or Registration Number	Trial Type	Setting	Chemotherapy	Dose or Schedule	Patient Count (Treatment/Control)	Median Follow-Up, Months	Evaluated Outcomes
Pazopanib for metastatic soft-tissue sarcoma (PALETTE) [11]	Randomized, double-blind, placebo-controlled phase 3 trial	Adjuvant	Pazopanib		246/123	14.9	PFS, OS, response rate, safety and quality of life
EORTC 62931 [17]	Multicenter randomized controlled trial	Adjuvant	Doxorubicin, Ifosfamide, Lenograstim	800 mg daily	175/176	95.88	PFS, OS, toxic effects
Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles [18]	Randomized cooperative trial	Adjuvant	Epidoxorubicin, Ifosfamide	Five cycles of doxorubicin 75 mg/m^2, ifosfamide 5 g/m^2, and lenograstim every 3 weeks	53/51	59	DFS, OS, toxicity
SU2C-SARC032 [19]	Randomized clinical trial	Neoadjuvant	Pembrolizumab	5 cycles of 4′-epidoxorubicin 60 mg/m^2 days 1 and 2 and ifosfamide 1.8 g/m^2 days 1 through 5, with hydration, mesna, and granulocyte colony-stimulating factor	64/63	43	DFS, OS, grade 3 or higher adverse events
Neo-adjuvant chemotherapy for 'high-risk' adult soft tissue sarcoma [20]	Randomized phase II study	Neoadjuvant	Doxorubicin and Ifosfamide	200 mg i.v. every 3 weeks	67/67	88	Estimated 5-year DFS, 5-year OS, toxicity
Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma [21]	Randomized controlled trial	Adjuvant	Cyclophosphamide, Vincristine, Doxorubicin, Dacarbazine	3 cycles of 3-weekly doxorubicin 50 mg/m^2 intravenous (i.v.) bolus and ifosfamide 5 g/m^2 (24 h infusion)	145/172	80	RFS, OS, local recurrence, distant metastases, toxicity
Intensified adjuvant IFADIC chemotherapy in combination with radiotherapy versus radiotherapy alone for soft tissue sarcoma: long-term follow-up of a prospective randomized feasibility trial [22]	Randomized controlled trial	Adjuvant	Ifosfamide, Dacarbazin, Doxorubicin	Ifosfamide (1500 mg/m^2, days 1–4), DTIC (200 mg/m^2, days 1–4) and doxorubicin (25 mg/m^2, days 1 and 2) i.v., in a 14-day cycle.	31/28	97	RFS, time to local failure, time to distant failure, OS

Table 1. *Cont.*

Study Title or Registration Number	Trial Type	Setting	Chemotherapy	Dose or Schedule	Patient Count (Treatment/Control)	Median Follow-Up, Months	Evaluated Outcomes
Eastern Cooperative Oncology Group: a comparison of adjuvant doxorubicin and observation for patients with localized soft tissue sarcoma [23]	Randomized controlled trial	Adjuvant	Doxorubicin	70 mg/m^2 (slow push, every 3 weeks for seven courses for a maximum of 550 mg/m^2)	17/13	30	DFS, OS
Vinorelbine and continuous low-dose cyclophosphamide in patients with high-risk rhabdomyosarcoma [24]	Multicenter, open-label, randomized, phase 3 trial	Maintenance Therapy	Vinorelbine, Cyclophosphamide	Cyclophosphamide 500 mg/m^2 intravenously (i.v.) bolus on day 1, vincristine 1.4 mg/m^2 i.v. bolus on day 1, doxorubicin (Adriamycin; Adria Laboratories, Columbus, OH, USA) 50 mg/m^2 i.v. bolus on day 1, and dacarbazine (DTIC) 400 mg/m^2 by 1-h infusion on days 1 to 3 (CYVADIC) cycles repeated every 28 days for eight courses	185/186	60.3	5-year DFS, 5-year OS, toxicity
Safety and efficacy pf regorafenib in patients with advanced soft tissue sarcoma [15]	Randomized, double-blind, placebo-controlled, phase 2 trial		Regorafenib	6 cycles of i.v. vinorelbine 25 mg/m^2 on days 1, 8, and 15, and daily oral cyclophosphamide 25 mg/m^2, on days 1–28	90/92	20	PFS, grade 3 or higher adverse events

The complete extraction dataset, statistical code, and figure templates are openly available on Zenodo (doi: 10.5281/zenodo.15848465).

Tables S1–S3 (Full search strings), Table S4 (Excluded full texts, with reasons), Table S5 (Detailed judgments), and Figure S1 (Risk of bias plot) accompany this article. The publicly deposited dataset and R scripts enable independent verification of all analyses.

3. Results

3.1. CTCAE Categories and Denominator Definitions

Eight of the ten eligible randomized trials reported sufficient safety data, providing 978 chemotherapy-exposed patients; three placebo control cohorts contributed 278 patients. Patient numbers per treatment arm ranged widely—from 45 to 239—so later frequency estimates are, if not otherwise specified, expressed with explicit numerators and denominators.

Adverse event terminology varied across time. Earlier trials used the WHO grading system or collapsed events into broad "clinical" versus "laboratory" categories, whereas more recent studies applied CTCAE v4.0 or v5.0. To ensure comparability, all reported events were recoded into the corresponding CTCAE organ classes (Tables 2 and 3).

Table 2. CTCAE categories and denominators for toxicity reporting.

Adverse Event	Van der Graaf et al. (2012) [11]	Woll et al. (2012) [17]	Frustaci et al. (2001) [18]	Mowery et al. (2024) [19]
General disorders [%]	13	1	0	6
Fatigue	30	nr	0	1
Fever	nr	1	0	0
Pain	nr	nr	0	3
Gastrointestinal disorders [%]	13	15	16	10
Diarrhea	11	0	0	2
Nausea/vomiting	16	19	2	5
Oral mucositis	3	5	5	0
Investigations [%]	0	43	38	1
Weight loss	0	nr	0	0
Increased creatinine	nr	0	0	0
Increased Alanine aminotransferase	nr	2	0	0
Increased aspartate aminotransferase	nr	0	0	0
Increased blood bilirubin	nr	1	0	nr
Decreased white blood cell count	nr	28	14	1
Decreased neutrophil count	nr	13	nr	nr
Decreased platelet count	nr	19	3	nr
Vascular disorders [%]	7	nr	0	9
Hypertension	16	nr	0	6
Blood and lymphatic system disorders [%]	nr	7	17	10
Anemia	nr	11	7	7
Infections and infestations [%]	nr	7	0	13
Wound infection	nr	0	0	7
Infection, general	nr	12	0	2
Metabolism and nutrition disorders [%]	6	nr	0	0
Anorexia	14	nr	0	0
Dysgeusia	0	nr	0	0

Table 2. *Cont.*

Adverse Event	Van der Graaf et al. (2012) [11]	Woll et al. (2012) [17]	Frustaci et al. (2001) [18]	Mowery et al. (2024) [19]
Skin and subcutaneous tissue disorders [%]	1	nr	0	3
Rash/desquamation	1	nr	0	2
Nervous system disorders [%]	nr	1	0	0
Cardiac disorders [%]	1	1	0	0

Table 3. CTCAE categories and denominators for toxicity reporting.

Adverse Event	Gortzak et al. (2001) [20]	Bramwell et al. (1994) [21]	Bisogno et al. (2019) [24]	Mir et al. (2016) [15]
General disorders [%]	nr	nr	29	22
Fatigue	nr	nr	nr	12
Fever	nr	nr	53	1
Pain	nr	nr	nr	7
Gastrointestinal disorders [%]	28	14	6	10
Diarrhea	nr	nr	9	4
Nausea/vomiting	18	18	1	1
Oral mucositis	nr	nr	nr	4
Investigations [%]	8	31	85	8
Weight loss	nr	nr	nr	nr
Increased creatinine	0	nr	nr	0
Increased Alanine aminotransferase	nr	0	nr	nr
Increased aspartate aminotransferase	nr	0	nr	1
Increased blood bilirubin	nr	0	nr	nr
Decreased white blood cell count	5	31	86	4
Decreased neutrophil count	nr	nr	66	1
Decreased platelet count	0	8	1	1
Vascular disorders [%]	nr	nr	nr	18
Hypertension	nr	nr	nr	16
Blood and lymphatic system disorders [%]	nr	nr	9	3
Anemia	nr	nr	16	3
Infections and infestations [%]	0	2	2	3
Wound infection	0	nr	nr	nr
Infection, general	0	3	3	3
Metabolism and nutrition disorders [%]	nr	5	nr	3
Anorexia	nr	6	nr	3
Dysgeusia	nr	nr	nr	nr
Skin and subcutaneous tissue disorders [%]	nr	nr	1	4
Rash/desquamation	nr	nr	1	4
Nervous system disorders [%]	1	5	1	1
Cardiac disorders [%]	1	2	0	1

In Tables 2 and 3, a reasonable range of adverse events reported across the studies is summarized. Not every subtype of adverse event was reported in every study. The concerned cells are annotated with "nr"= not reported (e.g., "fever" in Van der Graaf et al. [11]). We classified the adverse events in the CTCAE categories, which are highlighted in blue. The most frequently reported clinical and laboratory adverse events overall are highlighted in salmon. It is notable that the adverse events themselves are listed in absolute numbers, whereas the classifications are frequencies (%), which means that in the Woll et al. study [17], about 15% of the treated patients had a gastrointestinal adverse event—11 cases of diarrhea and 16 and 3 of nausea/vomiting and oral mucositis, respectively. One patient could also have more than one AE, since the protocols did not give information about which patients suffered from what kind of adverse event.

Denominator definitions also differed: five trials reported AEs per treated patient, two per intention-to-treat population, and one failed to define its safety cohort. To check for

every quantitative analysis that follows, event frequencies are therefore normalized to the number of patients explicitly evaluable for safety in each arm. This approach establishes a transparent foundation for comparing toxicity profiles across systemic therapy regimens in soft tissue sarcoma.

3.2. Frequency of CTCAE Grade 3–4 Adverse Events Across Trials

Pooled across the eight trials, grade 3 adverse events were documented in 978 treated patients, while grade 4 events were reported separately in seven studies (Tables 4 and 5). The frequently mentioned AE "alopecia" had to be excluded from all analyses, since it only exists as grade 1 or 2 AE in CTCAE v5.0. Leucopenia emerged as the most common grade 3 toxicity, occurring 169 times in the treated patients overall. Gastrointestinal events—principally nausea/vomiting—followed, at 80 cases, and fever was reported 55 times (Figure 2).

Table 4. Absolute event count of grade 3 adverse events across studies.

Adverse Event	Van der Graaf et al. (2012) [11]	Woll et al. (2012) [17]	Frustaci et al. (2001) [18]	Mowery et al. (2024) [19]	Gortzak et al. (2001) [20]	Bramwell et al. (1994) [21]	Bisogno et al. (2019) [24]	Mir et al. (2016) [15]
Fatigue	30	nr	0	1	nr	nr	nr	nr
Diarrhea	11	0	0	2	nr	nr	9	4
Nausea/vomiting	16	19	2	5	18	18	1	1
Weight loss	0	nr	0	0	nr	nr	nr	nr
Hypertension	16	nr	0	6	nr	nr	nr	16
Anorexia	14	nr	0	0	nr	6	nr	3
Dysgeusia	0	nr	0	0	nr	nr	nr	nr
Rash/desquamation	1	nr	0	2	nr	nr	1	nr
Mucositis	1	5	5	0	nr	nr	nr	4
Fever	nr	1	0	0	nr	nr	53	1
(Skin) infection	nr	12	0	2	0	3	3	3
Neurological problem	nr	1	0	0	1	5	5	nr
Cardiac	16	1	0	0	1	2	0	1
Pain	nr	nr	0	3	nr	nr	nr	7
Wound infection	nr	nr	0	7	nr	nr	nr	nr
Creatinine	nr	0	0	0	0	nr	nr	nr
Bilirubin	nr	1	0	nr	nr	0	nr	0
AST elevated	nr	0	0	0	nr	0	nr	1
ALT elevated	nr	2	0	0	nr	0	nr	1
Leucopenia	nr	28	14	1	5	31	86	4
Neutropenia	nr	13	nr	nr	nr	nr	66	1
Thrombocytopenia	nr	19	3	nr	0	8	1	1
Anemia	nr	11	5	7	nr	nr	16	3

This table shows the absolute event counts of the most frequently reported CTCAE grade 3 over all eight studies eligible for this analysis. The sum of the events does not represent the number of patients who had a grade 3 adverse event, since one patient could have had more than one side effect and the studies did not provide us with clear patient profiles. Not every subtype of adverse event was reported in every study. The concerned cells are annotated with "nr".

Table 5. Absolute event count of grade 4 adverse events across studies.

Adverse Event	Van der Graaf et al. (2012) [11]	Woll et al. (2012) [17]	Frustaci et al. (2001) [18]	Mowery et al. (2024) [19]	Gortzak et al. (2001) [20]	Bramwell et al. (1994) [21]	Bisogno et al. (2019) [24]	Mir et al. (2016) [15]
Fatigue	1	nr	0	0	nr	nr	nr	0
Diarrhea	0	0	0	0	nr	nr	0	0
Nausea/vomiting	0	0	0	0	1	1	0	0
Weight loss	0	nr	0	0	nr	nr	nr	nr
Hypertension	0	nr	0	0	nr	nr	nr	1
Anorexia	0	nr	0	0	nr	2	nr	0
Dysgeusia	0	nr	0	0	nr	nr	nr	nr

Table 5. *Cont.*

Adverse Event	Van der Graaf et al. (2012) [11]	Woll et al. (2012) [17]	Frustaci et al. (2001) [18]	Mowery et al. (2024) [19]	Gortzak et al. (2001) [20]	Bramwell et al. (1994) [21]	Bisogno et al. (2019) [24]	Mir et al. (2016) [15]
Rash/desquamation	0	nr	0	0	nr	nr	0	0
Mucositis	0	0	0	0	nr	nr	nr	0
Fever	nr	0	0	1	nr	nr	0	0
(Skin) infection	nr	0	0	0	1	1	0	0
Neurological problem	nr	0	0	0	1	1	1	nr
Cardiac	nr	0	0	0	1	0	0	1
Pain	nr	nr	0	0	nr	nr	nr	0
Wound infection	nr	nr	0	0	nr	nr	nr	0
Creatinine	nr	0	0	0	0	nr	nr	0
Bilirubin	nr	0	0	nr	nr	0	nr	nr
AST elevated	nr	0	0	0	nr	0	nr	0
ALT elevated	nr	0	0	0	nr	0	nr	nr
Leucopenia	nr	41	12	1	0	0	50	0
Neutropenia	nr	44	nr	nr	nr	nr	82	0
Thrombocytopenia	nr	11	2	nr	0	0	1	nr
Anemia	nr	2	1	0	nr	nr	3	1

This table shows the absolute event counts of the most frequently reported CTCAE grade 4 over all eight studies eligible for this analysis. The sum of the events does not represent the number of patients who had a grade 3 adverse event, since one patient could have had more than one side effect and the studies did not provide us with clear patient profiles. Not every subtype of adverse event was reported in every study. The concerned cells are annotated with "nr".

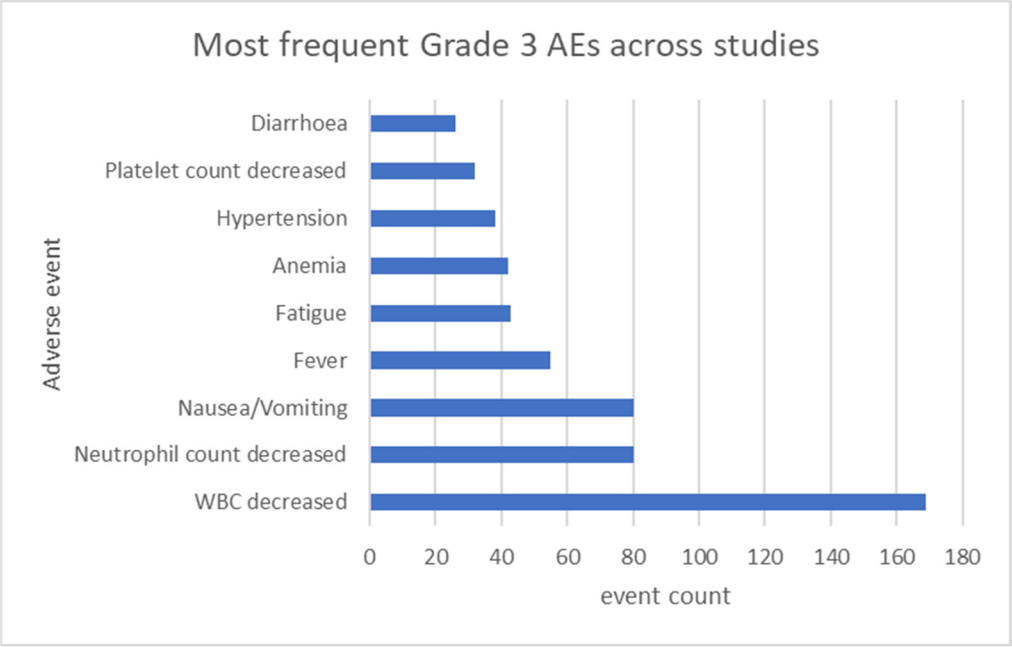


Figure 2. Bar plot of most frequent grade 3 AEs.

Subgroup DerSimonian–Laird random-effects model analyses were performed for two selected adverse events, "Leucopenia" and "Nausea/Vomiting" (Figures 3 and 4). Both analyses showed significant between-study heterogeneity ($p < 0.0001$).

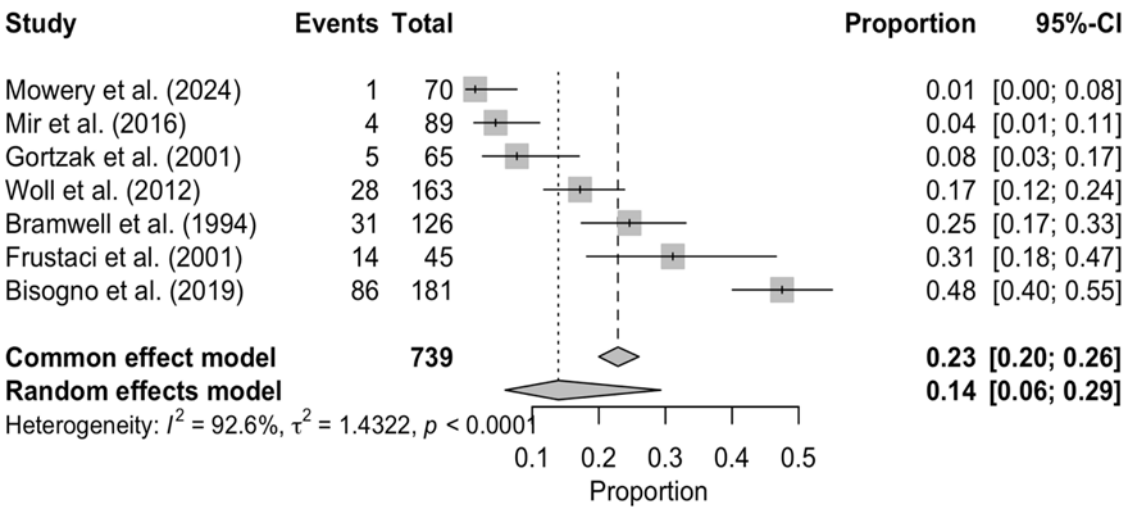


Figure 3. Forest plot of grade 3 leucopenia. This forest plot represents the absolute event count of grade 3 leucopenia in every study that reported this kind of AE, sorted in ascending order of frequency. Pooled effect estimates are denoted by the diamond. Mowery et al. (2024) [19]; Mir et al. (2016) [15]; Gortzak et al. (2001) [20]; Woll et al. (2012) [17]; Bramwell et al. (1994) [21]; Frustaci et al. (2001) [18]; Bisogno et al. (2019) [24].

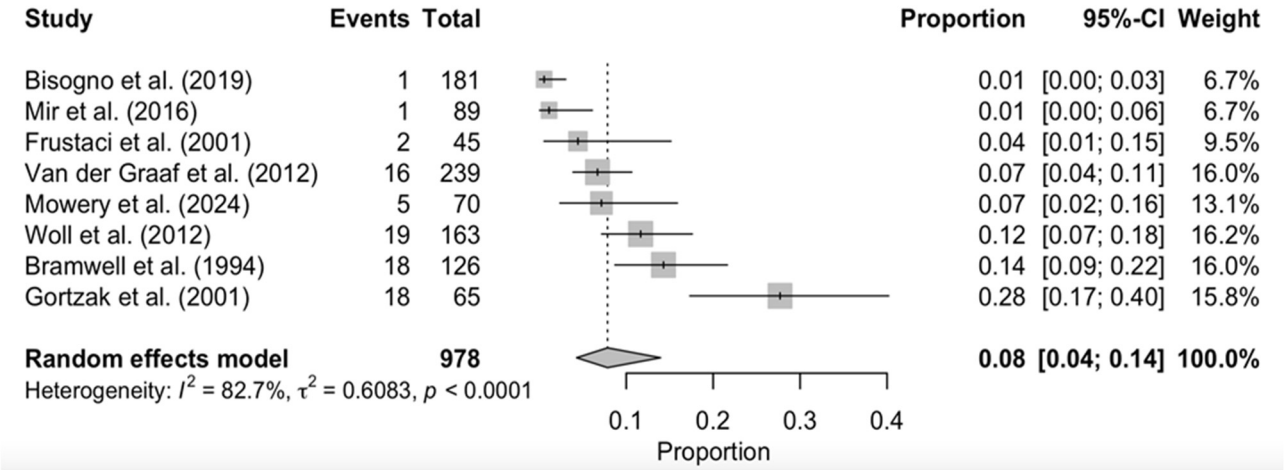


Figure 4. Forest plot of grade 3 nausea/vomiting. This forest plot represents the absolute event count of grade 3 nausea/vomiting in every study that reported this kind of AE, sorted in ascending order of frequency. Pooled effect estimates are denoted by the diamond. Bisogno et al. (2019) [24]; Mir et al. (2016) [15]; Frustaci et al. (2001) [18]; Van der Graaf et al. (2012) [11]; Mowery et al. (2024) [19]; Woll et al. (2012) [17]; Bramwell et al. (1994) [21]; Gortzak et al. (2001) [20].

3.3. Toxicity-Related Deaths and Treatment Discontinuation

Six studies reported toxic deaths, of which there were cumulatively four (0.4% of the treated patients). In total, 71 treatment discontinuations due to adverse events (5.5% of the treated patients) were noted.

3.4. Persisting/Late-Term Toxicities

Often persisting, late-term toxicities, such as cardiac, neurological, nephrological, and hepatic toxicities, were rarely assessed/reported as relatively uncommon, occurring in <1% of the patients. Cardiac toxicity, notably grade 3 decreases in left ventricular ejection fraction, were noted in five patients, while grade 3 hepatic toxicity, represented by ALAT elevation, occurred three times. No grade 3 nephrological toxicity (creatinine increase) or

grade 3 ASAT elevation was observed. Clinically frequently observed life quality-defining neuropathic side effects were basically not reported.

Only two grade 4 long-lasting AEs were reported.

Compared to acute events, late-effect toxicities were reported rarely.

