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Therapieoptimierung bei Weichgewebssarkomen

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Abkürzungsverzeichnis

ADL	*Activities of Daily Living*
ALK	*Anaplastic lymphoma kinase*
APACHE	*Acute Physiology and Chronic Health Evaluation*
ARFS	*abdominal recurrence-free survival*
ASCO	*American Society of Clinical Oncology*
ASPS	*Alveolar soft part sarcoma*
bzw.	beziehungsweise
C	Celsius
ca.	circa
CAR-T	chimärer Antigenrezeptor-T
CARG	*Cancer and Aging Research Group*
CCI	*Charlson comorbidity index*
CDK4/6	*Cyclin-dependent kinase 4/6*
CDKN2A	*Cyclin Dependent Kinase Inhibitor 2A*
CGA	*Comprehensive Geratric Assessment*
CI	*Confidence interval*
cKIT	*KIT proto-oncogene, receptor tyrosine kinase*
CR	*complete remission*
CRASH	*Chemotherapy risk assessment scale for high age patients*
CTA	*Cancer testis antigen*
CTCAE	*Common Terminology Criteria for Adverse Events*
CTX	Chemotherapie
DKFZ	Deutsches Krebsforschungszentrum
DKTK	Deutsches Konsortium für Translationale Krebsforschung
DTIC	Dacarbazin
EBV	Epstein-Barr-Virus
ECOG	*Eastern Cooperative Oncology Group performance status*
EFS	*Event-free survival*
EFT	*Ewing Family of Tumors*
EORTC	*European Organisation for Research and Treatment of Cancer*
EORTC QLQ-C30	*European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire*
ERG	*transcriptional regulator ERG*

ETS	*erythroblast transformation-specific*
et al.	*et alii*
ETV4	*ETS translocation variant 4*
EWSR1	*Ewing Sarcoma breakpoint region 1*
EZH	*Enhancer of zeste homolog 2*
EZH2	*enhancer of zeste 2 polycomb repressive complex 2 subunit*
FDA	*U.S. Food and Drug Administration*
FEV	*fifth Ewing variant*
FFDM	*freedom from distant metastases*
FLI1	*Friend leukemia integration 1*
FNCLCC	*Fédération Nationale des Centres de Lutte Contre le Cancer*
FUS	*FUS* Gen
ggf.	gegebenenfalls
GISAR	*German Interdisciplinary Sarcoma Registry*
GISG	*German interdisciplinary sarcoma group*
GIST	Gastrointestinaler Stromatumor
Gy	Gray
HFRT	hypofraktionierte Radiotherapie
HR	*Hazard ratio*
HRQoL	*Health-Related Quality of Life*
IADL	*Instrumental Activities of Daily Living*
ICU	*Intensive care unit*
ICU non-surv	*ICU non-survivors*
ICU surv	*ICU survivors*
ILP	*Isolated limb perfusion*
IMT	Inflammatorischer myofibroblastischer Tumor
L-Sarkome	Leiomyo- und Liposarkome
LC	*Local control*
LCR	*local control rate*
MAGE	*Melanoma antigen gene*
MASTER	*Molecularly Aided Stratification for Tumor Eradication*
MDM2	*Murine double minute 2*
MIDOS	minimales Dokumentationssystem
MMR	*Mismatch repair*

MNA	*Mini Nutrition Assessment*
MPNST	Maligner peripherer Nervenscheidentumor
MVA	multivariate Analyse
NCT	*National Clinical Trial number* (siehe ClinicalTrials.gov)
NCT	Nationales Centrum für Tumorerkrankungen
NRS	*Numeric pain scale*
NTRK	Neurotrophe Tyrosin-Rezeptor Kinase
NY-ESO 1	*New York esophageal squamous cell carcinoma-1*
o.g.	oben genannte/n
ORR	*Overall response rate*
OS	*Overall survival*
p	*p*-Wert
PD	*progressive disease*
PD-L1	*Programmed cell death 1 ligand 1*
PD1	*Programmed cell death protein 1*
PDGFRα	*platelet-derived growth factor receptor α*
PFS	*Progression free survival*
PR	*partial remission*
PRAME	*Preferentially expressed antigen in melanoma*
PRO	*patient-reported outcome*
QoL	*quality of life*
RCT	Radiochemotherapie
RFP	*rare fusion partners*
RHT	Regionale Tiefenhyperthermie
rhTNFα-1a	*recombinant human necrosis factor α-1a*
RNA	*Ribonucleic acid*
RT	Radiotherapie
SAPS II	*Simplified Acute Physiologic Score II*
SD	*stable disease*
SFT	Solitär fibröser Tumor
SIB	*simultaneous integrated boost*
SOFA	*Sequential Organ Failure Assessment*
STS	*Soft tissue sarcoma*
TCR-T	*T cell receptor-engineered T cells*

