Study Protocol – "10 000 STS patients"

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Project title: Multicentre, retrospective study on the clinical and oncological outcome of soft tissue sarcoma patients treated at sarcoma units worldwide.

Deutscher Projekttitel: Multizentrische, retrospektive Studie über das weltweite klinische und onkologische Outcome von an Sarkomzentren behandelte PatientInnen mit Weichteilsarkomen.

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Background: Soft tissue sarcomas (STS) constitute a rare tumour entity, accounting for <1% of malignancies diagnosed per year. For localized disease, treatment mainly consists of wide resection with clear surgical margins, as well as radiotherapy and chemotherapy. Local recurrence (LR), distant metastasis (DM), and overall survival (OS) are the main oncological outcome measures in STS patients. Available risk prediction tools as the SARCULATOR (1, 2) or PERSARC (3) incorporate established risk factors contributing to adverse outcome in STS patients, including age, tumour size, and histology, amongst others.(1, 3) These models have been successfully developed and externally validated on multinational STS cohorts. However, none of these studies reached a sample size >= 10.000, staying below 3000 to 4000 (1, 2, 4, 5) patients. This project is planned as a joint *ISOLS* and *EMSOS* study, and will also invite members of other worldwide societies (see below).

Research Questions: By joining efforts in a large, retrospective, multicenter study in the sarcoma community (including members from *EMSOS – European Society of Musculoskeletal Oncology; ISOLS – International Society of Limb Salvage; MSTS – Musculoskeletal Tumour Society; SLATME – Sociedad Latinoamericana de Tumores Músculo Esqueléticos, APMSTS – Asian Paciifc Musculoskeletal Tumour Society*, and beyond), we aim at further improving outcome prediction (LR-free, DM-free, OS) in patients with STS, based on large-scale patient cohorts from geographically different regions. Our goal is to collect data on > 10.000 patients with STS. This will also allow us to analyze potential variations in treatment and outcome depending on geography, and at the same time enable development of a more nuanced outcome prediction tool.

Primary hypothesis: It is hypothesized that outcome prediction in patients with STS can be improved by including large patient numbers from different centres across the globe.

Methods: As every participating centre and/or cancer registry has a slightly differing structure in terms of data collection and granularity, we ask from potential centres to provide some core variables that are compulsory (see below, similar to the *International Sarcoma Registry [ISR] Minimal Dataset [MDS]*), and additional variables whose documentation status may vary (see below).

Inclusion criteria: All patients diagnosed with STS between 01.01.1990 and 31.12.2025 are potentially eligible.

Exclusion criteria: Patients with a considerable amount of missing key variables (defined as missigness rate of ≥ 20%; see Table below for key variables and additional variables) will be excluded.

Key variable set (similar to the International Sarcoma Registry [ISR] Minimal Dataset [MDS])		
Variable	**Label**	**Value**
Age at diagnosis	In years	Number (0 – X)
Sex	Female Male	0 1
Primary sarcoma	No Yes	0 1
Tumour side	Left Right Midline	0 1 2
Tumour location	Upper extremity Axilla Shoulder Arm Elbow	 0 1 2 3

	Forearm	4
	Wrist	5
	Hand	6
	Lower extremity	
	Gluteal	7
	Pelvis	8
	Thigh	9
	Knee	10
	Popliteal fossa	11
	Leg	12
	Ankle	13
	Foot	14
	Axial	
	Trunk	15
	Flank	16
	Paraspinal	17
Longitudinal location	Proximal	0
	Midshaft	1
	Distal	2
	Not applicable	3
Tumour histology	Fibrosarcoma	
	Myxofibrosarcoma	1
	Solitary fibrous tumour (SFT)	2
	Inflammatory myofibroblastic tumour	3
	Fibromyxoid sarcoma	4
	Dermatofibrosarcoma protuberans	5
	Giant cell fibroblastoma	6
	Myofibroblastic sarcoma	7
	Sclerosing epithelioid sarcoma	8
	Liposarcoma	
	ALT/WDLS	9
	Myxoid liposarcoma	10
	Dedifferentiated liposarcoma	11
	Pleomorphic liposarcoma	12
	Uncertain differentiation	
	Extraskeletal osteosarcoma	13
	Extraskeletal myxoid chondrosarcoma	14
	Epithelioid sarcoma	15
	Alveolar soft part sarcoma	16
	Clear cell sarcoma	17
	Plexiform fibrohistiocytic tumor	18
	Malignant tenosynovial giant cell tumor	19
	Giant cell tumor of soft tissue	20
	Angiomatoid fibrous histiocytoma	21
	Malignant ossifying fibromyxoid tumor	22
	Myoepithelial carcinoma	23
	Hemosiderotic fibrolipomatous tumor	24
	Malignant phosphaturic mesenchymal tumor	25
	Extrarenal rhabdoid tumor	26
	Ewing’s sarcoma	27
	Desmoplastic small round cell tumor	28
	Synovial sarcoma	29
	Vascular sarcoma	
	Angiosarcoma	30
	Kaposi sarcoma	31