3.5. Normalized Grade 3 Toxicity Burden

Because cohort sizes varied markedly, each grade 3 event was re-expressed as "patients affected per 100 treated" (Tables 6 and 7; Figure 5). After normalization, leucopenia affected, on average, 17 patients per 100 (95% CI 14–20); gastrointestinal toxicities clustered at 8–11 per 100, and fatigue at 4 per 100.

Table 6. Normalized grade 3 AE burden by study size.

Adverse Event	Van der Graaf et al. (2012) [11]	Woll et al. (2012) [17]	Frustaci et al. (2001) [18]	Mowery et al. (2024) [19]	Gortzak et al. (2001) [20]	Bramwell et al. (1994) [21]	Bisogno et al. (2019) [24]	Mir et al. (2016) [15]
Fatigue	13	nr	0	1	nr	nr	nr	13
Diarrhea	5	0	0	3	nr	nr	5	4
Nausea/vomiting	6	12	3	7	28	14	1	1
Weight loss	0	nr	0	0	nr	nr	nr	nr
Hypertension	7	nr	0	9	nr	nr	nr	18
Anorexia	6	nr	0	0	nr	5	nr	3
Dysgeusia	0	nr	0	0	nr	nr	nr	nr
Rash/desquamation	1	nr	0	8	nr	nr	1	nr
Mucositis	1	3	10	0	nr	nr	nr	4
Fever	nr	1	0	0	nr	nr	29	1
(Skin) infection	nr	7	0	7	0	2	31	3
Neurological problem	nr	1	0	0	1	5	1	nr
Cardiac	1	1	0	0	1	2	0	1
Pain	nr	nr	0	4	nr	nr	nr	8
Wound infection	nr	nr	0	10	nr	nr	nr	nr
Creatinine	nr	0	0	0	0	nr	nr	nr
Bilirubin	nr	1	0	nr	nr	0	nr	0
AST elevated	nr	0	0	0	nr	0	nr	0
ALT elevated	nr	2	0	0	nr	0	nr	1
Leucopenia	nr	19	30	1	8	25	48	4
Neutropenia	nr	9	nr	nr	nr	nr	37	1
Thrombocytopenia	nr	13	7	nr	0	6	1	1
Anemia	nr	8	17	10	nr	nr	9	3

This table shows the frequencies of the most frequently reported CTCAE grade 3 over all eight studies eligible for this analysis. Not every subtype of adverse event was reported in every study. The concerned cells are annotated with "nr" = not reported.

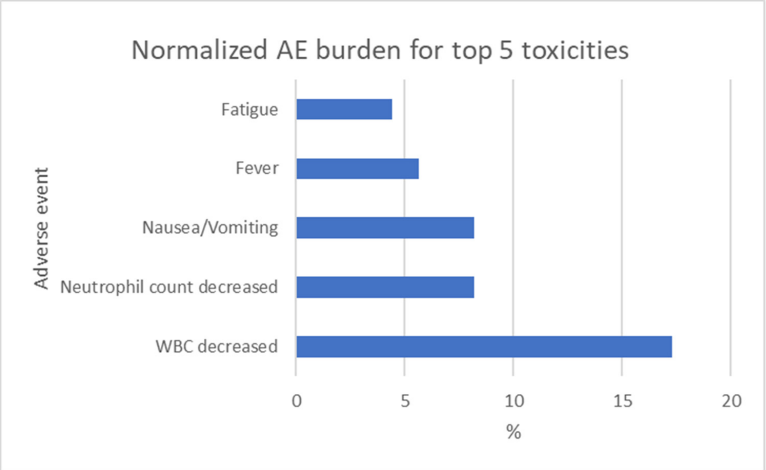


Figure 5. Normalized AE burden for top 5 toxicities.

Table 7. Normalized grade 4 AE burden by study size.

Adverse Event	Van der Graaf et al. (2012) [11]	Woll et al. (2012) [17]	Frustaci et al. (2001) [18]	Mowery et al. (2024) [19]	Gortzak et al. (2001) [20]	Bramwell et al. (1994) [21]	Bisogno et al. (2019) [24]	Mir et al. (2016) [15]
Fatigue	1	nr	0	0	nr	nr	nr	0
Diarrhea	0	0	0	0	nr	nr	0	0
Nausea/vomiting	0	0	0	0	1	12	0	0
Weight loss	0	nr	0	0	nr	nr	nr	nr
Hypertension	0	nr	0	0	nr	nr	nr	1
Anorexia	0	nr	0	0	nr	2	nr	0
Dysgeusia	0	nr	0	0	nr	nr	nr	nr
Rash/desquamation	0	nr	0	0	nr	nr	0	0
Mucositis	0	0	0	0	nr	nr	nr	0
Fever	nr	0	0	1	nr	nr	0	0
(Skin) infection	nr	0	0	0	1	1	0	0
Neurological problem	nr	0	0	0	1	4	1	nr
Cardiac	nr	0	0	0	1	0	0	1
Pain	nr	nr	0	0	nr	nr	nr	0
Wound infection	nr	nr	0	0	nr	nr	nr	0
Creatinine	nr	0	0	0	0	nr	nr	0
Bilirubin	nr	0	0	nr	nr	0	nr	nr
AST elevated	nr	0	0	0	nr	0	nr	0
ALT elevated	nr	0	0	0	nr	0	nr	nr
Leucopenia	nr	28	27	1	0	0	28	0
Neutropenia	nr	30	nr	nr	nr	nr	45	0
Thrombocytopenia	nr	8	7	nr	0	0	1	nr
Anemia	nr	1	7	0	nr	nr	2	1

This table shows the frequencies of the most frequently reported CTCAE grade 4 over all eight studies eligible for this analysis. Not every subtype of adverse event was reported in every study. The concerned cells are annotated with "nr" = not reported.

Normalization sharpens inter-study comparisons. For example, 18 cases of nausea/vomiting translated into 28% of patients in the 65-patient Gortzak trial [20] but only 14% in the 126-patient Bramwell study [21].

Grade 4 toxicities were widely distributed and almost exclusively hematologic. Three out of seven studies reported 27 to 45% grade 4 hematologic toxicity and the others < 1%. Non-hematologic grade 4 events were observed in fewer than 12% of patients. Nevertheless, reporting heterogeneity remains substantial: contemporary trials provided detailed and exhaustive matrices, whereas older studies listed only selected events.

Subgroup analysis of the cumulative normalized toxicity burden (indicated in [%] resulting from the total number of grade 3 AE divided by 100) in kinase-inhibitor-based and anthracycline-based treatments is shown in In Figure 6. The two regimens showed different composite rates but without statistical significance (84% vs. 58%; $p = 0.64$), suggesting that raw count disparities stemmed largely from sample-size differences rather than inherent pharmacological drug choice. The kinase-inhibitor-based treatment class includes the Van der Graaf et al. (Pazopanib) [11] and the Mir et al. (Regorafenib) [15] studies, whereas anthracyclines were used in the Woll [17], Frustaci [18], Bramwell [21], and Gortzak [20] studies. The remaining two studies used a PD-1 antibody (Pembrolizumab) and an alkaloid (Vinorelbine) and were excluded from this subgroup analysis for better comparability.

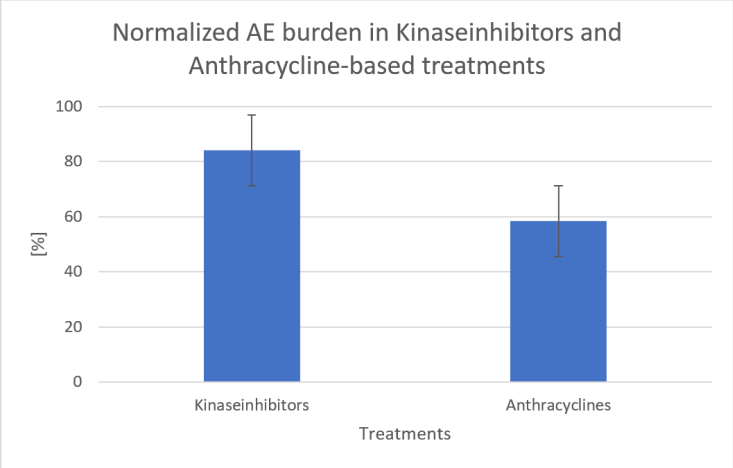


Figure 6. Toxicity burdens pooled by mechanism.

3.6. Treatment-Versus-Control Comparison of Toxicities

Three trials administered placebo to their control group, whereas the remaining protocols compared systemic therapy to surgery or radiotherapy alone. Therefore, only van der Graaf 2012 (pazopanib) [11], Mir 2016 (regorafenib) [15], and Mowery 2024 (pembrolizumab) [19] reported grade 3–4 adverse events (AEs) for both the experimental and control arms, which are listed in Table 8.

Table 8. Treatment vs. control comparison of grade 3 toxicities.

Adverse Event	Van der Graaf et al. (2012) [11] Treatment Group	Control Group	Mowery et al. (2024) [19] Treatment Group	Control Group	Mir et al. (2016) [15] Treatment Group	Control Group
Fatigue	30	6	1	0	12	6
Diarrhea	11	1	2	1	4	2
Nausea/vomiting	16	3	5	0	1	0
Weight loss	0	0	0	0	nr	0
Hypertension	16	4	6	3	16	2
Anorexia	14	0	0	0	3	4
Dysgeusia	0	0	0	0	nr	nr
Rash/desquamation	1	0	6	4	nr	nr
Mucositis	1	0	0	0	4	0
Fever	nr	nr	0	0	1	1
(Skin) infection	nr	nr	2	0	3	0
Neurological problem	nr	nr	0	0	nr	nr
Cardiac	16	3	0	0	1	0
Pain	nr	nr	7	0	7	5
Wound infection	nr	nr	7	6	nr	nr
Creatinine	nr	nr	0	0	0	0
Bilirubin	nr	nr	nr	nr	nr	nr
Increased AST	nr	nr	0	0	1	1
Increased ALT	nr	nr	0	0	1	1
Leucopenia	nr	nr	1	1	4	5
Neutropenia	nr	nr	nr	nr	1	0
Thrombocytopenia	nr	nr	nr	nr	1	0
Anemia	nr	nr	10	3	3	1

Not every subtype of adverse event was reported in every study. The concerned cells are annotated with "nr" = not reported.

Across these studies, the experimental regimens consistently produced higher rates of common grade 3 toxicities. Fatigue rose from 5% to 31% in van der Graaf [11] and from 7% to 13% in Mir [15]; gastrointestinal events (nausea/vomiting, diarrhea) increased by 4–8 percentage points, and hematologic events by 6–12 percentage points. A pooled *t*-test

of the study-level differences yielded $p = 0.001$, confirming an overall significant excess of toxicity with active treatment.

On the other hand, subgroup DerSimonian–Laird random-effects model analyses were performed for two selected adverse events, "Vomiting" and "Diarrhea" (Figures 7 and 8), showing only an indication of an increased risk in the treatment group, without statistical significance (RR > 1, 95% CI 0.89–18.5 and 0.89–8.65, respectively).

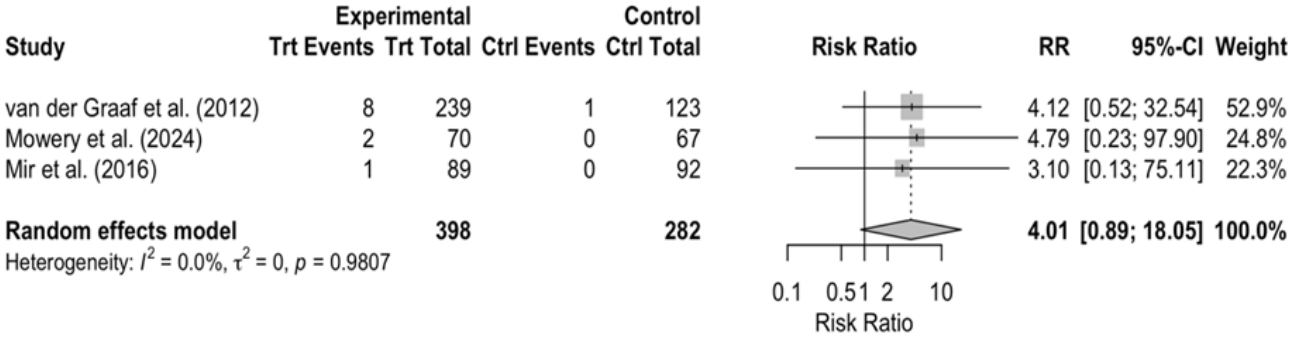


Figure 7. Treatment vs. control comparison—grade 3 vomiting. When analyzing one single AE, there is an indication of an increased risk in the treatment group compared to the control group (RR > 1), but the results remain insignificant, since the CI is wide and including 1. All studies show the same tendencies, resulting in very low between-study heterogeneity I^2 = 0.0%. Pooled effect estimates are denoted by the diamond. Van der Graaf et al. (2012) [11]; Mowery et al. (2024) [19]; Mir et al. (2016) [15].

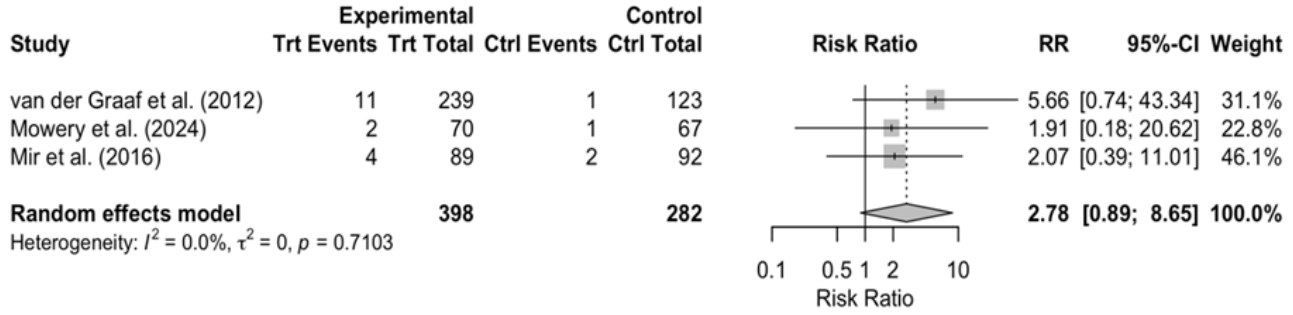


Figure 8. Treatment vs. control comparison—grade 3 diarrhea. When analyzing one single AE, there is an indication of an increased risk in the treatment group compared to the control group (RR > 1), but the results remain insignificant, since the CI is wide and including 1. All studies show the same tendencies, resulting in very low between-study heterogeneity I^2 = 0.0%. Pooled effect estimates are denoted by the diamond. Van der Graaf et al. (2012) [11]; Mowery et al. (2024) [19]; Mir et al. (2016) [15].

Interpretation of these findings is limited by incomplete and asymmetric AE reporting in the control arms of several earlier trials, where toxicities were either not collected prospectively or summarized only qualitatively (Figure 9). This reporting imbalance introduces bias and underlines the need for future sarcoma studies to document toxicities consistently.

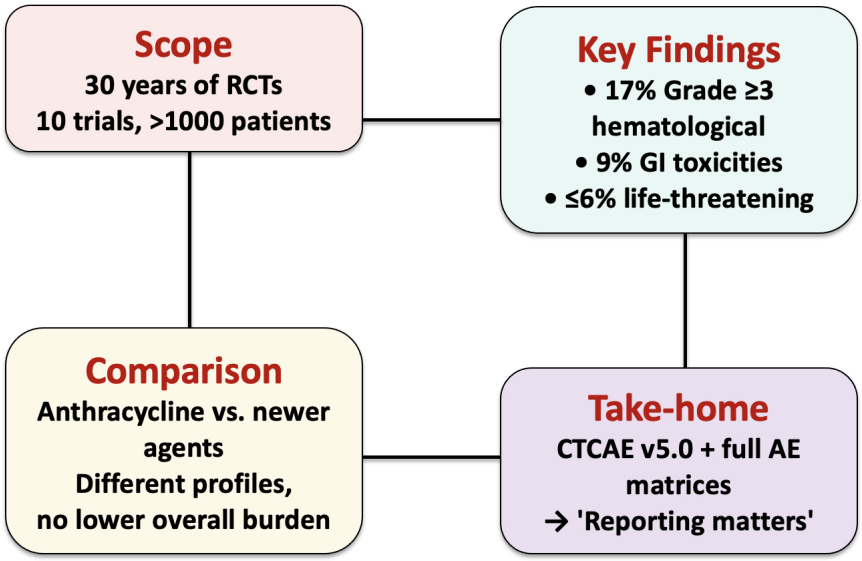


Figure 9. Overview of a 30-year systematic review of randomized STS systemic therapy trials (>1000 patients). Severe adverse events are common (≈17% hematological, ≈9% gastrointestinal, ≤6% life-threatening). Toxicity profiles differ between drug classes, but newer agents are not overall safer. Rigorous CTCAE v5.0 reporting and full AE matrices are required for reliable risk–benefit appraisal.

4. Discussion

This systematic review synthesizes three decades of randomized evidence and shows that severe adverse events (AEs) in systemic therapy for soft tissue sarcoma are moderately frequent yet markedly under-reported—mainly regarding potentially persistent late effects. After rigorous CTCAE re-mapping and denominator normalization, grade $\geq$ 3 hematological toxicities occurred in roughly one in six treated patients, severe gastrointestinal events in one in ten, and grade 4 events in no more than 6%. Despite this apparently manageable profile, substantial gaps in AE capture—two trials with insufficient toxicity data and seven lacking parallel control-arm reporting—limit the reliability of risk estimates and undermine confidence in risk–benefit appraisal.

Pooling 978 chemotherapy-exposed patients across eight RCTs revealed a consistent, "predictable" toxicity hierarchy: leucopenia dominated (17 patients/100), followed by nausea/vomiting (8–11/100) and fatigue (~4/100). Late-effect toxicities (cardiac, hepatic, neurological, and nephrological) were rarely assessed and reported, occurring only in <1% of the patients. Normalized burdens did not differ between anthracycline and kinase-inhibitor regimens (58% vs. 84%; p = 0.64), indicating that drug class selection alone is unlikely to mitigate severe toxicity (Figure 6). Where control data were available, experimental therapy increased common grade-3 AEs by 4–12 percentage points (p = 0.001), underscoring a tangible but clinically non-negotiable safety cost (Table 8).

Viewed through a bedside lens, the numbers translate into a clinically non-trivial but broadly manageable and predominantly short-term risk profile. A leucopenia rate of 17% (≈1 in 6 patients) is comparable to that seen with modern anthracycline regimens in breast cancer, where grade $\geq$ 3 neutropenia ranges from 20 to 30%—yet the efficacy dividend in STS is far smaller. In PALETTE (pazopanib) [11], the 3-month PFS gain was accompanied by a 14% AE-related discontinuation rate; REGOSARC (regorafenib) [15] improved median PFS by 1.6 months while prompting dose reductions or delays in 48% of patients. Across the eight trials with safety data, discontinuations for toxicity clustered between 1% and 14% (on average 5.5%), indicating that severe AEs routinely truncate therapy and may nullify any marginal survival benefit. Accordingly, chemotherapy in localized, high-risk STS

remains discretionary: clinicians must weigh a roughly 10–20% chance of therapy-limiting toxicity against PFS benefits measured in weeks and tailor prophylactic measures (G-CSF and guideline-based anti-emetic triplets) and close monitoring for the subset of patients who opt for systemic treatment.

Our toxicity estimates diverge notably from earlier sarcoma reviews, which cited grade ≥ 3 hematological rates as high as 40% and gastrointestinal rates exceeding 20% [25,26]. Those analyses pooled absolute counts from single-arm phase II studies or mixed heterogeneous denominators, thereby inflating frequencies in trials with small cohorts. After harmonizing denominators to "patients evaluable for safety," our leucopenia figure fell by ~50% and severe nausea/vomiting by ~60%, showing that denominator choice, rather than pharmacologic progress, explains much of the perceived decline. A second driver is the evolution of supportive care: nowadays, routinely administered prophylactic G-CSF, 5-HT_3 antagonists and NK_1 blockers, largely absent in trials from the 1990s, result in moderate myelosuppression and emesis. Consequently, our findings refine—not refute—earlier warnings by demonstrating that severe toxicity remains common but is quantitatively lower once methodological artefacts are removed and contemporary supportive measures are considered.

Methodological scrutiny reveals that reporting practices, not pharmacology, are the chief obstacle to reliable toxicity estimation. Of the ten eligible RCTs, seven failed to publish parallel control-arm AE matrices and two limited toxicity data to a very low level, forcing their exclusion from quantitative synthesis and inflating imprecision. Legacy WHO grading or narrative terms persisted in four trials, necessitating post hoc CTCAE mapping and introducing potential misclassification (Table 1). Denominators were equally problematic: only five studies specified a "patients-evaluable-for-safety" cohort, while two defaulted to intention-to-treat counts and one left the base population undefined. These deficits translated into serious or very serious concerns in the "Outcome Measurement" domain of our RoB 2 assessment for 4/10 trials (Supplementary Table S3). Encouragingly, all trials published since 2015 adopted CTCAE v4.0/5.0 and provided grade-stratified counts, indicating a shift toward better practice; however, until explicit denominators and full AE matrices become mandatory, certainty in toxicity estimates—and thus informed consent—will remain low. Our findings are supported by the results of a similar study, published in 2019 already, and also call for reporting to be carried out with more scrutiny [27].

The present study offers the largest pooled safety dataset in STS to date, achieved through an exhaustive multi-database search, duplicate screening, double data extraction, and public release of the full dataset and R code—steps that bolster transparency and reproducibility. A further strength is the systematic harmonization of AE terminology to CTCAE v5.0, which enabled denominator-normalized comparisons across three decades of trials and reduced inflation artefacts seen in prior reviews. Nevertheless, several constraints temper our conclusions. First, the evidence base is numerically small (ten RCTs; 1026 treated patients), with two trials providing insufficient toxicity data and seven lacking control-arm matrices. Second, between-study heterogeneity remained substantial for gastrointestinal and hematological AEs ($I^2 > 60\%$, Figures 3 and 4), and publication bias could not be assessed with so few studies.

This pooled data furnishes pragmatic toxicity benchmarks for patient counselling and supportive care planning. When systemic therapy is contemplated—typically as an optional adjunct in high-risk localized disease or for palliation—[28] clinicians can quote a 17% risk of grade ≥ 3 myelosuppression and an 8–11% risk of severe gastrointestinal events, with life-threatening toxicities seldom exceeding 6% (Table 7). Prophylactic G-CSF should therefore be standard when the anticipated incidence of grade ≥ 3 neutropenia exceeds 20% [29], and modern anti-emetic triplets (5-HT_3, NK_1, dexamethasone [30]) are justified

even for "moderately emetogenic" protocols. Because toxicity-driven discontinuation reached up to 14% in the reviewed trials, early integration of dose modification algorithms and real-time toxicity monitoring is essential. Most importantly, these figures should be presented as provisional lower bounds—acknowledging reporting gaps—in shared decision-making, enabling patients to weigh a tangible toxicity risk against often modest gains in progression-free or overall survival.

To convert "moderate and uncertain" toxicity estimates into high-certainty risk–benefit data, future sarcoma trials must treat adverse event capture as a primary endpoint rather than an afterthought. Reporting should follow a CTCAE v5.0 template with explicit safety denominators in both study arms, full grade stratification, and adherence to CONSORT-Harms extensions; the complete AE matrix should accompany every publication as a searchable supplement or within open repositories. Prospective safety pooling consortia—such as an expanded EORTC STS Net—could aggregate uniform toxicity data across simultaneously running studies, rapidly surpassing the 1000-patient threshold needed for precise, subtype-specific estimates. Regulators and funding bodies should incentivize such transparency by linking trial approval or reimbursement to publicly accessible AE datasets and by mandating inclusion of patient-reported outcome measures that capture symptomatic burdens often missed in clinician-graded CTCAE logs [31]. Only through these procedural guardrails can forthcoming systemic-therapy trials deliver toxicity evidence commensurate with their efficacy claims.

5. Conclusions

Systemic therapy for soft tissue sarcoma yields a moderate yet clinically relevant burden of severe acute adverse events—about one in six patients develops grade ≥ 3 myelosuppression and one in ten a severe gastrointestinal toxicity—while truly life-threatening events remain of $\leq$6%. However, the certainty of these estimates is constrained by inconsistent denominators, legacy grading scales, and missing control-arm data. Potentially persisting late-term effects were found to be substantially under-reported. "Reporting matters": without harmonized, CTCAE v5.0-based toxicity capture and open publication of full AE matrices, risk–benefit appraisals will continue to rest on shaky ground. Future sarcoma trials must elevate rigorous AE reporting to the same priority as efficacy if patients and clinicians are to make informed, evidence-based treatment decisions.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cancers17193118/s1, Table S1: PubMed search strategy for clinical studies of patients of all ages with STS (17 December 2024); Table S2: Cochrane search strategy for randomized controlled trials of patients of all ages with STS (16 December 2024); Table S3: Google Scholar search strategy for randomized controlled trials of patients of all ages with STS (8 January 2025); Table S4: Reasons for full-text exclusion [22,23,26,32–39]; Table S5: Detailed judgments [11,15,17–24]; Figure S1: Risk of bias plot.

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Abbreviations

The following abbreviations are used in this manuscript:

STS	Soft tissue sarcoma
RCT	Randomized controlled trial
AE	Adverse event
CTCAE	Common terminology criteria for adverse events
MFS	Metastatic free survival
PFS	Progression free survival
OS	Overall survival
HR	Hazard ratio

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PERSPECTIVES

From Lindbergh's cockpit to predictive, AI-driven health care: a roadmap for high-reliability medicine

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Modern health care remains largely intuition-driven, reactive, and fragmented, resulting in preventable errors and inefficiencies. In contrast, aviation has evolved into a highly structured, automated, and predictive safety system, achieving near-zero accident rates through standardization, automation, and artificial intelligence (AI)-assisted decision making. While medicine has incorporated certain aviation-inspired practices—such as checklists, crew resource management, and simulation training—it lacks the comprehensive data-driven framework and continuous oversight that underpins aviation's safety culture. This perspective proposes a four-phase roadmap for integrating AI into health care, drawing on lessons from aviation's transformation over the past century. Phase I emphasizes the standardization of clinical data and interoperability, mirroring aviation's shift from handwritten logs to digital flight recorders. Phase II introduces AI-assisted decision support, paralleling the emergence of autopilot and early flight control systems. Phase III highlights real-time predictive monitoring, analogous to continuous flight data monitoring, while phase IV envisions autonomous health care systems, reflecting modern aircraft's capacity for automated flight. However, aviation's experience also reveals the perils of over-reliance on technology, including automation bias and deskilling, underscoring the need for regulatory adaptation, transparent error reporting, and robust human—AI collaboration. By integrating these safeguards, medicine can carefully integrate AI's transformative potential to reduce errors, improve efficiency, and enhance patient outcomes, thereby shifting from an intuition-driven model to one of precision and reliability.

Key words: artificial intelligence (AI), high-reliability health care, predictive analytics, standardization, safety culture, human factors

INTRODUCTION

Despite significant technological advancements, health care remains replete with variability, gaps in care coordination, and frequent preventable errors.[1,2] According to estimates, medical mistakes rank among the leading causes of death worldwide, a level of harm that aviation would not tolerate.[3,4] Indeed, if commercial airlines endured hundreds of thousands of fatalities each year, drastic reforms would have been implemented decades ago.[5,6] The disconnect between these two industries spurs the core question of how health care might emulate aviation's trajectory, transitioning from manual, seat-of-the-pants operations to structured, data-driven processes with AI at the helm.[7,8] However, we explicitly acknowledge that direct comparisons between aviation and health care have intrinsic limitations, as health care uniquely involves biological variability, complex psychosocial dynamics, critical ethical considerations, and the primacy of patient autonomy—all factors which aviation does not comparably face. Therefore, the aviation analogy in this manuscript serves strictly as a conceptual roadmap rather than a direct equivalence. Furthermore, this manuscript is intended as a conceptual perspective rather than an empirical review. Our goal is to offer a structured framework and long-term vision that may guide health care leaders, policymakers, and digital architects in shaping high-reliability, AI-supported systems. Rather than providing granular implementation protocols, we focus on aligning the core principles of transformation with lessons drawn from aviation. Aviation's evolution can be illustrated through two iconic touchpoints: Charles Lindbergh's 1927 transatlantic flight and the present-day Airbus A380. Lindbergh flew solo with minimal instrumentation and no real-time oversight, relying on raw skill and intuition.[9] By contrast, the A380

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operates within a meticulously monitored environment of automated flight controls, predictive maintenance, and real-time data feeds.[10,11] While health care has partially embraced aviation's culture of safety—adapting surgical checklists, crew resource management (CRM), and simulation-based training—the sector still lacks a cohesive ecosystem for data interoperability, predictive analytics, and robust artificial intelligence (AI).[12,13] Various calls to action emphasize that partial measures, although beneficial, will not achieve the kind of radical safety improvements that aviation accomplished.[8,14] It is important to recognize, however, that aviation's transformation spanned several decades. While health care faces additional complexities, recent rapid advancements in health care technology, data infrastructure, and global digital collaboration—accelerated notably by the coronavirus disease 2019 (COVID-19) pandemic—suggest potential for a comparatively accelerated yet still cautious and realistic evolution toward high-reliability medicine. Therefore, the roadmap presented represents an illustrative trajectory rather than an exact chronological forecast. As Captain Chesley 'Sully' Sullenberger has emphasized, the aviation industry works relentlessly to eliminate preventable errors, a determination that must be mirrored by health care systems.[3,15]

LESSONS FROM AVIATION: FROM INTUITION TO AUTOMATION

Early aviation bore striking similarities to modern medicine's fragmentation.[6,9] Pilots were akin to today's clinicians, relying on individual expertise and localized processes rather than standardized best practices.[5,16] Accidents were frequent, often attributed to human error and inconsistent protocols.[15,17] Over subsequent decades, the aviation industry deployed a suite of interventions—common terminology, structured training, universal operating procedures—that collectively enhanced safety.[10,18] Automated systems emerged as cornerstones of modern flight operations, reducing pilot workload and preventing mistakes.[19,20]

Yet automation also introduced novel risks. The crash of Air France Flight 447 in 2009—sparked by autopilot disengagement and pilot confusion—highlighted how deskilling can arise if operators over-rely on technology.[4] When automation fails or encounters an edge case, human intervention is critical.[21,22] Translating this lesson into medicine, it becomes clear that AI should be viewed as an assistive tool rather than a replacement for clinical judgment.[2,13] If clinicians become complacent and blindly accept AI recommendations, patient safety could be compromised. Hence, health care leaders must embed checks and balances, ensuring AI augments rather than undermines medical expertise.[1,3]

Some aviation principles have already taken root in health care. Surgical checklists patterned after pre-flight protocols reduce errors in operating rooms.[8,23] CRM-based teamwork training fosters open communication and shared situational awareness.[12,24] Simulation exercises, akin to flight simulators, help clinicians practice crisis scenarios in a low-risk environment.[25] Incident reporting systems encourage disclosure of near-misses and adverse events, mirroring aviation's data-driven approach to safety.[15,26] Nonetheless, these measures stop short of integrating real-time monitoring and predictive analytics—the cornerstones of aviation's modern safety nets.[11]

A ROADMAP FOR AI-DRIVEN HEALTH CARE TRANSFORMATION

Realizing a fundamental shift toward structured, high-reliability medicine demands a phased, systematic approach.[1,8] Each phase addresses key infrastructural needs: data standardization, AI-assisted decision making, continuous monitoring, and eventually autonomous interventions. Throughout, preserving clinician engagement and preventing over-reliance on algorithms are vital (Figure 1).[2]

Phase I: standardization and structured data

The foundation of effective AI deployment is reliable, high-quality data.[7] Aviation confronted a similar challenge, evolving from rudimentary logbooks to highly detailed flight data recorders.[26] Health care's fragmented electronic health record landscape must unify around interoperability standards such as Fast Healthcare Interoperability Resources (FHIR) and the Observational Medical Outcomes Partnership (OMOP) Common Data Model.[7,12] These frameworks harmonize clinical data, enabling algorithms to parse information consistently. Moreover, institutions must instill a culture that rewards detailed, structured documentation.[15,27] Real-time dashboards that compile laboratory values, imaging data, and vital signs in a single interface mirror the cockpit's instrumentation, affording clinicians a comprehensive view of patient status.

Phase II: AI-assisted decision support

Once data are standardized, AI can begin aiding clinicians, much like early autopilot systems alleviated pilot workload.[19,20] AI-driven clinical decision support tools may enhance diagnoses in radiology, pathology, and cardiology or predict deterioration in intensive care units (ICUs).[13] The co-pilot model is apt: AI manages mundane tasks, sifts through vast data, and flags concerns, freeing clinicians for nuanced judgment.[21,22] Mitigating automation bias demands algorithmic transparency and robust training.[2,14] It was emphasized that clinicians should maintain final authority, evaluating AI recommendations rather than deferring blindly. Regulatory agencies can formalize graded autonomy levels for medical AI, much like different categories of autopilot function, ensuring each stage undergoes thorough validation before broader adoption.[7]

Phase III: real-time predictive monitoring

Aviation's commitment to continuous flight data monitoring and proactive maintenance transformed safety

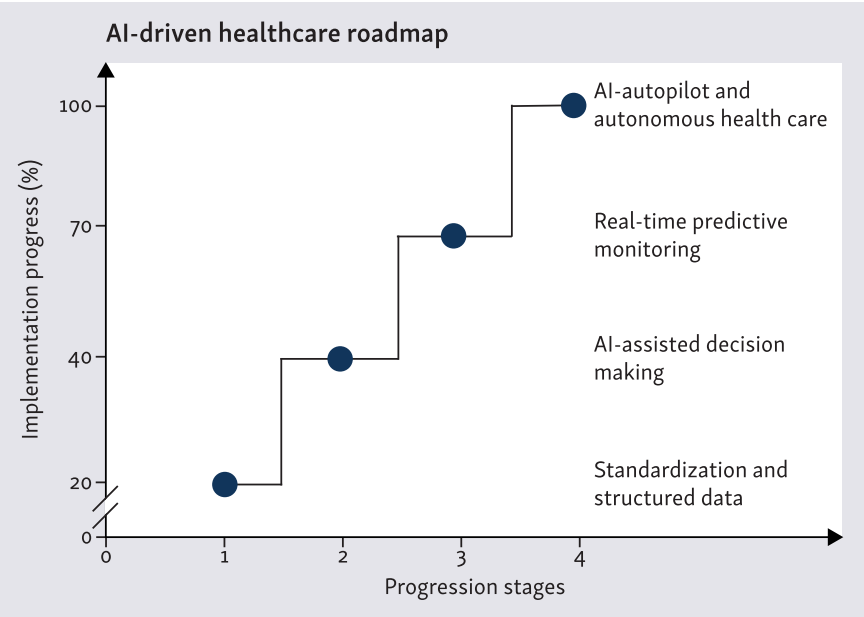


Figure 1. The artificial intelligence (AI)-driven health care roadmap. This schematic illustrates a four-phase progression from basic standardization and structured data (lower left) to AI-assisted decision making, then real-time predictive monitoring, and ultimately AI-autopilot and autonomous health care (upper right). The *y*-axis represents approximate levels of 'implementation progress', showing incremental advancements in AI integration at each phase. Each dot signifies a key milestone or transition. As health care matures through these stages—mirroring aviation's shift from manual piloting to automated flight control—systems move closer to truly high-reliability medicine. The figure provides a conceptual and illustrative representation of AI integration stages and key milestones. It does not intend to depict precise timelines or rigidly defined phases. Minor graphical simplifications have been made to enhance readability and clarity.

outcomes.[10] Health care can similarly shift from episodic checkups to ongoing patient surveillance.[3,13] Wearable sensors and networked medical devices create streams of physiological data that feed predictive models, enabling clinicians to anticipate complications and intervene earlier.[28] In intensive care settings, advanced analytics can dynamically stratify risk, prompting targeted measures for those most vulnerable to sudden decline.[1,8] Robot-assisted surgery may also benefit from real-time AI inputs, enhancing precision and reducing surgeon fatigue. As in aviation, robust governance is imperative. Systems must incorporate 'black box' recording functions for post-event analysis, while continuous performance audits catch errors or biases that may emerge under real-world conditions.[2]

Phase IV: autonomous health care systems

Fully autonomous systems represent the pinnacle of aviation technology—modern aircraft can execute entire flights, including landings, with minimal pilot input.[9] Health care might similarly develop AI-driven platforms capable of autonomously diagnosing conditions, recommending treatments, and initiating select interventions.[8,13] Such autonomy could improve access in underserved regions, where specialists are scarce.[3] However, just as aviation retains pilots who can override automation, autonomous health care must preserve pathways for human intervention.[21,22] Continuous oversight, fail-safe mechanisms, and real-time performance checks will remain indispensable.[2] Regulators should enforce lifecycle monitoring—similar to aviation's airworthiness checks—where AI models are periodically revalidated to confirm their safety and equity profiles.[5] This ensures autonomous systems maintain performance across evolving clinical contexts and patient populations.[7]

CHALLENGES AND BARRIERS TO IMPLEMENTATION

Regulatory and ethical complexities

Unlike aviation, which operates under robust global standards, health care AI is hampered by inconsistent regulations and liability frameworks.[2] Who bears responsibility if an AI-guided treatment causes harm?[3] Clarifying this question is imperative. We suggest that AI governance frameworks mirror aviation's tiered certification models, incorporating staged validation (pre-market), post-market performance audits, and periodic re-approval. Responsibility for AI-assisted decisions should be explicitly allocated: developers for model validity, institutions for system integration, and clinicians for context-aware application. Emerging FDA guidance on software as a medical device provides a foundational template, though global harmonization remains essential. Moreover, sensitive patient data must be safeguarded.[7,12] Aviation benefits from shared data on aircraft performance without privacy concerns; medicine, in contrast, must navigate strict data protection laws.[14] The introduction of 'black box' recorders in health care could enable investigators to pinpoint when AI malfunctions or clinicians misapply algorithmic suggestions.[15] Yet these recorders also raise ethical questions about data ownership and patient consent.[27] To address these concerns, consent mechanisms must evolve toward

more flexible, patient-centered models such as dynamic consent, which allows individuals to adjust their preferences over time. Clear data ownership policies should be implemented, ensuring that patients retain control over their health information while institutions act as transparent stewards. Privacy-preserving architectures, including federated learning and encrypted auditing, offer technical pathways to uphold data protection standards such as General Data Protection Regulation while enabling scalable AI deployment. This is particularly relevant for large language models, which—despite their utility in summarization and documentation—must undergo rigorous clinical validation and operate strictly under human oversight. Their known limitations, including hallucination risks and lack of explainability, necessitate cautious, context-specific deployment in health care settings.

Algorithmic bias and equity

Algorithmic bias is a profound concern. It was demonstrated that AI can inadvertently reinforce health care disparities if trained on unrepresentative datasets.[2] For example, some widely deployed sepsis prediction algorithms have underperformed in minority populations, and dermatological classifiers trained predominantly on light skin tones have shown reduced diagnostic accuracy in patients with darker skin. Effective mitigation requires inclusive data sourcing, such as efforts modeled by the National Institutes of Health (NIH) All of Us initiative, which explicitly aims to ensure representation across age, ethnicity, and socioeconomic status. Additionally, algorithms must undergo stratified validation across demographic subgroups, with regular bias auditing embedded into the model lifecycle. Regulatory frameworks, including recent Food and Drug Administration guidelines, now increasingly call for transparency in model training and evaluation pipelines.[7,13] Without such safeguards, AI might systematically underdiagnose certain groups or allocate resources inequitably, exacerbating existing health inequities.[8,12] Aviation's success in creating uniform safety standards for all passengers underscores the moral imperative for health care AI to function equitably.[15,18]

Cultural resistance and skill preservation

Clinicians may resist advanced automation, fearing that AI could diminish their professional roles or deskill their practice, just as early pilots doubted autopilot technology.[20] A smooth transition requires reimagined training programs that include AI literacy, algorithmic auditing, and error analysis.[9] Just as pilots retain manual flying capabilities, physicians must maintain core diagnostic and procedural skills even as AI takes on routine tasks.[21,22] Institutions should foster a 'just culture', encouraging open discussion of AI mistakes and near-misses.[15,29] To explicitly mitigate risks associated with automation bias and clinician deskilling, structured clinician training programs must be implemented. These programs should include mandatory simulation-based scenarios, regular proficiency evaluations to maintain core diagnostic and procedural skills, and structured AI-literacy training that emphasizes critical assessment of AI-generated recommendations. Analogous practices from aviation, such as routine manual flight training and proficiency checks for pilots, can serve as practical models for health care. This cultural orientation, critical in aviation, promotes learning from errors rather than punishing individuals, accelerating technological maturation.[3,24]

Infrastructure and financial constraints

Implementing AI systems is capital-intensive, requiring investment in data storage, analytics platforms, and continuous software updates.[28] Smaller clinics and low-resource hospitals may lack the financial means to adopt advanced AI, raising the risk of a two-tier system.[5] Aviation addressed comparable challenges through coordinated international efforts and financial models that emphasized safety as a collective good.[10] Health care may need a parallel approach, leveraging public—private partnerships and policy incentives to ensure equitable access to AI innovations.[8,15] For resource-limited settings, scalable solutions such as modular, cloud-based AI platforms can reduce upfront infrastructure costs. Public—private partnerships may also support shared-service models that pool resources across institutions. These approaches mirror aviation's use of centralized safety programs to ensure that smaller carriers meet uniform safety standards.

THE CRITICAL ROLE OF HUMAN-FACTOR SPECIALISTS

Just as aviation integrates human-factor experts to refine cockpit design, health care can benefit from specialists who focus on optimizing AI—clinician interactions.[29] These experts study how clinicians engage with AI recommendations, identify points of confusion, and develop guidelines for safe handoffs between human and automated processes.[19] By involving human-factor specialists early in AI implementation, hospitals can anticipate and address issues such as overreliance, user-interface errors, and workflow disruptions.[15,20] In practice, human-factor specialists may be embedded in multidisciplinary teams tasked with developing and deploying clinical AI systems. Their responsibilities can include conducting simulation-based usability tests in controlled settings (e.g. ICUs), carrying out cognitive walkthroughs with clinicians to identify potential friction points, and co-designing user interfaces that minimize distraction and reduce alert fatigue. For example, in ICU settings where predictive analytics are used to anticipate patient deterioration, human-factor experts have helped optimize alert thresholds and visual cue design to align with clinical workflows and shift patterns. Such integration ensures that AI tools enhance, rather than hinder, clinician performance. The ultimate goal is to maintain a delicate balance: AI should streamline decision making without overshadowing clinical reasoning.[8,16]

HARNESSING INTERDISCIPLINARY COLLABORATION AND RESEARCH

Much like aviation's continual data-driven refinements, health care AI demands iterative research involving technologists,

Table 1. Aviation evolution versus health care's AI progression

Aviation evolution	Health care evolution
Manual pilot-only flight (Lindbergh's era)	Intuition-based, physician-centered medicine
Autopilot assists pilots (modern aviation)	AI-assisted diagnostics and treatment
Automated navigation and predictive safety	Predictive analytics in real-time monitoring
Fully automated landing in adverse conditions	AI-driven, autonomous medical interventions

This table illustrates how each phase in aviation's journey toward automation parallels the transition from clinician-centered, intuition-based medicine to AI-driven health care systems. By aligning milestones in flight technology with corresponding steps in health care AI integration, the table provides a succinct visual analogy to guide the forthcoming four-phase roadmap.

clinicians, ethicists, and patients.[7,13] Interdisciplinary teams can pilot AI tools in controlled environments, gather real-time feedback, and optimize algorithms to better reflect clinical realities. By systematically collecting outcomes data—both successful interventions and near-misses—developers can pinpoint failure modes and refine system performance.[4,15] Such a cycle echoes aviation's decades-long push for incremental improvements grounded in empirical evidence.[10] When combined with transparent incident reporting and a just culture, the result can be a continuously learning system that progressively boosts safety and efficiency (Table 1).[12,14]

PRACTICAL STEPS FOR IMPLEMENTATION

1. Establish a unified data infrastructure built on interoperability standards (FHIR, OMOP) to ensure that AI algorithms receive consistent, high-quality inputs.
2. Develop comprehensive AI governance frameworks, drawing on aviation's continuous airworthiness model, to mandate regular performance audits and post-market surveillance.
3. Incorporate human-factor specialists in AI deployment teams to identify workflow conflicts, user-interface pitfalls, and potential points of automation bias.
4. Train clinicians to interpret AI outputs critically, maintaining the capacity for manual decision making even when automated recommendations are available.
5. Introduce transparent 'black box' recorders for AI-driven clinical decisions, balancing the need for patient privacy with the goal of error analysis and system learning.
6. Encourage a just culture that prioritizes reporting and learning from AI-related incidents, analogous to aviation's established safety reporting networks.
7. Leverage public—private partnerships to finance AI adoption, particularly in resource-limited settings, ensuring that technological progress does not exacerbate health care inequalities.

CONCLUSIONS

Borrowing from aviation's evolution, health care can transform from an intuition-oriented paradigm to a structured, AI-empowered, high-reliability system. By systematically implementing the four-phase roadmap—standardizing data, deploying AI decision support, enabling real-time predictive monitoring, and ultimately embracing autonomous systems—medicine can mirror the structured processes and minimal accident rates that distinguish modern aviation.

Nevertheless, automation alone does not guarantee safety. As Air France Flight 447 demonstrated, technology can fail spectacularly if operators grow overly dependent on it. Health care's AI journey thus hinges on robust oversight, ongoing validation, and a human-centered design ethos. Regulators, clinicians, and developers must collaborate to establish transparent performance metrics, lifecycle monitoring, and equitable data governance. When AI tools are introduced responsibly, they can relieve clinicians' cognitive load, expand access to specialized care, and curb preventable harm. It remains crucial that AI be adopted thoughtfully, preserving human oversight and clinician expertise, rather than passively relied upon without critical engagement.