	Pseudomyogenic hemangioendothelioma Epithelioid hemangioendothelioma Leiomyosarcoma Neural sarcoma Malignant peripheral nerve sheath tumor Melanotic schwannoma Malignant perineuroma Malignant granular cell tumor Rhabdomyosarcoma Embryonal Pleomorphic Alveolar Spindle cell Undifferentiated sarcoma Undifferentiated pleomorphic sarcoma Undifferentiated round cell sarcoma Undifferentiated spindle cell sarcoma Undifferentiated epithelioid sarcoma	32 33 34 35 36 37 38 39 40 41 42 43 44 45 46
If Tumour histology does not cover the histological subtype Other tumour histology	Histological subtype	Free text
Tumour grade	Grade 1 Grade 2 Grade 3 Grade X (non-gradeable histology)	1 2 3 4
Tumour size	< 5 cm > 5 cm and ≤ 10 cm > 10 cm and ≤ 15 cm > 15 cm	0 1 2 3
Tumour depth	Superficial Deep	0 1
Presence of DM at presentation	No Yes	0 1
Final margins	Intralesional resection Macroscopic positive (R2) Microscopic positive (R1) Marginal (R0, <1 mm) Wide (R0, >1 mm, no residual tumor)	0 1 2 3 4
Type of surgery	Limb salvage Amputation	0 1
CTX (use of CTX, regardless of timing)	No Yes	0 1
If CTX = Yes (1) Use of preoperative CTX	No Yes	0 1
If CTX = Yes (1): Use of postoperative CTX	No Yes	0 1
RTX	No	0

(use of RTX, regardless of timing)	Yes	1
If RTX = Yes (1) Use of preoperative RTX	No Yes	0 1
If RTX = Yes (1) Use of postoperative RTX	No Yes	0 1
If RTX = Yes (1) Use of intraoperative RTX	No Yes	0 1
If RTX = Yes (1) Use of definite RTX (no surgery)	No Yes	0 1
Additional variable dataset		
Variable	**Label**	**Value**
Country	Of contributing center	Free text
Intitution name	Of contributing center	Free text
Educational level	Primary education (e.g. elementary school) Secondary education (e.g. middle school, junior high-school, senior high school) Academic (university)	1 2 3
Biopsy at referral centre	No Yes	0 1
Type of biopsy (core needle, fine-needle, open)	Core needle biopsy Fine-needle biopsy Open biopsy	0 1 2
MDT meeting	No Yes	0 1
Bone resection necessary to achieve wide margins	No Yes	0 1
Bony involvement (of primary tumour)	No Yes	0 1
If "Bony involvement" = Yes (1) Type of bone resection	Periosteal stripping Prophylactic nailing/plating Tumour endoprosthesis	0 1 2
Soft tissue involvement (of primary tumour)	No Yes	0 1
If "Soft tissue involvement" = Yes (1) Type of soft tissue reconstruction	None Neurovascular Skin graft Local flaps Free flaps	0 1 2 3 4