Yet the road ahead is challenging. Liability remains unresolved, algorithmic biases persist, and many institutions struggle to finance cutting-edge technologies. Overcoming these barriers will require a broad cultural shift toward continuous improvement, echoing aviation's relentless pursuit of safety. With thoughtful implementation, health care can achieve the reliability gains that aviation now takes for granted, ushering in an era where medical errors are as rare as plane crashes. Through interdisciplinary collaboration, proactive governance, and careful adaptation of aviation's frameworks, medicine can transcend its deeply rooted fragmentation and embrace AI-driven precision, equity, and trust.

FUTURE DIRECTIONS AND LIMITATIONS OF THE AVIATION ANALOGY

Although drawing parallels to aviation provides a compelling framework, certain limitations must be acknowledged.[2,5] Health care deals with biological variability, complex psychosocial factors, and ethical considerations that differ markedly from operating an aircraft.[3,14] Patient preferences, shared decision making, and individualized care complicate the standardization and automation processes that aviation found comparatively easier to implement.[1,12] Furthermore, the financial incentives driving health care systems can disincentivize broad-scale investments in safety and interoperability.[1] Shifting to a value-based model aligned with AI-driven, high-reliability care requires overcoming entrenched fee-for-service paradigms.[8,13]

Nevertheless, the aviation analogy underscores key principles that remain universally applicable: the importance of continuous oversight, rigorous data collection, and a safety culture that prioritizes learning from errors.[9,15] Future research should focus on developing AI algorithms that incorporate patient-reported outcomes, social determinants of health, and population-level data to inform

preventive strategies.[7] Implementing these models at scale will likely require not only robust technical solutions but also policy interventions and global coordination akin to aviation's standard-setting bodies.[10]

Advancements in federated learning and privacy-preserving technologies could address some of the data-sharing barriers that have historically hampered multi-institutional collaborations. By enabling AI development without centralizing sensitive patient data, these innovations may encourage broader participation while respecting patient privacy.[12,13] Additionally, as AI systems gain autonomy, ethical frameworks must evolve in tandem to clarify questions of responsibility, informed consent, and equitable resource allocation.[3] The interplay between clinicians and AI should remain adaptive, allowing for graduated increases in automation as trust and evidence accumulate.[21,22]

Finally, a deeper exploration of human—machine teaming is warranted. Pilots do not simply monitor autopilot systems; they engage in complex interactions that blend trust and vigilance.[4] Health care can replicate this synergy by training clinicians to actively cross-check AI outputs, manage unforeseen anomalies, and intervene decisively when automated processes reach their limits.[19,20] Through iterative refinement, robust governance, and inclusive design, the aviation analogy can guide medicine's journey toward safer, more efficient, and patient-centered care—while respecting the complexities that make health care a uniquely human endeavor.[1,15] Embracing both technological innovation and the irreplaceable nuance of clinical expertise, health care can move beyond its current fragmentation. In doing so, it stands to replicate aviation's minimal accident record, providing safer, equitable, and higher-value care for all patients.[2,8]

This perspective offers a conceptual scaffolding—a roadmap that encourages health care systems to think strategically about the phased integration of AI, drawing parallels from aviation while acknowledging the sector's inherent complexity. Readers are not expected to find prescriptive implementation guidance here, but rather a structured, systems-level vision that can inform further translational work, institutional strategies, and future empirical studies.

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Communication

Triangulating Timing, Tropism and Burden of Sarcoma Metastases: Toward Precision Surveillance and Therapy in a Real-World-Time Cohort

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Simple Summary

Patients with sarcoma—the rare cancers of soft tissue and bone—do not all have the same clinical course once the tumor is removed. By following nearly 300 adults in a nationwide, real-time database, we discovered that metastases (new tumors appearing elsewhere) differed when they developed, where they landed, and how many appeared. About one-third of patients already had—or quickly developed—metastases within six months, while others stayed free of spread for many years. Many tumors went only to the lungs and stayed there, but some jumped rapidly to the bones, liver, or lymph nodes. Roughly half the patients had only a few small spots that could be treated with surgery or focused radiation; the rest had many lesions in several organs and needed immediate drug therapy. These patterns suggest that everyone should not get the same scan schedule or the same first-line treatment. Tailoring follow-up and therapy to a tumor's timing, destination, and tumor-load could improve care while sparing low-risk patients unnecessary tests.

Abstract

Background: Sarcoma surveillance guidelines still apply uniform imaging intervals based on tumor grade and stage that ignore histotype-specific metastatic behavior. We prospectively analyzed metastatic timing, organ tropism, and lesion burden across a real-world sarcoma cohort to generate an evidence base for risk-adapted follow-up and treatment stratification. **Methods**: In a prospective multicenter study, 1850 patients with suspected sarcoma were screened. SHAPEHub, a real-world-time data warehouse, captured clinicopathological variables and imaging. Adults with histologically confirmed soft-tissue or bone sarcoma (n = 295) formed the analytic cohort. Metastases were classified as synchronous (≤6 months) or metachronous (>6 months), lung-only versus multi-organ, and oligometastatic (≤5 lesions, ≤2 organs) versus polymetastatic. TTME was illustrated with Kaplan–Meier curves for the full cohort (descriptive); where subgroup comparisons are shown, log-rank tests are reported. **Results**: Ninety-three patients (31.5%) developed metastases after a median follow-up of 20.9 months. Metastatic risk was front-loaded: 36.6% were synchronous, and 67.8% of metachronous events occurred within year 1. The lung was the

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initial site in 62.4% of events, bone in 18.3%, and liver in 11.8%. Half of the lung-metastatic patients remained pulmonary-confined; the remainder followed a multi-organ route involving bone and lymph nodes. Oligometastatic spread predominated in the lung-only subgroup (61%) versus multi-organ (28%). Histotype influenced both timing and tropism: angiosarcoma and Ewing sarcoma metastasized earliest (median 3.7 and 5.0 months) and multi-organ; leiomyosarcoma and UPS were lung-dominant; Ewing sarcoma and epithelioid haemangioendothelioma were bone-tropic; and angiosarcoma was liver-tropic. **Conclusions**: Metastatic sarcoma displays three intersecting dimensions—early versus late onset, organ-specific tropism, and oligo- versus polymetastatic burden—none of which are addressed by the current "one-size-fits-all" surveillance. Recognizing these patterns delineates windows for tailored imaging and stratified therapy selection (e.g., local ablation for oligometastatic lung disease, intensified systemic regimens for early, polymetastatic spread). These findings lay the groundwork for precision-adapted surveillance and treatment protocols. Pattern-stratified trials and health-economic evaluations are now needed to assess whether this approach improves outcomes and optimizes resource allocation.

Keywords: soft-tissue sarcoma; metastasis; oligometastatic disease; real-world-time data; surveillance strategies; organ tropism; precision medicine

1. Introduction

Soft-tissue and bone sarcomas constitute a rare, heterogeneous family of malignancies whose metastatic behavior differs markedly by histologic subtype [1]. Current follow-up recommendations from the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) assign uniform imaging intervals largely on the basis of tumor grade and stage [2–4]. This "one-size-fits-all" paradigm risks under-surveillance of aggressive phenotypes, over-surveillance and over-treatment of indolent tumors, and exposes patients to avoidable imaging and therapeutic burden while also inflating healthcare costs.

Metastatic spread in sarcoma is governed by three inter-linked dimensions: temporal dynamics: synchronous ($\leq$6 months) versus metachronous (>6 months) dissemination [5,6]; spatial organ tropism; and metastatic burden ranging from oligometastatic disease (typically $\leq$3–5 lesions amenable to local control) to polymetastatic dissemination [7–14]. While the lung remains the dominant target [15], several histotypes exhibit characteristic extra-pulmonary patterns: bone involvement in Ewing sarcoma, hepatic spread in angiosarcoma, and nodal metastases in epithelioid sarcoma, among others [16]. In addition, late-metastasizing entities such as clear-cell sarcoma or low-grade fibromyxoid sarcoma frequently evade the conventional five-year surveillance window. Conversely, angiosarcoma and Ewing sarcoma may metastasize within weeks, demanding intensified early imaging [17–19]. These divergent timelines are clinically consequential. Early-appearing metastases tend to signal intrinsically aggressive biology that benefits from close surveillance and rapid intervention, whereas late-occurring lesions in indolent histotypes invite a more measured, long-term follow-up strategy. Understanding where a patient's tumor falls on this temporal spectrum is therefore pivotal for balancing diagnostic yield against surveillance intensity and therapeutic burden. Equally, recognizing metastatic burden and timing has therapeutic consequences: a patient with a handful of lung nodules detected within months of diagnosis differs fundamentally from one who presents years later with multi-organ disease, and who is unlikely to derive identical benefit from the same type of

therapy; for instance, chemotherapy. Failing to stratify trials and clinical decisions by these parameters may obscure true treatment effects and exaggerate toxicity–efficacy trade-offs.

Despite these observations, the systematic and prospective evaluation of the temporal, spatial, and burden-related metastatic variation across sarcoma subtypes is scarce. Existing series are often retrospective, single-centered, and underpowered for rare histologies [5,6,12]. Crucially, no large real-world-time data set has yet been leveraged to design a histotype-adapted surveillance algorithm.

The present multicenter study characterizes both the timing, organ distribution, and lesion burden of metastases across a broad sarcoma cohort and aims to inform precision therapy and surveillance. We therefore set out to generate a comprehensive, prospectively-acquired picture of sarcoma dissemination across three complementary axes. First, we quantified the temporal course of metastasis, discriminating between synchronous and metachronous onsets. Second, we mapped the spatial footprint of disease by cataloguing both initial and cumulative organ tropisms. Third, we evaluated metastatic burden, contrasting oligometastatic presentations—typically $\leq$3–5 lesions amenable to local control—with polymetastatic spread. In addition, we traced sequential progression pathways to elucidate how tumors transition from one compartment to another. By triangulating these dimensions, this study provides a biologic foundation for risk-adapted surveillance and for a more granular stratification of patients in therapeutic trials.

2. Materials and Methods

2.1. Study Design and Setting

We performed a prospective, multicenter observational cohort study within the Swiss Sarcoma Network (SSN). All consecutive patients evaluated for a suspected sarcoma at participating SSN institutions were entered into SHAPEHub (SHAPE4PM, Schindellegi, Switzerland), a real-world-time data warehouse that prospectively captures clinical, radiological, and pathological variables in a harmonized format.

2.2. Eligibility Criteria

Inclusion criteria were: (i) age $\geq$ 18 years; (ii) histologically-confirmed soft-tissue or bone sarcoma according to the 2020 WHO classification; and (iii) treatment and/or follow-up in an SSN institution between August 2017 and February 2023. Exclusion criteria comprised benign/borderline tumors, Kaposi sarcoma, and insufficient baseline data.

2.3. Data Collection and Quality Assurance

Demographic, clinicopathological, and treatment data were prospectively collected with SHAPEHub. Automated integrity checks (range, type, and logic rules) and quarterly manual audits ensured <3% missingness across the core variables. Histological grade followed FNCLCC criteria, and staging employed the AJCC 8th edition. All imaging and pathology reports were centrally reviewed by the SSN weekly tumor board.

2.4. Surveillance Imaging Protocol

Baseline work-up included contrast-enhanced thoraco-abdominopelvic computed tomography (CT), or whole-body MRI (WBMRI) for myxoid liposarcoma [15]. Follow-up imaging adhered to the SSN consensus protocols which align with the ESMO/NCCN guidelines [2–4] as follows: for high-grade tumors, CT every 3–4 months for years 1–2, then every 6 months until year 5; for low-grade tumors, CT every 6–12 months. WBMRI supplanted CT for histotypes with a predominantly extra-pulmonary spread (e.g., myxoid liposarcoma, epithelioid haemangioendothelioma). During the 2020/2021 COVID-19 surges, SSN centers preserved oncologic imaging capacity, and the above surveillance

cadence remained our target schedule. Occasional short operational delays did not alter the protocol.

2.5. Definitions and Outcomes

Metastasis was radiologically or histologically confirmed distant disease. Metastatic burden was categorized at first presentation as oligometastatic ($\leq$5 radiologically detectable lesions across a maximum of two organs, each potentially amenable to local control) or polymetastatic (>5 lesions or diffuse multi-organ involvement). Synchronous metastases were diagnosed $\leq$6 months from primary tumor diagnosis; metachronous metastases occurred >6 months thereafter [5,19]. For descriptive timing analyses, we used time-to-first metastatic event (TTME), defined as the time interval from index histopathologic diagnosis to the first radiologic or histologic confirmation of distant disease. Patients with metastases identified at baseline staging (metastatic at presentation) are displayed as events at $t = 0$; instances where staging preceded histologic sign-out, yielded negative intervals that were normalized to zero. In contrast, metastasis-free survival (MFS) is conventionally defined only in patients without metastasis at diagnosis (M0) and was not used for inferential comparisons in this report.

2.6. Statistical Analysis

Continuous variables are presented as medians with interquartile ranges (IQR) and compared using the Mann–Whitney U test. Categorical data are expressed as counts and percentages; comparisons employed χ^2 or Fisher's exact tests. The TTME was illustrated with Kaplan–Meier curves for the full cohort (descriptive); where subgroup comparisons are shown, log-rank tests are reported. The statistical significance was set at $p < 0.05$ (two-sided). Analyses were performed in R v4.3.2 (The R Foundation for Statistical Computing).

3. Results

3.1. Subsection

Between August 2017 and February 2023, we screened 1850 individuals with suspected sarcoma across the Swiss Sarcoma Network (SSN) centers. After histopathological confirmation, 295 patients (40.1%) were diagnosed with soft-tissue or bone sarcoma and constituted the analytic cohort (Figure 1). Ninety-three patients (31.5%) developed metastatic disease during follow-up, whereas 202 (68.5%) remained metastasis-free.

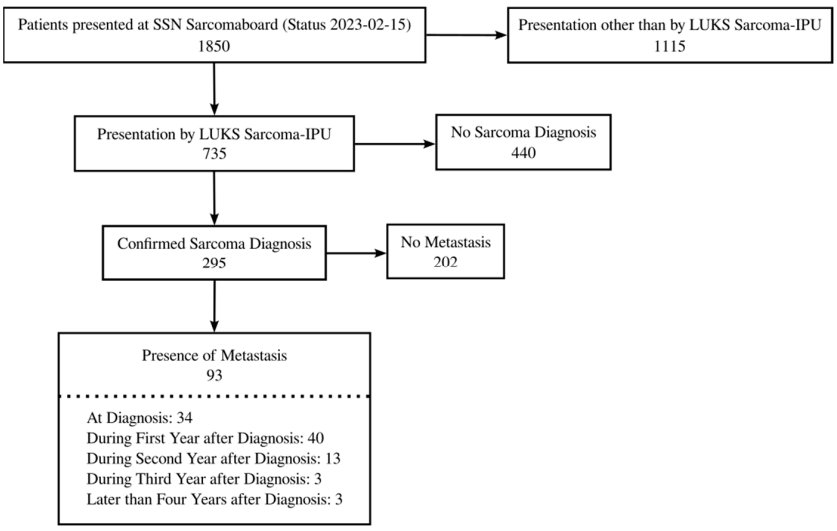


Figure 1. This flowchart provides an overview on the selection process for patients to be included in this study.

3.2. Baseline Characteristics

Baseline clinicopathological features are summarized in Table 1. Median age at diagnosis was 58.1 years (interquartile range [IQR] 46.7–71.2) with a balanced sex distribution (151/295; 51.2% male). High-grade tumors (FNCLCC G3) were significantly more frequent among metastatic patients (69.9% vs. 37.1%; $p < 0.001$). Median primary-tumor size showed a non-significant trend toward larger lesions in the metastatic group (90 mm vs. 80 mm; $p = 0.175$). Histotypes enriched in the metastatic cohort included angiosarcoma, leiomyosarcoma, and Ewing sarcoma.

Table 1. Baseline characteristics (age at diagnosis, sex) and the distribution of initial metastatic sites at presentation by histologic subtype (N = 93). Cells show n (% within histology). "Total initial metastasis sites" is the sum of sites observed across patients within a subtype; the multiplier in parentheses (e.g., 2.3×) denotes the mean number of metastatic sites per patient at diagnosis. Follow-up is reported as median [IQR] months from diagnosis to last contact or death (median follow-up may be estimated by reverse Kaplan–Meier).

Factor	Level	Overall	Non-Metastatic	Metastatic	*p*
n		295	202	93	
Sex (%)	Male	151 (51.2)	101 (50)	50 (53.8)	0.634
	female	144 (48.8)	101 (50)	43 (46.2)	
Age (median years (IQR)		58.1 (46.7; 71.2)	59.1 (47.7; 73.0)	56.4 (41.8; 67.8)	0.067
Follow-up (median months (IQR))		20.9 (9.9; 36.2)	18.9 (8.5; 33.4)	23.9 (14.2; 41.5)	0.025
Histologic Type (%)	Angiosarcoma of soft tissues	9 (3.1)	3 (1.5)	6 (6.5)	0.002
	Chondrosarcoma grade II, grade III	9 (3.1)	8 (4.0)	1 (1.1)	
	Dedifferentiated liposarcoma	28 (9.5)	24 (11.9)	4 (4.3)	
	Ewing sarcoma	9 (3.1)	3 (1.5)	6 (6.5)	
	Leiomyosarcoma (excluding skin)	31 (10.5)	17 (8.4)	14 (15.1)	
	Myxofibrosarcoma	22 (7.5)	20 (9.9)	2 (2.2)	
	Myxoid liposarcoma	19 (6.4)	15 (7.4)	4 (4.3)	
	Solitary fibrous tumor	13 (4.4)	10 (5.0)	3 (3.2)	
	Undifferentiated sarcoma (UPS)	53 (18.0)	35 (17.3)	18 (19.4)	
	Other	102 (34.6)	67 (33.29	35 (37.6)	
Grading (%)	Suspicious of malignancy	10 (3.4)	10 (5.0)	0 (0.0)	<0.001
	G1	62 (21.0)	55 (27.2)	7 (7.5)	
	G2	61 (20.7)	48 (23.8)	13 (14.0)	
	G2/3	6 (2.0)	3 (1.5)	3 (3.2)	
	G3	136 (46.1)	75 (37.1)	61 (65.6)	
	N/A	20 (6.8)	11 (5.4)	9 (9.7)	
Primary Tumor Size (median mm (IQR))		85.0 (51.8; 135.0)	80.0 (50.0; 130.0)	90.0 (63.0; 140.0)	0.175
Primary Tumor Site (%)	Extraperitoneal	37 (11.5)	25 (11.8)	12 (10.8)	0.090
	Head/Neck	15 (4.7)	10 (4.7)	5 (4.5)	
	Intraperitoneal	18 (5.6)	8 (3.8)	10 (9.0)	
	Intrathoracic	19 (5.9)	10 (4.7)	9 (8.1)	
	Lower limb	103 (32.0)	8 (3.8)	31 (27.9)	
	Lower limb girdle	46 (14.3)	29 (13.7)	17 (15.3)	
	Trunk wall	42 (13.0)	33 (15.6)	9 (8.1)	
	Upper limb	22 (6.8)	14 (6.6)	8 (7.2)	
	Upper limb girdle	8 (2.5)	6 (2.8)	2 (1.8)	
	Viscera	12 (3.7)	4 (1.9)	8 (7.2)	

3.3. Incidence and Timing of Metastasis

Overall median follow-up was 20.9 months (IQR 9.9–36.2). Metastatic events clustered early: 34/93 patients (36.6%) presented with synchronous metastases ($\leq$6 months from diagnosis), and a further 40/59 metachronous events (67.8%) arose within the first year. The time-to-first metastatic event (TTME) curve shows the steepest drop within the first

12 months. Events at $t = 0$ reflect patients who were metastatic at presentation, as detected on baseline staging (Figure 2).

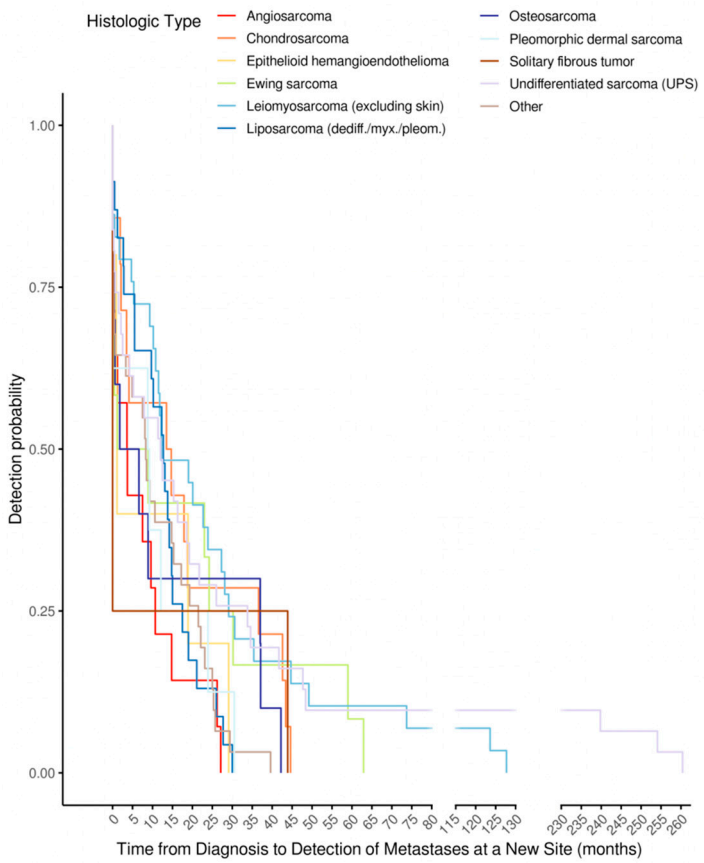


Figure 2. Time-to-first metastatic event (TTME) from index diagnosis for the full cohort. Patients metastatic at presentation are shown at $t = 0$. In cases where baseline staging preceded histopathology sign-out, negative intervals were normalized to zero.

3.4. Anatomic Distribution of First Metastatic Sites

The lung was the predominant first metastatic site (58/93; 62.4%), followed by bone (17/93; 18.3%), lymph nodes (14/93; 15.1%), and liver (11/93; 11.8%) (Table 2a). Subtype-specific organ tropism was evident:

- Leiomyosarcoma and undifferentiated pleomorphic sarcoma (UPS) showed strong pulmonary predilection (78.6% and 72.2%, respectively).
- Ewing sarcoma and epithelioid hemangioendothelioma (EHE) favored bone (83.3% and 66.7%), in line with large Ewing-specific series [20].
- Angiosarcoma and EHE exhibited increased hepatic involvement (14.3% and 66.7%).

3.5. Cumulative Metastatic Burden

When all the metastatic events were considered, pulmonary involvement remained the most common (78/93; 83.9%). Secondary spread frequently affected the bone (37/93; 39.8%) and lymph nodes (30/93; 32.3%) (Table 2b).

Table 2. (**a**) Initial Metastasis by histologic subtype. Distribution of initial metastatic sites at diagnosis by histologic subtype (N = 93). Each cell shows number of patients with ≥1 lesion at the indicated site followed by the percent of patients within that histologic subtype in parentheses. "Total Initial Metastases Sites" gives the sum of sites observed across patients within each subtype; the value in parentheses (e.g., 2.3×) denotes the mean number of metastatic sites per patient in that subtype at diagnosis. Patients can contribute to multiple sites; therefore row sums exceed the number of patients (**b**) Any-time metastases by histologic subtype. Distribution of metastatic sites at any time during the disease course by histologic subtype (N = 93). Cells report count of patients and % within subtype. "Total Metastasis Sites" represents the cumulative number of sites recorded per subtype over the course of follow-up; the parenthetical multiplier (e.g., 3.2×) indicates the mean number of metastatic sites per patient in that subtype across time. Patients may appear in multiple sites.

(a)

Histologic Type	Bone	CNS/Meninges	Head/Neck	Intraperitoneal	Liver	Lungs	Lymph Nodes	Retroperitoneal	Skeletal Muscle	Skin/Subcutaneous Tissue	Thorax	Other	Total Initial Metastases Sites	Total Patients
Angiosarcoma	3 (42.9)	0 (0.0)	0 (0.0)	2 (28.6)	1 (14.3)	2 (28.6)	4 (57.1)	0 (0.0)	2 (28.6)	1 (14.3)	1 (14.3)	0 (0.0)	16 (2.3×)	7
Chondrosarcoma	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (71.4)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.1×)	7
Epithelioid hemangioendothelioma	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	8 (2.7×)	3
Ewing sarcoma	5 (83.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	2 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	12 (2.0×)	6
Leiomyosarcoma (excluding skin)	1 (7.1)	0 (0.0)	0 (0.0)	1 (7.1)	1 (7.1)	11 (78.6)	1 (7.1)	0 (0.0)	3 (21.4)	0 (0.0)	0 (0.0)	0 (0.0)	18 (1.3×)	14
Liposarcoma (dediff./myx./pleom.)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (50.0)	1 (10.0)	1 (10.0)	1 (10.0)	1 (10.0)	0 (0.0)	2 (20.0)	12 (1.2×)	10
Osteosarcoma	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0×)	4
Pleomorphic dermal sarcoma	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	4 (1.0×)	4
Solitary fibrous tumor	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3×)	3
Undifferentiated sarcoma (UPS)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (5.6)	13 (72.2)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	18 (1.0×)	18
Other	1 (5.9)	1 (5.9)	1 (5.9)	3 (17.6)	5 (29.4)	11 (64.7)	2 (11.8)	3 (17.6)	1 (5.9)	1 (5.9)	2 (11.8)	1 (5.9)	32 (1.9×)	17
Total	17 (18.3)	2 (2.2)	1 (1.1)	7 (7.5)	11 (11.8)	58 (62.4)	14 (15.1)	4 (4.3)	9 (9.7)	5 (5.4)	3 (3.2)	5 (5.4)	136 (1.5×)	93

(b)

Histologic Type	Bone	CNS/Meninges	Head/Neck	Intraperitoneal	Liver	Lungs	Lymph Nodes	Retroperitoneal	Skeletal Muscle	Skin/Subcutaneous Tissue	Thorax	Other	Total Metastasis Sites
Angiosarcoma	4 (57.1)	1 (14.3)	1 (14.3)	2 (28.6)	2 (28.6)	4 (57.1)	5 (71.4)	0 (0.0)	3 (42.9)	1 (14.3)	1 (14.3)	0 (0.0)	24 (3.4×)
Chondrosarcoma	4 (57.1)	1 (14.3)	1 (14.3)	1 (14.3)	0 (0.0)	7 (100.0)	3 (42.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (14.3)	19 (2.7×)
Epithelioid hemangioendothelioma	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	3 (100.0)	0 (0.0)	0 (0.0)	1 (33.3)	3 (100.0)	0 (0.0)	0 (0.0)	12 (4.0×)
Ewing sarcoma	6 (100.0)	1 (16.7)	1 (16.7)	0 (0.0)	1 (16.7)	6 (100.0)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0.0)	1 (16.7)	21 (3.5×)
Leiomyosarcoma (excluding skin)	6 (42.9)	1 (7.1)	0 (0.0)	2 (14.3)	3 (21.4)	14 (100.0)	4 (28.6)	2 (14.3)	5 (35.7)	2 (14.3)	0 (0.0)	2 (14.3)	41 (2.9×)
Liposarcoma (dediff./myx./pleom.)	3 (30.0)	2 (20.0)	0 (0.0)	1 (10.0)	1 (10.0)	8 (80.0)	2 (20.0)	3 (30.0)	4 (40.0)	3 (30.0)	3 (30.0)	2 (20.0)	32 (3.2×)

Table 2. *Cont.*

(b)													
Histologic Type	**Bone**	**CNS/Meninges**	**Head/Neck**	**Intraperitoneal**	**Liver**	**Lungs**	**Lymph Nodes**	**Retroperitoneal**	**Skeletal Muscle**	**Skin/Subcutaneous Tissue**	**Thorax**	**Other**	**Total Metastasis Sites**
Osteosarcoma	2 (50.0)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	3 (75.0)	1 (25.0)	1 (25.0)	1 (25.0)	0 (0.0)	1 (25.0)	0 (0.0)	11 (2.8×)
Pleomorphic dermal sarcoma	2 (50.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (50.0)	1 (25.0)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (2.8×)
Solitary fibrous tumor	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)	2 (66.7)	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	9 (3.0×)
Undifferentiated sarcoma (UPS)	1 (5.6)	1 (5.6)	0 (0.0)	2 (11.1)	1 (5.6)	14 (77.8)	4 (22.2)	2 (11.1)	3 (16.7)	2 (11.1)	2 (11.1)	1 (5.6)	33 (1.8×)
Other	4 (23.5)	1 (5.9)	1 (5.9)	5 (29.4)	6 (35.3)	15 (88.2)	6 (35.3)	5 (29.4)	2 (11.8)	1 (5.9)	6 (35.3)	1 (5.9)	53 (3.1×)
Total	37 (39.8)	9 (9.7)	5 (5.4)	15 (16.1)	18 (19.4)	78 (83.9)	30 (32.3)	15 (16.1)	21 (22.6)	15 (16.1)	15 (16.1)	8 (8.6)	266 (2.9×)

3.6. Metastatic Burden at First Presentation

Details are summarized in Table 3. At the initial metastatic diagnosis, 41/93 patients (44%) displayed an oligometastatic pattern—defined as ≤5 lesions confined to a maximum of two organs—whereas 52/93 (56%) presented with polymetastatic disease. Oligometastatic burden was disproportionately associated with the lung-only trajectory (28/46; 61%) compared with the multi-organ pathway (13/47; 28%). Timing also differed: 14/34 synchronous cases (41%) and 27/59 metachronous cases (46%) were oligometastatic, suggesting that lesion count alone does not fully account for biology; rather, it interacts with timing and organ tropism to define treatment opportunity windows.

3.7. Temporal Dynamics Across Histotypes

The median time to first metastasis varied markedly by histotype (Figure 3). Angiosarcoma progressed fastest (median 3.7 months; IQR 0.5–22.8), followed by Ewing sarcoma (5.0 months; IQR 0.4–25.7). Chondrosarcoma (14.1 months; IQR 2.5–32.2) and dedifferentiated liposarcoma (12.7 months; IQR 4.2–16.2) displayed delayed spread.

		Time from Diagnosis to Detection of Metastases at a New Site (months)											
Histologic Type	**n**	**min**	**q5**	**q10**	**q25**	**median**	**q75**	**q90**	**q95**	**max**	**mean**	**IQR**	**stdev**
Angiosarcoma	14	-0.2	-0.1	-0.1	0.5	3.7	10.4	22.8	26.5	27.1	7.5	10.0	9.4
Chondrosarcoma	14	-1.7	-0.8	0.4	2.5	14.1	32.2	43.2	43.8	44.6	17.3	29.7	17.5
Epithelioid hemangioendothelioma	7	-0.5	-0.5	-0.4	-0.3	0.9	10.0	23.0	26.0	29.1	7.0	10.3	12.0
Ewing sarcoma	12	0.0	0.0	0.0	0.4	5.0	25.7	56.1	60.8	62.9	17.5	25.3	23.1
Leiomyosarcoma (excluding skin)	29	-9.2	-1.2	-0.3	5.3	12.2	29.1	54.1	103.6	127.7	25.3	23.8	32.9
Liposarcoma (dediff./myx./pleom.)	23	-0.5	-0.2	0.6	4.2	12.7	16.2	25.0	27.5	30.0	11.9	12.1	9.0
Osteosarcoma	10	-0.2	-0.2	-0.2	0.5	4.2	30.0	37.6	39.9	42.2	13.4	29.5	17.8
Pleomorphic dermal sarcoma	9	-4.8	-3.0	-1.2	-0.3	8.8	12.1	25.2	27.9	30.5	8.8	12.4	11.9
Solitary fibrous tumor	6	-4.1	-3.4	-2.8	-1.4	-1.1	-0.6	21.7	32.8	43.9	5.9	0.8	18.6
Undifferentiated sarcoma (UPS)	31	-114.5	-2.7	-1.0	1.1	12.0	29.9	48.4	246.9	260.4	32.8	28.8	77.7
Other	34	-56.5	-25.1	-1.4	-0.1	7.8	18.8	25.2	27.0	39.6	6.8	18.9	17.8

Figure 3. Time from diagnosis to detection of metastases at a new site (months), stratified by histologic subtype (n per row shown). Columns report the minimum, 5th, 10th, and 25th percentiles; median; 75th, 90th, and 95th percentiles; maximum; mean; interquartile range (IQR = q75 − q25); and standard deviation. Negative values indicate cases where the metastatic site was detected prior to or at the time of the index diagnosis due to back-dating or pre-diagnostic imaging.

3.8. Metastatic Progression Pathways

Sequential mapping (Figure 4) identified two dominant trajectories:

1. Lung-dominant pathway—About half of the patients with an initial pulmonary metastasis remained confined to the lungs, particularly those with leiomyosarcoma, UPS, and osteosarcoma.
2. Multi-organ pathway—The remainder progressed to extrapulmonary sites, most commonly the bone and lymph nodes, a pattern typical of angiosarcoma and Ewing sarcoma.

3.9. Key Clinical Signals

Early temporal clustering, histotype-specific organ tropism, and burden stratification (oligo-versus polymetastatic) delineate the windows for tailored imaging and burden-informed systemic or local therapy selection. Detailed clinical implications are developed in Section 4 (Discussion). To aid clinical interpretation, Figure 5 integrates timing (synchronous vs. metachronous), organ tropism at the first event, and metastatic burden (oligo vs. poly) into a single visual summary with example care windows.

Table 3. Metastasis site × histology with prevalence. Cross-tabulation of metastatic site by histologic subtype with cohort totals and prevalence. Cells contain the number of patients with ≥1 lesion at the site and the % of patients within that subtype. Bottom rows summarize: Total Metastasis Sites (sum across sites per subtype, with mean sites per patient in parentheses), Total Patients, counts with/without metastasis, and Prevalence of Metastasis (patients with any metastasis ÷ total patients per subtype). Patients may contribute to multiple sites.

Metastasis Site	Angiosarcoma	Chondrosarcoma	Epithelioid Hemangioendothelioma	Ewing Sarcoma	Leiomyosarcoma (Excluding Skin)	Liposarcoma (dediff./myx./pleom./NOS)	Osteosarcoma	Pleomorphic Dermal Sarcoma	Solitary Fibrous Tumor	Undifferentiated Sarcoma (UPS)	Other	Total
Bone	4 (57.1)	4 (57.1)	3 (100.0)	6 (100.0)	6 (42.9)	3 (30.0)	2 (50.0)	2 (66.7)	1 (5.6)	4 (23.5)	37 (39.8)	
CNS/Meninges	1 (14.3)	1 (14.3)	0 (0.0)	1 (16.7)	1 (7.1)	2 (20.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (5.6)	1 (5.9)	9 (9.7)
Head/Neck	1 (14.3)	1 (14.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	5 (5.4)
Intraperitoneal	2 (28.6)	1 (14.3)	0 (0.0)	0 (0.0)	2 (14.3)	1 (10.0)	1 (25.0)	0 (0.0)	1 (33.3)	2 (11.1)	5 (29.4)	15 (16.1)
Liver	2 (28.6)	0 (0.0)	2 (66.7)	1 (16.7)	3 (21.4)	1 (10.0)	0 (0.0)	0 (0.0)	2 (66.7)	1 (5.6)	6 (35.3)	18 (19.4)
Lungs	4 (57.1)	7 (100.0)	3 (100.0)	5 (100.0)	14 (100.0)	8 (80.0)	3 (75.0)	2 (50.0)	2 (66.7)	14 (77.8)	15 (88.2)	78 (83.9)
Lymph nodes	5 (71.4)	3 (42.9)	0 (0.0)	2 (33.3)	4 (28.6)	2 (20.0)	1 (25.0)	2 (50.0)	1 (33.3)	4 (22.2)	6 (35.3)	30 (32.3)
Skeletal muscle	3 (42.9)	0 (0.0)	1 (33.3)	1 (16.7)	5 (35.7)	4 (40.0)	1 (25.0)	1 (25.0)	0 (0.0)	3 (16.7)	2 (11.8)	21 (22.6)
Skin/Subcutaneous tissue	1 (14.3)	0 (0.0)	3 (100.0)	1 (16.7)	2 (14.3)	3 (30.0)	0 (0.0)	0 (0.0)	1 (33.3)	2 (11.1)	1 (5.9)	15 (16.1)
Thorax	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	3 (30.0)	1 (25.0)	0 (0.0)	1 (33.3)	2 (11.1)	0 (0.0)	6 (35.3)	15 (16.1)
Retroperitoneal	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (14.3)	3 (30.0)	1 (25.0)	1 (25.0)	0 (0.0)	2 (11.1)	5 (29.4)	15 (16.1)
Other	0 (0.0)	1 (14.3)	0 (0.0)	1 (16.7)	2 (14.3)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (5.9)	8 (8.6)
Total Metastasis Sites	24 (3.4×)	19 (2.7×)	12 (4.0×)	21 (3.5×)	41 (2.9×)	32 (3.2×)	11 (2.8×)	11 (2.8×)	9 (3.0×)	33 (1.8×)	53 (3.1×)	266 (2.9×)
Total Patients	10	18	5	9	31	52	7	6	13	53	91	295
. . .without Metastasis	3	11	2	3	17	42	3	2	10	35	74	202
. . .with Metastasis	7	7	3	6	14	10	4	4	3	18	17	93
Prevalence of Metastasis	70.0%	38.9%	60.0%	66.7%	45.2%	19.2%	57.1%	66.7%	23.1%	34.0%	18.7%	31.5%

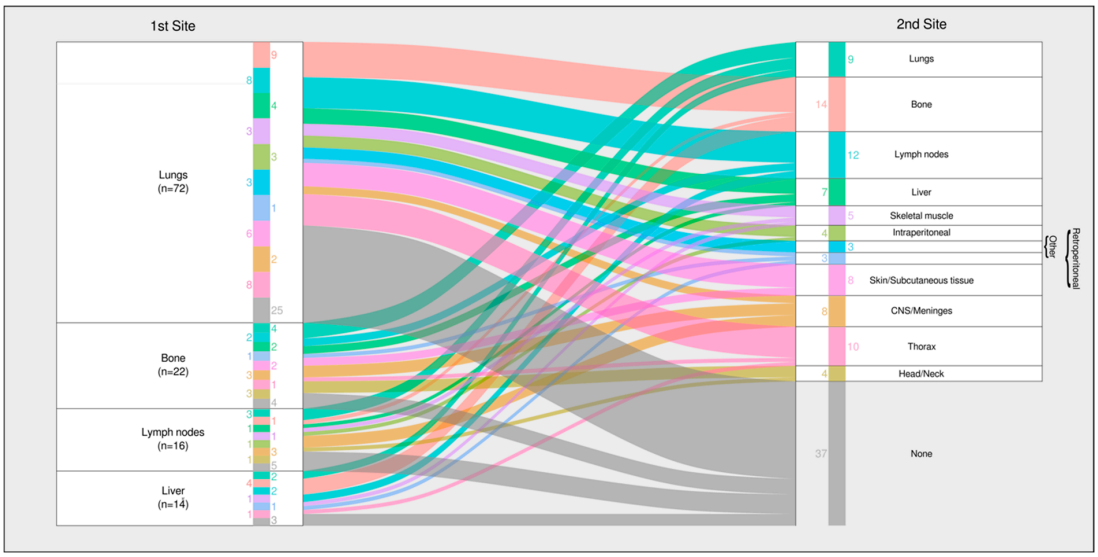


Figure 4. Histotype-specific time-to-first metastatic event (TTME). Values at $t \leq 0$ indicate metastases identified during baseline staging around the diagnostic work-up and are displayed at $t = 0$.

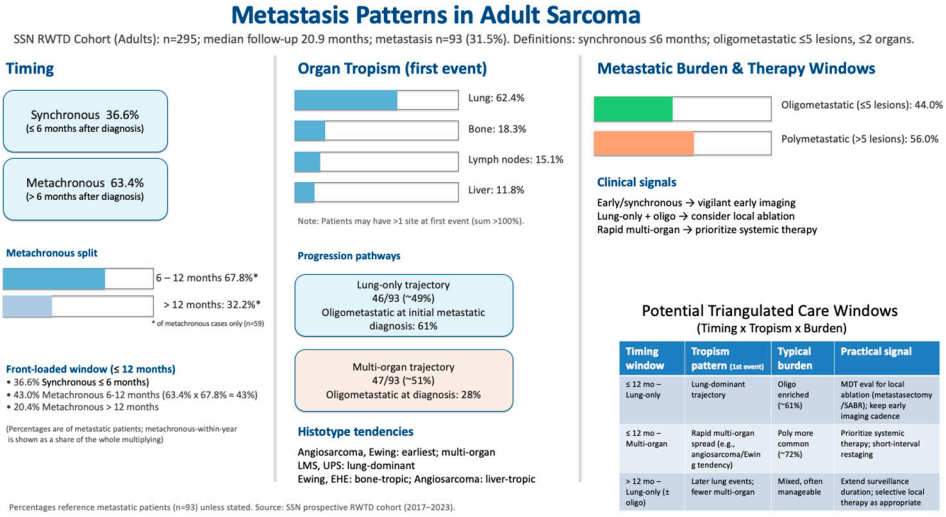


Figure 5. Integrated summary of first-metastasis patterns in adult sarcoma (SSN prospective RWTD cohort).

4. Discussion

Our prospective, multicenter analysis reveals three complementary dimensions of sarcoma dissemination. First, metastatic risk is markedly front-loaded with more than one-third of affected patients presenting with synchronous disease ($\leq$6 months), and a further two-thirds of metachronous events emerging within the first year of follow-up. Second, the cohort displays a clear spatial dichotomy. For roughly half of the patients who develop pulmonary disease, the lesion remains confined to the lungs, whereas the remaining patients embark on a multi-organ trajectory that typically incorporates bone and lymph node involvement [21]. Third, metastatic burden diverges sharply, that is, 44% of patients manifest an oligometastatic pattern ($\leq$5 lesions, $\leq$2 organs) at first presentation, while 56% are polymetastatic. Collectively, these findings underline the inadequacy of the surveillance and treatment frameworks that rely solely on grade and stage. An integrative schematic (Figure 5) summarizes these relationships and illustrates the pragmatic windows for imaging intensity, and local versus systemic therapy selections.

The coexistence of lung-only and multi-organ phenotypes suggests distinct biological programs [22–24]. Lung-confined spread may reflect early vascular seeding with limited subsequent adaptability. This pattern is amenable to local interventions, such as metastasectomy, stereotactic ablative radiotherapy, or radiofrequency ablation. By contrast, rapid systemic progression—typical of angiosarcoma and Ewing sarcoma—demands vigilant early imaging and early initiation of systemic or combined-modality therapies. Because our median follow-up was intentionally short and focused on pattern recognition, we did not analyze survival, progression-free survival, or patient-reported outcomes. Linking these dissemination signatures to treatment efficacy and long-term prognosis will require longer, ideally international, follow-up. Even so, recognizing metastatic patterns already delivers practical value because it guides imaging cadence and supplies a biologic stratification framework for future trials (whether evaluating intensified systemic therapy for aggressive polymetastatic disease, or focal ablative approaches in the oligometastatic setting.)

Parallel stratification by synchronous versus metachronous onset refines this picture. Synchronous dissemination signals intrinsically aggressive biology, whereas late events in indolent histotypes (e.g., clear-cell sarcoma) highlight the inadequacy of a fixed five-year follow-up. Moreover, mounting real-world evidence shows that the baseline outcomes for polymetastatic sarcoma have improved—partly due to the wider adoption of focal therapies—causing recent systemic trials [25,26]) to underperform against control arms. Understanding whether a cohort is enriched for oligo- or polymetastatic disease, and synchronous or late-metastatic disease, is therefore critical for both trial design and clinical decision-making. Adequate monitoring and instant access to respective data are therefore critical [27–29].

Retrospective single-center series have hinted at organ-specific tropism. Our multicenter data corroborate those findings and add temporal and burden dimensions. Current ESMO and NCCN recommendations remain grade-centered and time-invariant [2–4]. Incorporating histotype, timing, organ risk, and burden could rationalize imaging frequency. This could spare indolent tumors from unnecessary radiation while safeguarding early-spreading entities. While skeletal MRI is highly sensitive for osseous metastases, FDG PET–CT or PET–MRI can complement both detection and the treatment-response assessment, particularly for osseous and mediastinal disease in selected histotypes. Our results thus supply the empirical substrate for ongoing guideline refinement.

The patterns identified above delineate a spectrum of surveillance and treatment needs. Histotypes such as angiosarcoma, Ewing sarcoma, and high-grade UPS concentrate their metastatic events within the first year, making that window pivotal for frequent thoracic imaging and potentially timely systemic therapy [7–14]. By contrast, tumors that metastasize late—clear-cell sarcoma, low-grade fibromyxoid sarcoma, and myxoid liposarcoma—exhibit protracted risk and may benefit more from sustained, lower-frequency but prolonged monitoring, coupled with deferred systemic intervention.

Metastatic burden further nuances management [30–33]. Patients with a limited number of pulmonary nodules are plausible candidates for local therapy aimed at durable control, whereas those presenting with widespread multi-organ disease may require immediate systemic strategies [31,34,35]. Imaging modality choice should also align with tropism; thus, liver MRI or abdominal CT is warranted when hepatic spread dominates, skeletal MRI for bone-predominant histologies, and chest CT suffices for lung-only patterns. These reflections are hypotheses for prospective validation rather than being immediate directives.

Strengths of this study include prospective data capture, unified imaging pathways, and the central review, which minimized ascertainment bias. Limitations reflect the rarity of ultra-rare histotypes, potential referral bias, and a median follow-up of ~21 months,

which may under-detect very late recurrences. Finally, while the study illuminates patterns, it was not designed to test whether tailored surveillance or burden-adapted treatment improve survival—an essential next step. Pandemic-related scheduling strain may have introduced a minor ascertainment lag; such delays would bias events toward later detection and thus render the observed early clustering as being conservative.

This work provides a descriptive template rather than a prescriptive algorithm. Three avenues merit prospective evaluation. First, pattern-stratified surveillance and treatment trials should test whether imaging intensity and therapeutic modality matched to timing, tropism, and metastatic burden translate into improved outcomes and enable biomarker-guided selection. Second, systematic appraisal of local ablative interventions is needed to ascertain which dissemination patterns derive the greatest survival or quality-of-life benefit. Finally, health-economic modelling must balance the cost of additional imaging and interventions against the potential gains from the timely, pattern-adapted management in high-risk subgroups.