If presence of DM at presentation = Yes (1) Location of DM at presentation	Lung Liver Soft tissues Bone Lymph nodes Brain Other	0 1 2 3 4 5
If CTX = Yes (1) Type of CTX	E.g. “ifosfamide”	Free text
If CTX = Yes (1) Number of CTX cycles	Number of cycles	Number (0 – X)
If RTX = Yes (1) Dose of RTX	In Gray (Gy)	Number (0 – X)
Use of isolated limb perfusion (ILP)	No Yes	0 1
Postoperative complications	No Yes	0 1
If postoperative complications = Yes (1) Type of postoperative complication	Wound healing deficit* Infection* Haematoma formation* Dislocation* Deep vein thrombosis Pulmonary embolism Fracture Vascular Neurologic Other **With or without revision surgery*	0 1 2 3 4 5 6 7 8 9
If Type of postoperative complication = Other (9) Description of other postoperative complication	Detailed description of other postoperative complication	Free text
Local follow-up modality	Ultrasound of affected site CT of the affected site MRI of the affected site	0 1 2
Systemic follow-up modality	Chest x-ray Chest CT-scan* PET-CT scan **with or without abdomen/pelvis*	0 1 2
Occurrence of LR	No Yes *LR either verified via biopsy or imaging (MRI scan)*	0 1

Time to LR	Calculated from date of definite surgery to date of LR *Date of LR defined as first clinical or histological verification of LR (e.g. either date of biopsy for LR or date of imaging at which time point locally recurrent tumour disease was apparent)*	In months
Occurrence of DM	No Yes *DM either verified via biopsy or unequivocal imaging (earlier indeterminate findings [e.g., small nonspecific pulmonary nodules] are not considered metastatic until they show progression or typical features consistent with metastases)*	0 1
Time to DM	Calculated from date of definite surgery to date of DM *Date of DM either verified via biopsy or unequivocal imaging (earlier indeterminate findings [e.g., small nonspecific pulmonary nodules] are not considered metastatic until they show progression or typical features consistent with metastases)*	In months
Follow-up time	Calculated from date of definite surgery to date of last follow-up Date of last follow-up one of the following: 1. Last contact or visit to study center 2. Last telephone contact with study center 3. Last contact with study center	In months
Outcome	Alive without evidence of disease Alive with disease (AWD) Death of disease (DOD) Death of other causes (DoC) Death of unknown causes Lost to follow-up	0 1 2 3 4 5
Status	Alive Dead Lost to follow-up	0 1 2
Type of latest functional outcome score	MSTS TESS	0 1
If Type of latest functional outcome score = Yes (1) Value of outcome score	Percent of total score (for MSTS and TESS)	Percent (0-100)
If Type of functional outcome score = Yes (1)	Calculated from date of definite surgery to date of functional outcome score	In months

Time to functional outcome		

***Abbreviations**: AWD, alive with disease; CT, computed tomography; CTX, chemotherapy; DM, distant metastasis; DOC, death of other causes; DOD, death of disease; LR, local recurrence; MDT, multidisciplinary team; MRI, magnetic resonance imaging; MSTS, Musculoskeletal Oncology Society; RTX, radiotherapy; SFT, solitary fibrous tumour; TESS, Toronto Extremity Salvage Score*

Analyses: We aim at carrying out conventional statistics and at developing artificial intelligence (AI)-enhanced models for outcome prediction in patients with STS, considering complex non-linear relationships and competing events (in case of recurrence [LR, DM] prediction).

Data management: Data will be collected at each participating site in a pseudonymised manner using a template to capture data for clinical research (e.g. password-secured Excel spreadsheet) or a web-based application designed to facilitate data collection and management for research studies like REDCap. The final dataset will be safely transferred to the primary study site (Department of Orthopaedics and Trauma, Medical University of Graz) in a pseudonymised manner, thus allowing for potential later re-checking of original data sources in case of uncertainty. Prior to data transfer, data transfer agreements (DTAs) will be established between the institutions.

Publication rights: All scientists involved in the study will be included – provided that criteria for authorship are fulfilled – as co-authors of the manuscript(s). Each co-author will be forwarded the manuscript draft for review and will have to agree to publication of the work in the final form.

Prospect: Additional project proposals may be raised during data collection and initial analyses. Participating centres are strongly encouraged to suggest further research questions to be answered.

Further information: The variable list (key and additional variables) will be forwarded to centres as soon an agreement for participation has been reached.

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References

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