5. Conclusions

A uniform, grade-based sarcoma follow-up paradigm is no longer defensible. Our real-world data reveal distinct timelines, destinations, and burdens of metastatic spread that can be harnessed to personalize surveillance and therapy. Adopting a histotype-specific, burden- and timing-adapted algorithm promises earlier detection for high-risk patients, reduced imaging exposure for low-risk groups, and the rational allocation of healthcare resources. Multicenter validation—and eventual guideline integration—are now imperative.

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SwissSarcomaNetwork (SSN) – Fakten und erste Zahlen zur Verbesserung der Qualität der Behandlung von Patienten mit Sarkomen

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1. Hintergrund und bisherige Entwicklung

Sarkome sind maligne mesenchymale Neoplasien und zählen zu den seltenen Erkrankungen mit einer Altersstandardisierten Inzidenz und Mortalität für die Schweiz von 4.43 und 1.42 pro 100 000 Einwohner für Weichteilsarkome, und 0.42 für Knochensarkome [1]. Die Behandlung erfolgt vorwiegend transdisziplinär und ist häufig komplex, weswegen ein nationaler und internationaler Austausch von zentraler Bedeutung sind.

Im Luzerner Arzt 118/2019 [2] stellten wir das überregionale Schweizerische Sarkom-Netzwerk (SSN, www.swiss-sarcoma.net) vor, und dann im Anschluss die Pläne, wie die Behandlungsqualität gezielt verbessert werden soll [3].

Primäres Ziel und Aufgabe des SSN ist die ab initio transdisziplinär orchestrierte, zeitnahe «state-of-the-art»-Abklärung, Behandlung, Betreuung und Verlaufsbeobachtung unserer Patienten mit sarkomatösen Erkrankungen, im nationalen und internationalen Austausch.

Eine Darstellung der Meilensteine in der historischen Entstehung und Entwicklung des SSN bietet Abb. 1.

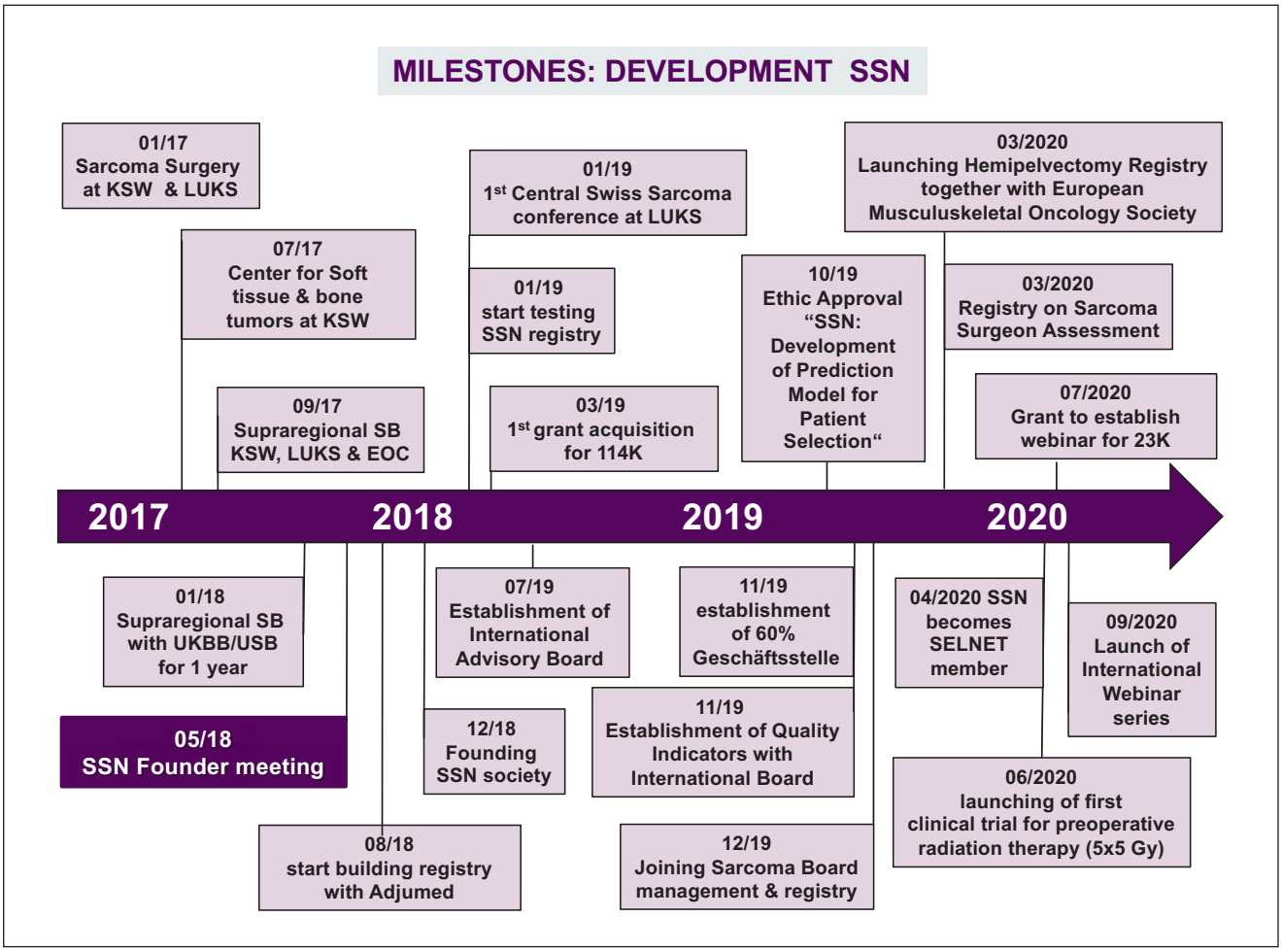


Abb. 1: *Entwicklung des SSN über die letzten 3 Jahre*

Vertragliche Mitglieder sind derzeit die Kantonsspitäler Luzern (LUKS), Winterthur (KSW), Chur (KSGR) und Bellinzona (EOC), unter Mitwirkung des Pathologie-Instituts Enge, Zürich, mit einer Sarkom-Referenzpathologin; Fallbasierte Kooperationen bestehen mit zahlreichen weiteren Institutionen und Praxen.

Wir stellen im Folgenden die bisherigen (09/2017–08/2020) Fakten und Zahlen sowie weitere Meilensteine des SSN vor.

1.2. Wöchentliches SSN Sarkom-Board: Fakten und Zahlen

In Tab. 1 sind die jährlichen Fallzahlen nach diversen Parametern und Tumor-Charakteristika gelistet.

Insgesamt wurden in 3 Jahren ca. 1500 Fallpräsentationen mit Verdacht auf oder bereits diagnostizierter sarkomatöser Erkrankung am überregionalen wöchentlichen SSN-Sarkomboard interdisziplinär besprochen; die Hälfte davon waren Primärfall-Präsentationen, bei annähernd 300 Patienten (43%) wurde eine Sarkom-Diagnose gestellt. Pro Jahr wurden damit über 100

neue Patienten mit einem Sarkom diagnostiziert und behandelt, was im internationalen Vergleich die Definition eines Hochvolumen Zentrum erfüllt. Nebst benignen muskuloskelettalen Entitäten müssen auch Karzinom-Metastasen, Tumor-Simulatoren (also Raumforderungen nicht-maligner Art) oder aber Tumoren aus dem hämatologischen Formenkreis abgeklärt werden, bei denen der initiale Verdacht auf ein Sarkom differentialdiagnostisch im Vordergrund stand, deren weitere histopathologische Abklärungen ein nicht-sarkomatöses Geschehen verifizierte. Diese Zahlen zeigen, dass in lediglich 4 von 10 Patienten, bei denen eine unklare Schwellung und der Verdacht auf ein Sarkom in Betracht gezogen werden muss, ein solches auch bioptisch bestätigt wird. Insgesamt beinhalten 22% aller Vorstellungen Knochentumore, 12% epifasziale, 66% subfasziale Tumore. Diese Zahlen beziehen sich auf alle Vorstellungen inkl. Primärvorstellungen. Pro Jahr wurden 234 Biopsien durchgeführt, wobei die bildgebend geführte Stanzbiopsie in 73% aller Patienten verwendet wurde. Von grösster Bedeutung ist der Umstand, dass 35% aller Biopsien entweder durch eine offene Inzisionsbiopsie oder aber Exzisionsbiopsie ohne Sarkomverdacht durchgeführt wurde, und 20% aller Sarkome durch sogenannte Whoops-Operationen (‹Whoops›: Überraschungsdiagnose, Eingriff entsprechend nicht unter den erforderlichen onkologischen Aspekten durchgeführt, mit erwiesenem prognostischem Nachteil für die betroffenen Patienten) diagnostiziert wurden.

1.3 SwissSarcomaRegister und Qualitätsindikatoren (QI)

Das SwissSarcomaRegistry ist seit Dezember 2019 mit der Anmeldung zum Sarkomboard gekoppelt und erlaubt damit die effiziente real-time-Datenerfassung und -Analyse (keine Mehrfacheingabe derselben Daten). Diese Kopplung erlaubt höchste Datenqualität, da offene Fragen (zB. chirurgischer Margin) bereits im Rahmen der Sartkomboard-Anmeldung eingegeben werden und, falls fehlend, am Sarkomboard geklärt werden können (nicht erst retrospektiv durch einen Datenmanager erfasst werden). Zudem wurden zusammen mit dem Internationalen SSN advisory Board von weltweit bekannten Sarkomexperten 18 Qualitätsindikatoren (QI) betr. der initialen Abklärung und Behandlung von Sarkom Patienten definiert [Tab. 2]. Diese Parameter werden zurzeit im Register programmiert, sodass diese QI's direkt erfasst werden können.

Diese QI's wiedergeben das initiale Patientenmanagement und werden im Sinne eines Quality Management Systems erfasst. Zentralste Schlüssel-Information ist die korrekte histopathologische Sarkom-Diagnose, so ist auch vom French Sarcoma Network die Referenzpathologie zur Etablierung (oder Ausschluss) einer Sarkomdiagnose als von zentraler Bedeutung für

09/2017 - 08/2020	Total	1. Präsentation	FU - Präsentation
Fallpräsentationen (alle)	1494 / 100%		
Primärfallpräsentationen	733 / 49%		
Follow up -Präsentationen	760 / 51%		
Dignität der Diagnosen			
•Benigne	20.7%	14.5%	7.2%
•Intermediär	17.9%	8.6%	1.2%
•Maligne	43.4%	12.4%	30.9%
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•Simulatoren	7.2%	5.4%	1.8%
•Metastasen	3.2%	1.6%	1.6%
•Hämatologische Tumore	1.2%	1.0%	0.2%
•andere	6.4%	5.6%	0.8%
Lokalisationen, alle			
•Knochen (total / primär / follow up)	22.2%	11.6%	16.6%
•Weichteile epifaszial (total / primär / follow up)	11.4%	7.4%	3.8%
•Weichteile subfaszial (total / primär / follow up)	62.4%	29.9%	17.7%
Anteil sarkomatöse 1° Diagnosen (vs alle 1° Diagn.)	43%		
Anteil sarkomatöse 1° Diagnosen (vs alle Vorstellungen)	21%		
Anzahl Biopsien, total	702		
•Feinnadel	5.1%		
•Stanze	73.5%		
•offene Inzision mit Sarkomverdacht	2.6%		
•offene Inzision ohne Sarkomverdacht	3.4%		
•Exzisionsbiopsie mit Sarkomverdacht	4.7%		
•Exzisionsbiopsie ohne Sarkomverdacht	32.1%		

Tabelle 1: *Überblick über die SSN. Sarkomboard Aktivitäten*

QUALITY INDICATORS: Standards of care based on CPG's Quality indicators / Outcome measures	
QI-1	appropriate local imaging before biopsy/treatment initiation (yes/no)
QI-1.1	Diagnosis of malignant tumor considered/noted in the radiological report (yes/no)
QI-2	time from 1st patient contact to biopsy (if performed)
QI-3	type of biopsy: FNA, tru-cut (CT- or US-guided), open incisional, excisional biopsy, enucleation/whoops
QI-4	time from biopsy to establishing diagnosis (1st path review & reference review)
QI-5	time from biopsy until sarcoma board presentation
QI-6	biopsy before initiation of treatment (yes/no)
QI-7	biopsy performed in the center where the patient is operated: (yes/no)
QI-8	extent of disease at diagnosis
QI-9	time from SB to initiation of treatment
QI-10	margin status (R0, R1, R2) at definitive surgery (STS
QI-11	preoperative radiation therapy: (yes/no)
QI-12	postoperative radiation therapy: (yes/no)
QI-13	neo-adjuvant chemotherapy: (yes/no)
QI-14	adjuvant chemotherapy (yes/no)
QI-15	local relapse: yes/no
QI-16	local recurrence: yes/no within 1st year of tumor resection (Bone)
QI-17	metastatic relapse: yes/no
QI-18	Latest follow-up: no evidence of disease (NED); alive with disease (AWD); dead of disease (DOD); dead of other reasons (DOR); no assessment possible; lost to follow-up; other status; unknown

Tabelle 2: *Liste der bislang definierten Qualitäts-Indikatoren betreffend Abklärung / outcome bei Patienten mit muskuloskelettalen Tumoren*

die Qualität der Behandlung nachgewiesen. Eine korrekte Therapie kann nur erfolgen, wenn die richtige Diagnose erstellt wird. Im SSN werden in Konsequenz alle Diagnosen durch die Referenzpathologie begutachtet. Selbstverständlich stellt sich dabei auch hier die Frage nach der Definition des Experten-Levels. Die definierten QI's beinhalten nebst der eigentlichen Diagnose auch die einzelnen Schritte und Durchlaufszeiten bis zur korrekten Diagnosestellung. Da die Abklärung hochkomplex sein kann, und nicht jede Institution die entsprechenden Investitionen tätigen kann oder will, und auch nicht alle Expertise zur Verfügung haben kann, ist es substanziell, bei kleinem Patientenvolumen in der Schweiz im Netzwerk auszutauschen, bzw. Standards zu definieren, innerhalb derer eine fundierte Abklärung in Zukunft erfolgen soll.

1.4 Ausbildung / Forschung

Der Wissenstransfer innerhalb des Netzwerkes mit internationalem Anschluss und Austausch ist für die Weiterentwicklung von zentraler Bedeutung (www.sarcoma.academy). Das SSN hat nun eine Webinar-Serie von acht Veranstaltungen organisiert, wobei alle zwei Monate ein internationaler Sarkomexperte zu einem spezifischen Thema vorträgt (www.swiss-sarcoma.net/pdf/20200910-webinar-invitation.pdf). Die webbasierte Plattform erlaubte zudem, den internationalen Austausch insbesondere während Covid-Zeiten zu forcieren.

Das SSN möchte u.a. auf die Versorgungsforschung fokussieren. Das SSN baut eine Sarcoma Quality Management System auf, um in real-time einen transdisziplinären Qualitätsstandard zu erfassen und womöglich in der Folge zu verbessern. In Arbeit sind derzeit weitere quality and complexity scores der Sarkombehandlung.

1.5 Zusammenfassung und Ausblick

Tab. 3 zeigt im Ueberblick die verschiedenen Aktivitätsfelder des Netzwerks. Das SSN etablierte ein überregionales transdiziplinäres wöchentliches Sarkomboard, wo die sich vertraglich verpflichteten Institutionen alle konsekutiven Patienten mit Sarkom(-Verdacht) vorstellen. Die Anmeldung zum Sarkomboard ist – wie oben erwähnt – gekoppelt mit dem SwissSarcomaRegistry, um eine real-time Datenerfassung zu ermöglichen. Einerseits wird dadurch die Datenqualität maximiert, und andererseits können im Rahmen des Quality Management System die einzelnen Behandlungsschritte erfasst und die Qualität der Ergebnisse ausgewiesen

SwissSarcomaNetwork (www.swiss-sarcoma.net)	
Trägerverein	von nationalen Institutionen geführt, seit 2018 Mitgliedschaft für alle Institutionen mit Bereitschaft, die Daten vorzustellen und zu erfassen
SwissSarcomaRegistry	Firma Adjumed (www.adjumed.ch) als Provider aktuell > 3000 Patienten-Daten erfasst, seit 2019 Kopplung von Sarkomboard und Datenbank zur real-time Datenerfassung
wöchentliches Sarkom-Board (Vidyo® -System)	~ 500 Falldiskussionen/Jahr
SOP / GCP	www.swiss-sarcoma.net
Qualitäts-Management-System (QMS, s.a. unter 1.3.)	Q-Parameter im Daten-Register erfasst
International Advisory Board	international anerkannte Sarkom-Experten der beteiligten Disziplinen stehen dem SSN für Zweitmeinungen zur Verfügung, was bestmögliche Qualität der Therapieentscheide sicherstellt. Zwei-monatliches Webinar (www.sarcoma.academy)
Wissenschaftliche Aktivität	Versorgungsforschung zur Etablierung von Qualitäts- und Komplexität-Scores

Tabelle 3: *Zusammenfassung der SwissSarcomaNetwork-Aktivitäten*

und definiert werden. Dadurch wird ein System geschaffen, welches erlaubt, nicht herkömmliche Aspekte neu zu definieren, um den Fokus auszurichten.

Unsere Zahlen zeigen, dass 35% aller Biopsien (!) durchgeführt wurden, ohne vorgängig ein Sarkom in Betracht zu ziehen. Darüber hinaus wurden 20% aller Sarkomdiagnosen durch sogenannte Whoops-Operationen gefunden. Häufig geschieht dies in der Annahme, dass eine Schwellung/Tumor ‹sowieso› entfernt werden müsste, womit dann gleich die Diagnose gestellt werden könnte. Leider erfolgen solche scheinbar banalen Eingriffe/Gewebeentnahmen häufig ohne Einhaltung der spezifischen Sarkomchirurgischen Prinzipien, was unter Umständen für den Patienten zu unangenehmen Nachresektionen mit weitreichenden unnötigen funktionellen Einbussen führt, wenn nicht sogar mit dem Verlust der Tumorkontrolle einhergehen kann. Zudem zeigen unsere Zahlen aber auch, dass nur gerade 4 von 10 Patienten mit einem möglichen Verdacht auf ein Sarkom auch mit einem solchen diagnostiziert werden. Interessanterweise werden diese Verdachtsfälle, bei denen kein Sarkom diagnostiziert wird, in der Literatur nicht diskutiert (Dunkelziffer; es wird nur vom gesicherten Sarkom-Subkollektiv gesprochen, nicht aber von den Verdachtsfällen). Möglicherweise aber bietet diese skotomisierte Patientengruppe eine Erklärung für die historisch unverändert hohe Whoops-Operationsrate wie oben diskutiert. Die Kapazität einer Abklärungsleistung eines international kompetitiven Sarkom-Zentrums dürfte überfordert werden, wenn auch alle diese Verdachtsfälle zentralisiert abgeklärt werden müssten. Zudem sind Infrastruktur und Kultur derzeit so, dass der Patient erwartet, zumindest diagnostische Abklärungen vor Ort zu erhalten. Konsequenterweise kann es deswegen sinnvoll sein, an regionalen Zentrumsspitälern Sarkom-Abklärungseinheiten einzurichten, die in einem Netzwerk organisiert als Eintrittspforte den Patienten zur bestmöglichen Therapie-Einheit triagieren und weiterweisen können.

Diese Ergebnisse und Ueberlegungen zeigen, wie wichtig es ist, im Sinne der Versorgungsforschung die Zahlen eines Sarkomboards zu erfassen und zu analysieren, um durch neue Ansätze Rückschlüsse für die Patientenversorgung zu gewinnen. Eventuell lässt sich mit diesem neuen Ansatz ein jahrzehntelanges Problem lösen.

Über Behandlungsresultate der SSN Sarkom-Patienten-Kohorte werden wir zu einem späteren Zeitpunkt mit ausreichend langer Verlaufsbeobachtung berichten.

Zur Dunkelziffer (Patienten mit Sarkomerkrankungen ohne prätherapeutische Präsentation und Prozedere-Besprechung im Rahmen eines Boards) kann entsprechend leider keine Aussage gemacht werden (Anzahl? Outcome?).

2. aktualisierte Informationen zum SSN für Ihren praktischen Alltag *(s.a. Luzerner Arzt 118/2019 [2])*

1) Wer kann Mitglied werden?

- jede medizinische Institution

2) Was bedeutet Mitgliedschaft?

- Mitgliedschaft beinhaltet die Bereitschaft, alle konsekutiven Patienten mit einer Sarkom-Erkrankung bzw. Verdacht auf eine sarkomatöse Erkrankung präthera-peutisch gemäss unten abgebildetem Algo-rithmus im gemeinsamen Tumorboard vorzustellen/vorstellen zu lassen (mit vor-gängigem PatientenEinverständnis).
- die Daten dieser Patienten im gemeinsamen Register zu erfassen/erfassen zu las-sen (mit vorgängigem Patienten-Einverständnis)

3) Wie können Sie auch als Nicht-Mitglied Ihre Patienten zur Fallbesprechung einbringen?

- Sie schalten sich via Videokonferenz ans Tumorboard direkt zu (Vidyo®-System; weitere Information: Beatrice.meier@ksw.ch)
- oder: Sie präsentieren selber «live» an einem der Standorte LUKS/KSW/KSGR/ BELLINZONA oder Pathologie Enge (jeden Dienstag, 17–18 Uhr, weitere Infor-mation: beatrice.meier@ksw.ch)
- oder: Sie weisen Ihren Patienten an die Sarkom-Sprechstunde LUKS, mit dann in der Folge Fall-Präsentation durch ein ärztliches Mitglied des Sprechstunde-Teams (Kontakt LUKS: Jehona.vishaj@luks.ch

4) wo/wie findet das SSN-Sarkomboard LUKS statt?

- Ort: Rapportraum 414, EG Hauptgebäu-de, Luzerner Kantonsspital (LUKS)
- Zeit: jeweils dienstags, 17–18 Uhr
- Wie: per Videokonferenz (Vidyo®System; Information: beatri-ce.meier@ksw.ch)

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Prätherapeutische Abklärung und Strategie-Festlegung bei Patienten mit Knochen- und Weichteiltumoren

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1. Einleitung

Sarkome sind seltene bösartige Knochen- und Weichgewebstumoren des Binde- und Stützgewebes, sie gehören zur Kategorie «rare diseases», und machen lediglich ca. 1% aller Krebsarten aus. Sie werden traditionell multidisziplinär behandelt. Die prätherapeutische histopathologische Diagnostik ist eine Herausforderung, da es mittlerweile mehr als 100 verschiedene, zum Teil klar molekular definierte Subtypen gibt, viele davon mit eigenständigem biologischem Verhalten, was das weitere therapeutische und Nachsorge-Vorgehen entscheidend beeinflusst, und die Einzelsituation noch rarer macht. Die Histo- und Molekularpathologie hat hier die zentrale Funktion der «guidance» der Kliniker (Gewichtung von Aggressivität der Entität, Ausbreitungs- und Metastasierungverhalten, etc). Hierbei ist insbesondere das korrekte Vorgehen (Quantität/Qualität) bei der Materialgewinnung, resp. der Aufbereitung für die histo- und molekular-pathologische Diagnose-Erhebung und für die nachfolgende chirurgische und radiotherapeutische Behandlung von zentraler Bedeutung. Ungünstige Schnittführung ebenso wie vermeidbare Kontamination intakter anatomischer Kompartimente zwecks Gewebe-Entnahme erschweren und/oder vergrössern den nachfolgenden onkologisch-chirurgischen Eingriff unnötig (anatomisch ausgedehntere Chirurgie = oft negativer Effekt auf die resultierende Organ-Funktion). Dasselbe gilt für die radiotherapeutische Volumendefinition (grössere Volumina = geringere Therapietoleranz).

Die Chirurgie stellt den Hauptpfeiler der Therapie dar, die Bestrahlung ist Teil der Behandlung grösserer und/oder tief gelegener Tumore. Die prätherapeutische Schichtbildgebung ist daher unabdingbar, und sollte eine prätherapeutische MRI im Bereiche des Lokalbefundes und für die Umgebungs-Abklärung («Staging») eine Lungen-CT beinhalten, (die Metastasen-Suche kann sich meist auf die Lungen-CT beschränken.

Die Basis für eine optimale Sarkombehandlung beruht auf der multidisziplinären Vorbesprechung und Behandlung innerhalb eines Sarkom-Netzwerkes. Die initiale interdisziplinäre Koordination zur **prätherapeutischen** Festlegung des Therapiekonzeptes ist dabei prognostisch entscheidend für den Patienten (s.o.). Dieser strategische Schritt erfolgt heutzutage für Sarkome – wie für alle anderen onkologischen Spezialitäten – im Rahmen eines interdisziplinären Tumorboards mit Anwesenheit aller relevanten Fachexperten. Derzeit werden in der Schweiz leider immer noch zu viele Sarkom-Patienten ausserhalb eines solchen Netzwerks auf ärztlicher Individualbasis «anbehandelt», was nicht selten zur Sarkom-Überraschungs-Diagnose (einer sogenannten «whoops» -lesion) führt. Das weitere «salvage»-Procedere solcher Fehlstarts wird meist zusätzlich substanziell erschwert durch eine nicht erfolgte prätherapeutische Schichtbildgebung und eine – vom onkologischen Standpunkt her ungünstige – Schnittführung. Aktuell werden in der Schweiz ca. 20% aller Weichteilsarkome durch solche ungeplante «whoops»-Exzisionen (keine vorausgehende Histopathologie, keine Schichtbildgebung, kein onkologischer Ansatz bei der Erstchirurgie, entsprechend meist keine suffizienten Schnittränder) diagnostiziert [5] – zu häufig mit negativen prognostischen und/oder funktionellen Konsequenzen für diese Patienten, bis hin zur vermeidbaren Amputation.

Es ist deshalb die Absicht dieses Beitrages, die Konzepte der modernen Abklärung von Knochen- und Weichteiltumoren darzulegen.

2. Minimal Work-up Requirements

Die Abklärung von Knochen- und Weichteiltumoren ist mitunter komplex, da es für die Definition von Malignität keine klaren klinischen Parameter gibt. Dies wird insbesondere für lipomatöse Weichteiltumoren offensichtlich, da das «klassische» Lipom nicht definiert ist. Wir stellen hier 6 initiale Fragen, die uns in einem konkreten Fall leiten sollen hinsichtlich optimaler prätherapeutischer Vorgehensweise bei Vorliegen einer Weichteilraumforderung bzw. Knochenläsion leiten sollen.

a.) Wann ist eine Veränderung malignitätsverdächtig?

Bei Vorliegen einer Raumforderung mit rascherer Wachstumstendenz, Symptome und Kriterien, die nicht dem «klassischen» Lipom entsprechend (Zeitverlauf, Palpation, Ultraschall), muss an eine maligne Läsion gedacht werden. In dieser Situation ist eine Gewebe-Entnahme zur histopathologischen Sicherung der Diagnose indiziert (siehe unter b.). Die Abgrenzung zum «klassischen» Lipom ist dabei die grösste Schwierigkeit; im Zweifelsfall ist eine nach Sarkomkriterien entnommene Gewebeprobe (s.u.) oder aber die Weiterweisung an ein Sarkomzentrum indiziert.

b.) Wann soll eine Biopsie durchgeführt werden?

Der alleinige Verdacht auf ein Sarkom soll die Indikation zur Biopsie rechtfertigen. Dies gilt sowohl für Knochen sowie auch für Weichgewebsveränderungen. Dabei ist es wichtig zu berücksichtigen, dass die lokale Bildgebung immer vor der Biopsie stattfinden soll, weil jede invasive Handlung zu Struktur- resp. Signalalterationen im MRI führen kann.

c.) Wann ist eine lokale Bildgebung indiziert?

An den Extremitäten wird die anatomische Lage der Weichteilläsion in Bezug auf die Faszie beurteilt. Jede subfaszial gelegene Weichteilmasse ist bis zum Beweis des Gegenteils als maligne zu betrachten. Eine oberflächlich gelegene, d.h. epifasziale Läsion, ist dann malignitäts-verdächtig, wenn diese rasch wächst, symptomatisch wird, oder grösser als 5 cm ist und nicht einem «klassischen» Lipom entspricht.

Eine weiterführende Schichtbildgebung ist zwingend indiziert bei in der konventionellen Bildgebung in zwei Ebenen verdächtigen Knochenveränderungen.

Die prätherapeutische Schichtbildgebung ist für Weichteilläsionen unverzichtbar; die i. v.-**Kontrast-verstärkte Magnetresonanztomographie** (MRI-KM) ist hierbei die Bildgebung der Wahl, um eine Läsion ausreichend zu charakterisieren. Dabei sollen insbesondere die Lage zu den neurovaskulären Strukturen und zum Periost oder Gelenksstrukturen erfasst werden; die Kontrastmittel-Aufnahme gibt Information über Durchblutung der Läsion und damit deren potentiellen Aggressivität.

d.) Wie soll eine Biopsie durchgeführt werden?

Die Wahl des Biopsieweges ist kritisch

und soll immer so erfolgen, dass dieser während der später folgenden Operation ohne vermeidbare Gewebekontaminierung oder Eröffnung zusätzlicher Kompartimente mit der Inzision entfernt werden kann, um das Tumorzell-Seeding und damit die Gefahr des Lokalrezidivs zu minimieren. Wenn immer möglich, soll die Biopsie mittels Stanzbiopsie unter Bildgebung mit CT- oder aber US-geführt erfolgen. Es konnte gezeigt werden, dass ein Tumorzell-Seeding bei perkutaner Stanzbiopsie bei lediglich 0.37% liegt [3], wohingegen diese Rate bei offener Biopsie mit 32% viel höher liegt, was in einem statistisch signifikant unterschiedlichen Rezidiv-freien Überleben resultierte [2, 3]. Eine Feinnadelbiopsie für primäre Sarkome ist in der Regel nicht indiziert, da die Trefferquote zu tief liegt. Eine histo- und molekularpathologische Diagnosestellung bei diesen «rare diseases» – ist substantiell abhängig von der Expertise des Pathologen, welcher wiederum auf qualitativ repräsentatives Gewebe angewiesen ist.

e.) Wie weiter, wenn die histo- resp. molekularpathologische Diagnose eines Sarkoms bestätigt ist?

Spätestens bei etablierter Diagnose eines Sarkoms sollte der Patient einem Sarkomzentrum resp. einer etablierten interdisziplinärer Sarkomeinheit zugewiesen werden zur Festlegung der weiteren Nachbehandlung. So wird die initiale interdisziplinäre Diskussion sichergestellt, in welcher die optimale Therapie-Strategie des individuellen Patienten festgelegt wird, und der Zeitverlust bis zum Behandlungsstart reduziert. Der enge Austausch zwischen Radiologen, Pathologen und Sarkomchirurgen und Radiotherapeuten und Onkologen in einem solchen Gremium garantiert ein raschmögliches orchestriertes Vorgehen, und verhindert unnötige zeitliche Verzögerungen, Re-Biopsien oder inkorrekte Diagnosen. Der pädiatrische Onkologe ist bei betroffenen Kindern und jüngeren Erwachsenen zwingend einzubeziehen, da das therapeutische Vorgehen sich von jenem bei Erwachsenen unterscheiden kann und seine Expertise deshalb im Hinblick auf Systemtherapien unverzichtbar ist. Die Sequenz des therapeutischen Vorgehens (alleinige Chirurgie versus prä-/postoperative Radiatio versus Induktionschemotherapie oder postoperative Systemtherapie) ist von den Entitäten abhängig und kritisch, um ein optimales Outcome zu erreichen. Ein solcher Abklärungsprozesses sollte idealerweise die Zeitspanne einer Woche nicht überschreiten **(Abbildung 1)**.

f.) Was beinhaltet ein initiales Staging bei Sarkom-Diagnose?

Da Sarkome in aller Regel hämatogen in die Lungen metastasieren, soll in erster Linie ein Thorax-CT durchgeführt werden. Ein thorako-abdominales CT kann sinnvollerweise ergänzt werden, um weitere Metastasen auszuschliessen, insbesondere z.B. beim myxoiden Liposarkom. Ein PET-CT ist in der Regel nicht notwendig/nicht indiziert, da nicht alle Sarkome FDG-positiv sind.

3. Swiss National Sarcoma Advisory Board (SNSAB) / Sarkomboard / Sarkomzentrum: organisierte Interdisziplinarität im Netzwerk

Die Charakteristik seltener Krankheiten, wie die Sarkome, beinhaltet naturgemäss meist limitierte Erfahrung und Kenntnis seitens der Behandelnden, mit entsprechend wenig routinierten Abläufen bezüglich Diagnosestellung und therapeutischem Vorgehen, was oft zu zeitlicher Verzögerung, wenig standardisiertem Vorgehen und inhomogener Qualität der Therapien führt. Definierte interdisziplinäre Vorgehensweisen und Patientenwege sind deshalb bei häufigen onkologischen Entitäten zwingend erforderlich und bei

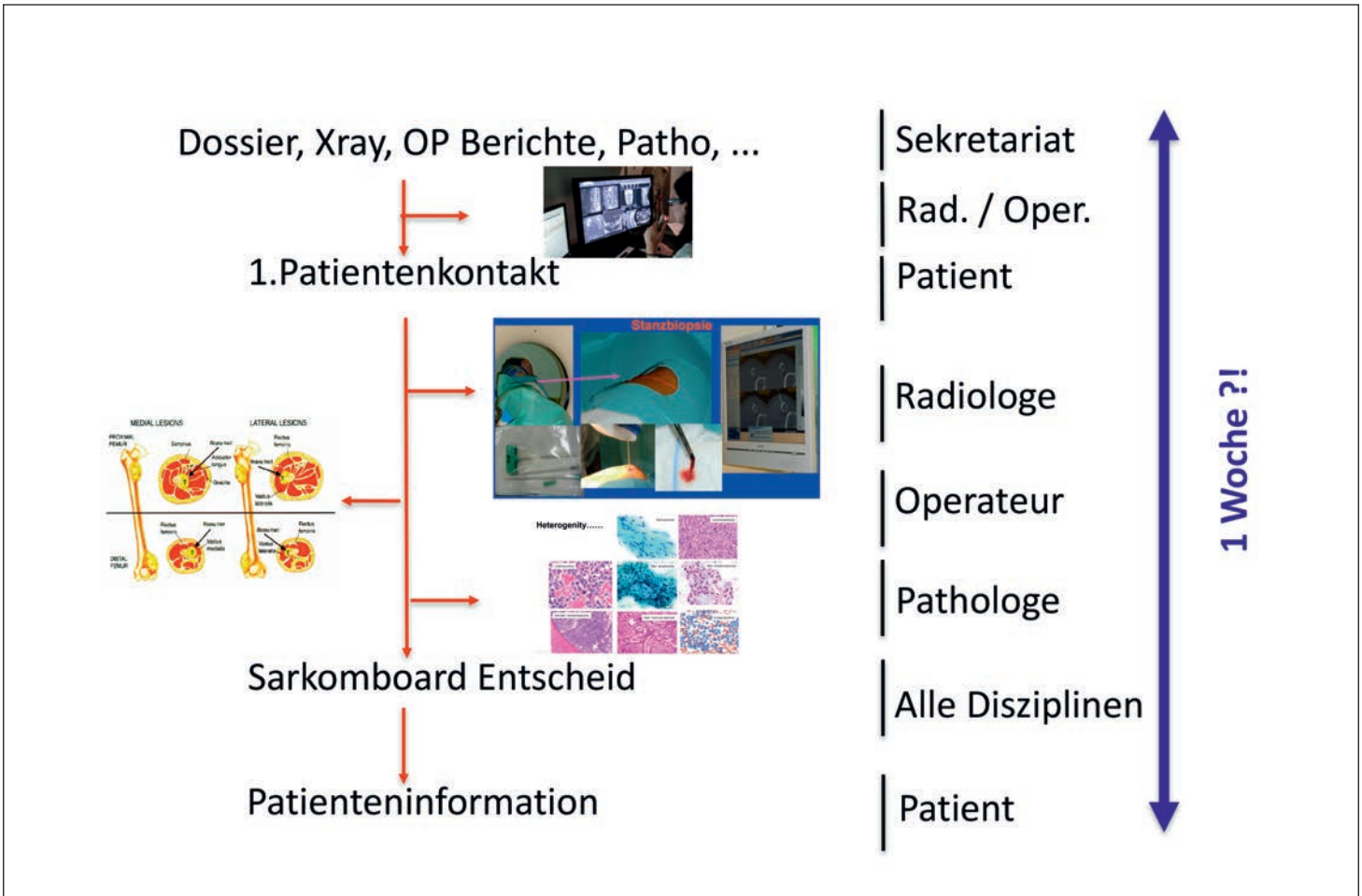


Abbildung 1: *Die Abklärung eines Patienten mit Sarkom-Verdacht ist logistisch anspruchsvoll und verlangt das Zusammenspiel von mehreren Disziplinen, die eng aufeinander abgestimmt sind. Es muss das Ziel sein, dass innerhalb einer Woche ein Verdacht entweder bestätigt oder aber ausgeschlossen wird.*

seltenen Erkrankungen sind sie umso wichtiger.

Eine Sarkomeinheit muss sicherstellen, Patienten möglichst zeitnah nach definierten Vorgehensweisen abzuklären – dies über ein definiertes kooperierendes Multidisziplinäres Team (MDT). Ein auf diese Weise potenziell erreichbares kritisches Volumen einer seltenen Krankheit ermöglicht eine klinisch fundierte Expertise der Beteiligten und die Teilnahme an klinischen Studien, den Vergleich mit internationalen Zentren (Qualitätskontrolle), sowie die Weiterbildung des Nachwuchses [1].

Aus diesen Gründen wurde in der Schweiz vor vier Jahren das Swiss National Sarcoma Advisory Board **(SNSAB; www.sarcoma.ch)** gegründet. Damit wurde eine **nationale Plattform** geschaffen, in der an der Sarkombehandlung beteiligte und interessierte Ärzte aller Disziplinen freiwillig teilnehmen und beitragen können. Die Ziele des SNSAB umfassen 3 Hauptpfeiler:

a.) Klinische Behandlungsrichtlinien oder «Guidelines»: ein Sarkom-Patient in der Schweiz soll den Anspruch haben können, unabhängig von Spital und Geografie nach einem einheitlichen Standard behandelt zu werden. Diese klinischen Richtlinien orientieren sich einerseits an internationalen Vorgaben.

b.) **SwissSARCOS (www.swisssarcos.memdoc.org)**: Ein Sarkom-Register soll die Kohorten-Daten der Behandlung aller nationalen Sarkom-Patienten, inkl. der jeweiligen Sarkomboard-Entscheide erfassen.

Demnächst wird die Registrierung von Krebspatienten in der Schweiz obligatorisch; SwissSARCOS antizipiert diesen Schritt für Sarkome und ist mit NICER (Nationales Institut für Krebsepidemiologie und Registrierung) abgestimmt; die Daten werden elektronisch am MEM (Maurice E. Müller Institute) in Bern erfasst. Diese Datenbank wird zukünftig Informationen über die Epidemiologie von Sarkomen und über die Behandlungsqualität in der Schweiz liefern.

c.) solide und flüssige Gewebebank: Um die Biologie der Sarkome besser zu verstehen, ist es unabdingbar, molekularen Analysen von Primärtumoren, Metastasen sowie Blut zu intensivieren. Voraussetzung dafür sind Gewebebanken mit ausreichend enthaltenen Gewebeproben. Eine der analytischen Herausforderungen ist diesbezüglich nebst der Logistik die bereits erwähnte ausgesprochene Heterogenität der Sarkome.

Definitionen:

- das Swiss National Sarcoma Advisory Board **(SNSAB)** bildet eine nationale Plattform und koordiniert alle Sarkomzentren in der Schweiz. Dieses Board tagt 1-2x pro Jahr abwechslungsweise in einem der schweizerischen Sarkomzentren.

- ein **Sarkomzentrum** führt ein Sarkomboard, organisiert die lokale Datenerhebung für SwissSARCOS und stellt sicher, dass Tumorproben aufbewahrt werden.

- ein **Sarkomboard** ist ein Tumorboard, welches mindestens neun Disziplinen umfasst alle Sarkompatienten wöchentlich bespricht. Nebst der Pathologie, der Radiologie und der Onkochirurgie, welche zur Abklärung und Diagnoseerstellung eine Einheit bilden, umfasst das Sarkomboard Vertreter aus Plastischer und Rekonstruktiver Chirurgie, Thorax- und Viszeralchirurgie, Radio-Onkologie sowie der Medizinischen Onkologie. Idealerweise ist die Pädiatrische Onkologie in einem Sarkomboard integriert.

- das **LUKS ist Teil des Sarkomzentrum-Netzwerkes (Abbildung 2)**, welches das wöchentliche Sarkomboard in Zürich durchführt (www.sarkomzentrum.ch) und die Kantonsspitäler Aarau, Baden, Bellinzona, Chur, Luzern, Münsterlingen, St. Gallen, Winterthur, und Zürich verbindet. So wird sichergestellt, dass Sarkom-Patienten einerseits heimatnahe behandelt und von der Expertise lokaler wie auch überregionaler Fachleute optimal profitieren können. Durch diese **überregionale Zentralisierung der Sarkompatienten an einem einzigen Sarkomboard** (dem diverse Partner regelmässig oder auch sporadisch nach Bedarf via **Telekonferenz** zugeschaltet sind, so auch das LUKS) erfahren die Beteiligten dieses Gremiums eine Patientenvolumen-Exposition, welche die kontinuierliche Weiterentwicklung der Expertise erlaubt und deren überregionalen Austausch optimiert und vereinfacht.

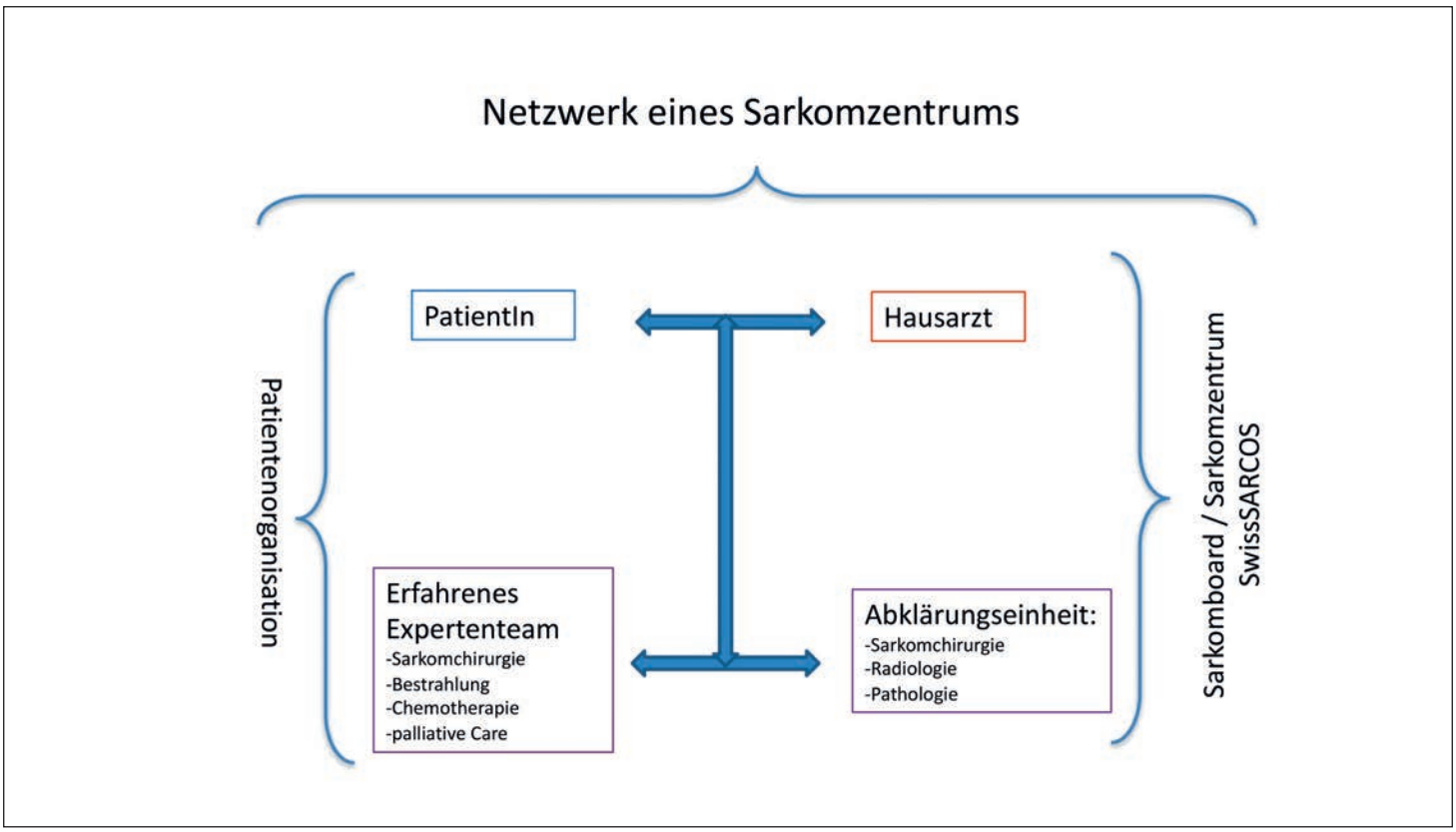


Abbildung 2: *Der Sarkompatient soll unmittelbar nach Äusserung eines Sarkomverdachts in ein erfahrenes Sarkom-Netzwerk eingeschleust werden, zeitnah und korrekt abgeklärt zu werden. Dabei ist entscheidend, dass alle Beteiligten dieses Netzwerkes Zugang zu allen Daten haben, z.B. durch SwissSARCOS.*

4. Interdisziplinarität und Case Management: Vorgehen im Einzelfall

Die Fortschritte der Sarkombehandlung über die letzten 40 Jahre haben eindrücklich gezeigt, wie erfolgreich Kombinationstherapien und damit interdisziplinäres Vorgehen sind. Ein multidisziplinärer Behandlungspfad ist so gut wie sein schwächstes Glied. Als Beispiel: die technisch beste Chirurgie nützt wenig, wenn die Diagnose nicht stimmt. Zurzeit werden gemäss WHO, wie bereits erwähnt mehr als 100 verschiedene Weichteiltumore klassifiziert [4]. Jeder dieser Tumoren hat seine eigene Biologie mit entsprechendem klinischem Verhalten. So weiss man z.B., dass ein Myxofibrosarkom, ein maligner peripherer Nervenscheidentumor, ein Dermatofibrosarcoma protuberans etc. lokal sehr aggressiv wachsen können, weshalb der Sarkomchirurge bei der Resektion einen viel grösseren chirurgischen Margin berücksichtigt als bei anderen Weichteilsarkomen, auch wenn sich diese Tumoren MRI-bildgebend nicht anders darstellen. Ein Sarkomchirurge ist deswegen auf eine korrekte Diagnose angewiesen, umgekehrt muss er die Biologie und das biologische Verhalten eines Tumors abschätzen können, um die bestmögliche Chirurgie durchführen zu können.

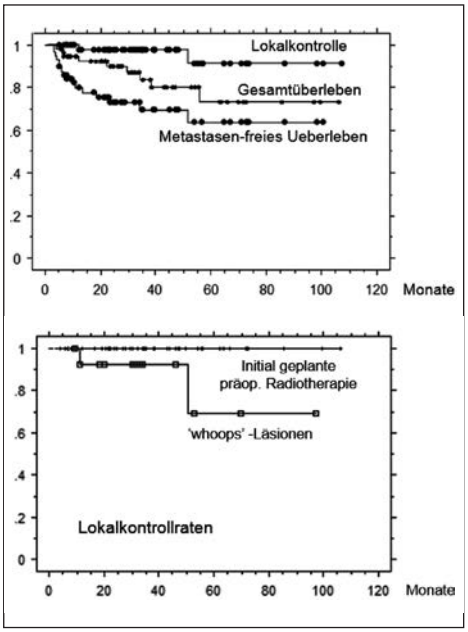


Abbildung 3: *Präoperativ bestrahlte Weichteilsarkome: Resultate einer Dekade Interdisziplinärer Kooperation (Sarkomchirurgie/Fuchs – Radioonkologie/Studer/Glanzmann – Pathologie/Bode vom Universitätsspital Zürich). Bei exzellenter interdisziplinärer Zusammenarbeit kann eine fast komplette Lokalkontrolle erreicht werden. A.) Es sind die Metastasen, die das Gesamtüberleben kompromittieren. B.) Die Lokalkontrolle beträgt 100% wenn die Patienten durch eine Sarkomeinheit initial behandelt werden, was stark kontrastiert zu Patienten mit vorausgehenden, ungeplanten («Whoops») Resektionen.*

Die Behandlung von Sarkomen bietet sich als Rollenmodell für gelebte Interdisziplinarität an, d.h. für die Zusammenarbeit der Disziplinen (MDT). Dies erfordert eine Lösung vom klassischen Denken in Disziplinen und Subdisziplinen (sogenannte «Disziplinenzentrierte Medizin»), hin zur «Problemzentrierten Medizin», um unsere Patienten optimal zu behandeln.

Seit der Einführung der Chemotherapie für die Knochensarkome in den späten 70-er und frühen 80-er Jahre und der Radiotherapie im Rahmen der Kombinationsbehandlung für die Weichteilsarkome, kam es zu einem signifikanten Anstieg der allgemeinen Überlebensrate und der Lokalkontrollraten von Sarkomen. Leider aber stagniert diese Überlebensrate seit ~20 Jahren, da wir weiterhin 30% bis 40% unserer Patienten aufgrund einer Metastasierung verlieren (**s. Abbildung 3**). Sobald eine Metastasierung diagnostiziert wird, gilt es wiederum, in der interdisziplinären Diskussion die individuell beste Vorgehensweise zu finden. Dies kann bei einer sogenannten Oligometastasierung nochmals ein kurativ intendiertes Behandlungskonzept mit Chirurgie und/oder Strahlentherapie als «lokal-kurative» Behandlungsoptionen beinhalten. In der palliativen Situation nehmen Hausarzt und/oder das regionale Spital eine entscheidende Rolle ein; das Zentrum kann stützend und beratend hinsichtlich der Evaluation palliativer Möglichkeiten mittragen.

Der Hausarzt nimmt im ganzen Krankheitsverlauf eine zentrale Rolle ein und ist in der Regel die erste Anlaufstelle für den Patienten – seine Erstbeurteilung ist entscheidend für die möglichst frühe Diagnosestellung. Um Patienten möglichst zeitnah am Zentrum abzuklären, ist es entscheidend, konkrete Ansprechpartner zu haben, die im interdisziplinären Sinne das ‚case management' übernehmen, (Ansprechpartner für das LUKS sind unten aufgeführt). Diese **Basis des gesamten Netzwerk bildet das Sarkomboard**, in dem die Patienten-Situationen rasch gepoolt zur wöchentlichen Board-Vorstellung gelangen und die Patienten gemäss dieser interdisziplinären Board-Empfehlung in standardisierter Weise zum nächsten Schritt geführt werden.

5. Patientenorganisation

Es kann für einen Patienten mit einer onkologischen Diagnose sehr hilfreich sein, sich mit anderen Betroffenen direkt auszutauschen. Weil solche Kontaktnahmen mit Betroffenen seltener Erkrankungen wie den Sarkomen über Eigeninitiative für Patienten sehr schwierig sein kann, haben Sarkompatienten in der Schweiz im Mai 2015 eine Patientengruppe resp. einen Verein gegründet (**www.sarkom-schweiz.ch**). Dieser Verein verfolgt das Ziel, ein öffentliches Bewusstsein für Sarkome zu generieren, die Vernetzung untereinander zu fördern, dh. auf Patienten Ebene, Fortbildungsveranstaltungen zum Verständnis der Therapieoptionen und der Nachsorge zu organisieren und Zugang zu den Sarkomzentren zu ermöglichen, sofern dies nicht schon erfolgt ist. Der Verein setzt sich zudem dafür ein, dass ein neu Betroffener und seine Angehörigen nicht nur medizinisch betreut, sondern sich im Alltag mit den neuen Herausforderungen und Limitierungen möglichst gut zurechtfinden kann. Damit bildet die Patientenorganisation ein kritisches Komplement in der erfolgreichen Behandlung und Betreuung von Sarkompatienten.

In den letzten Jahren zeigte sich die frühe Einbindung von Patienten in ein solches Patienten-Netzwerk als zunehmend wichtig und hilfreich, sowohl für Patienten wie auch für uns Behandelnde. Das sogenannte ‹patient reported outcome› (POR) spielt in den USA bereits eine wichtige Rolle auch hinsichtlich research und besserer Erfassung von Therapie-Toleranzen.

POR wird auch bei uns in Europa zunehmend als relevanter Support-Faktor sowie als wichtige Quelle zusätzlicher medizinischer Information erkannt.

6. Konklusionen

- Eine optimale Therapieplanung kann nur auf einer soliden prätherapeutischen histo- und molekularpathologischen und radiologischen Diagnostik basieren.
- Es ist sinnvoll, dass ein Patient bei Sarkom-Verdacht bereits zum frühest möglichen Zeitpunkt mit einem Sarkom-Chirurgen in Kontakt kommt, der eng abgestimmt mit dem Radiologen und dem Pathologen die Biopsie organisiert und die Diagnose etabliert.
- Die Therapieschritte werden prätherapeutisch strategisch am interdisziplinären Sarkomboard (www.sarkomboard.ch) festgelegt.
- Die initiale Behandlung dieser seltenen Entitäten sollte am Zentrum durch erfahrene Experten der genannten involvierten Disziplinen erfolgen.
- Der enge Austausch zwischen allen Beteiligten ist nur möglich durch eine exzellente Kommunikation; **SwissSARCOS** stellt diese Plattform und ermöglicht und erleichtert den hierfür nötigen Datentransfer.

Ich möchte einen Fall präsentieren am Sarkom-Board am LUKS:

– Informationen unter: www.sarkomboard.ch
– Anmeldungen über «tumoren@sarkomboard.ch»

Patienten-Kontakt-Adresse:
info@sarkom-schweiz.ch

KONTAKT-Möglichkeit bei Verdacht auf oder bei bereits gesicherter Sarkom-Diagnose am LUKS:

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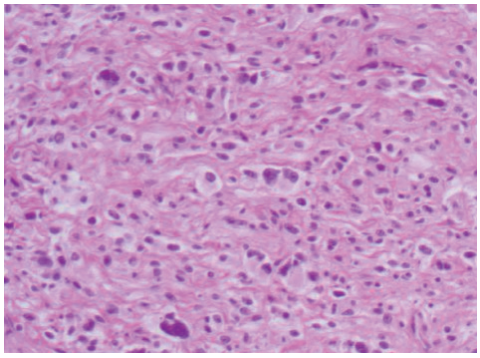
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Unter anderem in dieser Ausgabe:



08

Orthopädie und Unfallchirurg

Frühzeitig richtig handeln: Der Einfluss direkter Überweisungen auf Sarkom-Behandlungsergebnisse

Unkoordinierte Versorgungspfade führen bei Sarkomen oft zu Verzögerungen und schlechteren Ergebnissen. Mit der Sarcoma Integrated Practice Unit (IPU) am Luzerner Kantonsspital (LUKS) und dem Swiss Sarcoma Network (SSN) wurde eine multidisziplinäre Struktur geschaffen, die Diagnostik und Therapie effizienter koordiniert.

Ruben Jaeger, Georg Schelling, Philip Heesen, Riccardo Schweizer, Alexander Vogetseder, Beata Bode-Lesniewska, Esther Pardo, Christian Rothermundt, Peter Kestenholz, Andreas Scheiwiller, Gabriela Studer, Thomas Treumann, Kim van Oudenaarde, Björn-Christian Link, Bruno Fuchs



15

Schmerzmedizin

Chronische Diarrhoe und Ulcera duodeni – was steckt dahinter?

Ein 59-jähriger Patient berichtete, seit über 16 Jahren an Episoden postprandialer wässriger Diarrhoe zu leiden. Es habe keinen Gewichtsverlust und keine Begleitbeschwerden gegeben. Sowohl in der persönlichen als auch in der Familienanamnese waren keine relevanten Vorerkrankungen festzustellen.

Claudia Rebell, Martin Bolli et. al.

21

Dermatologie

Urogenitale Schistosomiasis

Eine 18-jährige, aus der Elfenbeinküste stammende Patientin wurde zur urologischen Abklärung vorgestellt. Anamnestisch bestand seit drei Monaten eine intermittierende Makrohämaturie ohne Begleitsymptome. Bisher waren keine Vorerkrankungen bekannt. Die Patientin war seit gut einem Jahr in der Schweiz wohnhaft, zuvor hatte sie in der Elfenbeinküste gelebt.

Ana Durovic, Rachel Groebli Bolleter et. al

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[2] nicht vom LUKS, of
[3] nicht vom LUKS, of
[4] Pathologie, LUKS, L Schweiz
[5] Medizinische Onkologie, LUKS, Luzern, Schweiz
[6] Klinik für Thoraxchirurgie, LUKS, Luzern, Schweiz
[8] Radio-Onkologie, LUKS, Luzern, Schweiz
[9] Radiologie, LUKS, Luzern, Schweiz

Schlüsselwörter
Sarkom; Zuweisung; Integrated Practice Unit; Swiss Sarcoma Network

Einleitung

Sarkome gehören zu den seltenen Tumoren und stellen eine besondere Herausforderung dar, nicht nur aufgrund ihrer Seltenheit, sondern auch wegen ihrer biologischen Heterogenität. Für die primär behandelnden Ärztinnen und Ärzte ist es oft schwierig, bei unspezifischen Symptomen wie Schwellungen oder Schmerzen die Möglichkeit eines Sarkoms in Betracht zu ziehen. Eine rasche Überweisung an ein spezialisiertes Zentrum ist jedoch entscheidend, um Fehldiagnosen und ungeeignete Eingriffe zu vermeiden. Um diesen Herausforderungen zu begegnen, wurde in enger Zusammenarbeit zwischen LUKS und SSN die Sarcoma Integrated Practice Unit (IPU) am LUKS etabliert. Diese multidisziplinäre Einheit setzt neue Massstäbe in Diagnostik, Therapie und Forschung und bietet eine Plattform für klinische Exzellenz [1, 2].

Das Problem der unkoordinierten Versorgung

Eine der zentralen Erkenntnisse des SSN ist, dass unkoordinierte und fragmentierte Versorgungspfade zu schlechteren Behandlungsergebnissen führen. Ungeplante «Whoops»-Resektionen, die oft ohne adäquate Bildgebung oder Biopsie durchgeführt werden, haben eine signifikant höhere Lokalrezidivrate und führen häufiger zu positiven Resektionsrändern.

Analysen des SSN im letzten Jahr haben gezeigt, dass bei Patie nnen, die in spezialisierten Zentren w er Sarcoma-IPU am LUKS behandelt werden, deutlich bessere Ergebnisse erzielt werden. Auf der Analysebasis von über 450 Patientendatensätzen konnten erstmals systematisch die Unterschiede zwischen geplanten und ungeplanten Resektionen dokumentiert werden. Diese Studien haben entscheidend dazu beigetragen, die Wichtigkeit einer frühzeitigen und direkten Überweisung zu unterstreichen [1–3].

Verzögerungen durch fragmentierte Überweisungsmuster

Effizienz und Qualität waren zentrale Schwerpunkte der Analysetätigkeit des SSN: Die Analyse der diagnostischen Intervalle zeigte, dass Überweisungen an nicht auf Tumoren spezialisierte Fachrichtungen mit zeitlichen Verzögerungen und eingeschränkter diagnostischer Präzision verbunden sein können. Dies unterstreicht die Notwendigkeit einer frühzeitigen Zuweisung an spezialisierte Tumorzentren, um Fehldiagnosen und Verzögerungen zu vermeiden. Die am LUKS angesiedelte IPU setzt dabei durch den Einsatz modernster Technologien wie prädiktiver Algorithmen und digitaler Zwillinge neue Massstäbe in der Diagnostik und trägt nachhaltig zur Optimierung der Patientenversorgung bei [2, 4, 5].

Die Konsequenzen ungeplanter Eingriffe

Ungeplante Resektionen haben unmittelbare Auswirkungen auf die chirurgische Qualität und vermindern die langfristigen Behandlungsergebnisse bzw. die Prognose. Die im Jahr 2023 durchgeführten Analysen des SSN haben gezeigt, dass ungeplante Eingriffe die Rate an Lokalrezidiven signifikant erhöhen und die Notwendigkeit von Nachoperationen steigern. Diese Nachoperationen sind tech-

Abb. 1

Die Grafik verdeutlicht den Unterschied zwischen einem direkten Behandlungsweg (Complete Care Pathway, CCP) und einem fragmentierten Behandlungsweg (Fragmented Care Pathway, FCP). Während der CCP eine direkte Überweisung an spezialisierte Sarkomzentren beinhaltet, verzögert der FCP Diagnose und Therapie durch zusätzliche Zwischenstationen.

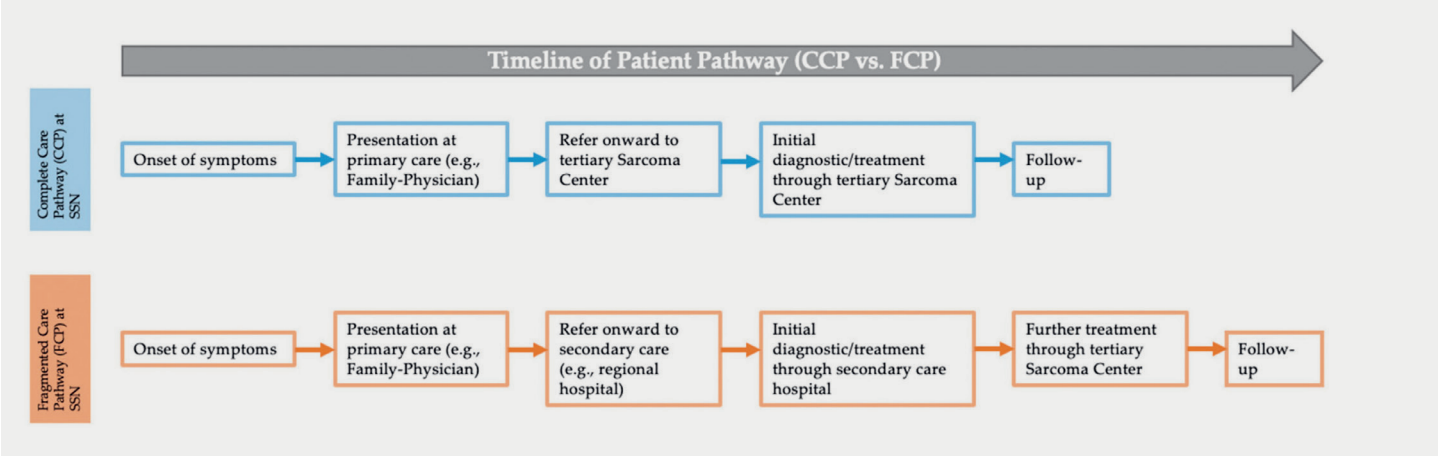
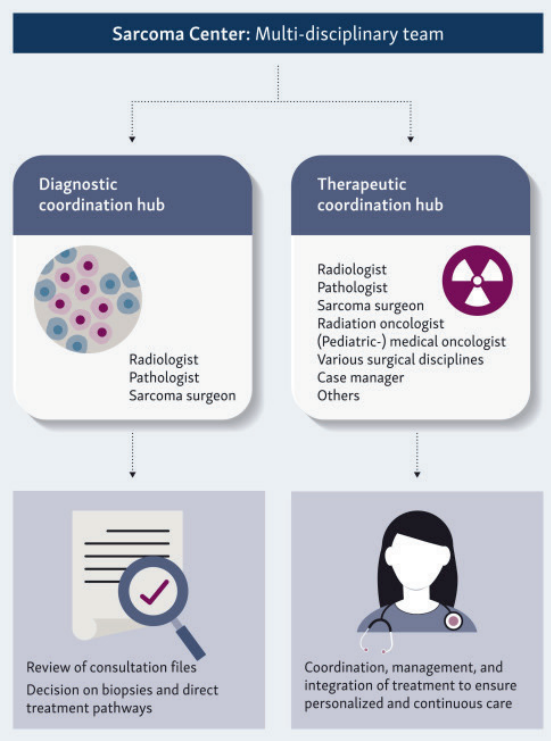


Abb. 2

Diese Abbildung zeigt das Sarkomzentrum, das aus zwei Hauptkomponenten besteht: dem diagnostischen und dem therapeutischen Koordinationszentrum. Im diagnostischen Koordinationszentrum prüfen Radiologen/-innen, Pathologen/-innen und Sarkomchirurgen/-innen eingehende Überweisungen und entscheiden über die Notwendigkeit sowie die Abfolge weiterer Untersuchungen, etwa von Biopsien. Das therapeutische Koordinationszentrum übernimmt anschliessend die individuelle Behandlungsplanung: Chirurgen/-innen, Radio-Onkologen/-innen und Onkologen/-innen stimmen im wöchentlichen Sarkomboard eine personalisierte Therapie ab und gewährleisten die kontinuierliche Versorgung. Gemeinsam optimieren beide Zentren den Patientenweg von der Diagnose bis zur Behandlung und stehen für eine umfassende, koordinierte und patientenzentrierte Versorgung.



nisch anspruchsvoll, oft mit einem höheren Komplikationsrisiko verbunden und haben einen direkten Einfluss auf die Lebensqualität der Patienten/-innen. Die Sarcoma Integrated Practice Unit (IPU) des LUKS ist dank diagnostischer und therapeutischer Fallbesprechung und der patientenzentrierten Koordination der individuellen Therapie in der Lage, diese negativen Folgen weitgehend zu vermeiden und so die Lokalkontrolle und die Langzeitüberlebensraten zu verbessern [1–3].

Lösungen und das Hub-and-Spoke-Modell

Das LUKS mit seiner Sarkom-IPU hat sich als Vorreiter in der Sarkomversorgung etabliert und fungiert als zentrale Drehscheibe innerhalb des SSN. Es zeichnet sich durch modernste Infrastruktur, interdisziplinäre Teams und die nahtlose Integration digitaler Plattformen aus. Zu den innovativen Ansätzen gehört der Einsatz von Echtzeit-Datenanalysen und digitalen Zwillingen, die eine präzise Diagnostik und Therapieplanung unterstützen. Durch die enge Zusammenarbeit zwischen zuweisenden Ärzten/-innen und der IPU können Patienten/-innen schneller und effizienter versorgt werden. Allein im Jahr 2024 wurden am SSN über 700 Patientenfälle evaluiert. Die Implementierung dieses Modells wurde wissenschaftlich begleitet und diente als Blaupause für den Aufbau weiterer nationaler und internationaler Netzwerke [6, 7].

Schlussfolgerung

Die Arbeit des SSN im vergangenen Jahr hat gezeigt, wie entscheidend ein ab initio integrierter und koordinierter Ansatz in der Sarkomversorgung ist. Die Sarcoma Integrated Practice Unit des LUKS ist nicht nur ein Modell für Exzellenz in der Versorgung, sondern auch ein Beispiel dafür, wie Innovation und Zusammenarbeit zu besseren Behandlungsergebnissen führen können. Für Hausärzte/-innen bedeutet dies, dass sie ihre zentrale Rolle in der Überweisung und frühzeitigen Erkennung von Sarkomen nutzen sollten, um von den Ressourcen des SSN und der IPU zu profitieren. Dieser koordinierte Ansatz verbessert die Behandlungsergebnisse und langfristig die Lebensqualität der Patienten/-innen.

So finden Sie uns

Für Rückfragen oder zur Anmeldung erreichen Sie uns jederzeit: Konsultationsfälle/Zuweisungen:
sarkomsprechstunde@luks.ch
Telefon 041 205 60 48

Sarkomboard
sarkomsprechstunde@luks.ch
Telefon 041 205 60 48

Scannen Sie den QR-Code, um direkt zur Website des LUKS mit weiteren Informationen zum Sarkomzentrum und zu den Anmeldemodalitäten zu gelangen.

Korrespondenzadresse

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Telefon 041 205 60 48
sarkomsprechstunde@luks.ch

Das Wichtigste für die Praxis

- Frühe Zuweisung ist entscheidend: Bei Verdacht auf ein Sarkom sollte die Überweisung frühzeitig an ein zertifiziertes Zentrum erfolgen – nur so kann das interdisziplinäre Team den optimalen diagnostisch-therapeutischen Weg festlegen.
- Teamarbeit von Beginn an: Radiologie, Pathologie, Chirurgie, Onkologie, Radio-Onkologie und Rehabilitation arbeiten im Tumorboard eng zusammen, um Diagnostik und Therapie individuell abzustimmen.
- Primäre Biopsie am Zentrum: Die Durchführung der Biopsie in einem erfahrenen Sarkomzentrum verhindert Komplikationen und verbessert die Planung von Operation, Strahlen- und Systemtherapie.
- Ganzheitliche Behandlung: Durch koordinierte, fachübergreifende Entscheidungswege sinken Reoperationsraten und Komplikationen, während funktionelle und onkologische Ergebnisse verbessert werden.
- Ziel: «Von Anfang an richtig» handeln: Frühzeitige Zuweisung und strukturierte Kommunikation zwischen Zuweisenden und Zentrum sind der Schlüssel zu einer sicheren, effizienten und patientenzentrierten Sarkomversorgung.

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