TET	*ten-eleven translocation*
TIL	Tumor-infiltrierende Lymphozyten
TLS	*tertiary lymphoid structures*
TNM	Klassifikation zur Einteilung von Tumorerkrankungen (T – Tumor; N – Nodus/Lymphknoten; M - Metastasen)
TMB	*Tumor mutational burden*
tw.	teilweise
u.a.	unter anderem
USA	*United States of America*
UVA	univariate Analyse
VDC/IE	Kombinationschemotherapie aus Vincristin, Doxorubicin, Cyclophosphamid, Ifosfamid und Etoposid
VEGFR	*Vascular Endothelial Growth Factor Receptor*
VIDE	Kombinationschemotherapie aus Vincristin, Ifosfamid, Doxorubicin, Etoposid
vs.	versus
WHO	*World Health Organization*
z.B.	zum Beispiel

1 Einleitung

1.1 Weichgewebssarkome

1.1.1 Einteilung und Epidemiologie

Sarkome gehören zu den seltenen Tumorerkrankungen. Die jenseits des Kindesalters am häufigsten auftretende Subgruppe sind Weichgewebssarkome (*soft tissue sarcoma*, STS). Sie machen insgesamt 1% aller Malignome der Erwachsenen bzw. 7% aller Krebserkrankungen bei Kindern aus [1].

Die jährliche Inzidenz wird international mit 1,8 bis 5,0 pro 100 000 Personen angegeben. Nach Schätzungen des Robert Koch Instituts waren es für das Jahr 2013 in Deutschland ca. 6 Neuerkrankungen pro 100 000 Personen. Da in den Krebsregisterdaten alle Tumore der Weichgewebe zusammengefasst und die organspezifischen Sarkome aber nicht inkludiert sind, ist die tatsächliche Inzidenz in Deutschland insgesamt vermutlich jedoch eher höher [2].

Sarkome repräsentieren eine sehr heterogene Erkrankungsgruppe mit unterschiedlichem pathologischen und klinischen Erscheinungsbild und einem Auftreten in praktisch jeder anatomischen Lokalisation. Nach der WHO Klassifikation von 2020 werden inzwischen mehr als 70 Subentitäten unterschieden [3].

Die häufigsten Diagnosen bei älteren Erwachsenen sind neben den Gastrointestinalen Stromatumoren (GIST) undifferenzierte Sarkome, komplexe Neoplasien, L-Sarkome (Leiomyosarkome, Liposarkome) und Angiosarkome [1].

Es liegen nur spärliche epidemiologische Daten zu Knochen- und Weichgewebssarkomen vor. Aufgrund der biologischen Heterogenität der verschiedenen Subtypen lassen sich diese auch nur eingeschränkt zusammenfassen. In ca. 30 % der Fälle liegt bei Erstdiagnose bereits ein metastasiertes Erkrankungsstadium vor, das 5-Jahresüberleben beträgt in Abhängigkeit des vorliegenden histologischen Subtyps 54 bis 99 % [4], [5].

Die Vorstellung des:der Patient:in an einem Sarkomzentrum sowie die prätherapeutische Falldiskussion im interdisziplinären Sarkom-Tumorboard hat eine entscheidende prognostische Rolle. Dies hat z.B. eine im Jahr 2017 publizierte Auswertung französischer Registerdaten eindeutig gezeigt [6]. Sowohl das lokalrezidivfreie als auch das rezidivfreie Überleben wurde durch die prätherapeutische Vorstellung in einer entsprechenden Tumorkonferenz signifikant beeinflusst.

Zu den modifizierbaren Risikofaktoren von Weichgewebssarkomen gehört eine EBV-Infektion bei gleichzeitig Vorliegen einer angeborenen oder erworbenen Schwäche der

Immunabwehr, eine vorhergehende Chemo- und/oder Strahlentherapie und eine berufliche Exposition gegenüber Vinylchlorid. Eine genetische Prädisposition findet sich bei 6 bis 14% der Patient:innen mit Weichgewebssarkomen [1].

Sarkome werden wie viele andere solide Tumore nach der TNM *Classification of Malignant Tumors* (TNM) eingeteilt, auch wenn diese Klassifikation eine deutlich geringere prognostische Aussagekraft besitzt als u.a. der histopathologische Subtyp [1]. Die Stadieneinteilung ist abhängig von der jeweiligen anatomischen Lage.

Wesentlichen Einfluss auf die Prognose sowie die Therapieentscheidung haben die Tumorgröße, die Lokalisation (Extremität vs. Stamm, subfaszial vs. epifaszial), der histologische Subtyp, das Grading nach FNCLCC (*Féderation Nationale des Centers de Lutte Contre le Cancer*) und der Resektionsstatus.

Die initiale Verdachtsdiagnose wird meist mittels lokaler Bildgebung (Sonographie, Computertomographie, Magnetresonanztomographie) gestellt. Optimalerweise erfolgt dann eine Vorstellung in einem spezialisierten Sarkomzentrum, wo die histologische Sicherung durchgeführt und das Staging ggf. komplettiert wird. Die Empfehlung bezüglich des weiteren Vorgehens wird durch das interdisziplinäre Sarkom-Tumorboard prätherapeutisch definiert.

Die vollständige Resektion mit ggf. perioperativer Radio-/Systemtherapie entspricht weiterhin der einzigen Behandlung mit der Möglichkeit einer Kuration.

1.1.2 Aktuelle Standards in der Therapie

1.1.2.1 Chirurgische Therapie

Eine Heilung von Sarkomerkrankungen kann nur durch eine vollständige Resektion mit mikroskopisch tumorfreien Schnitträndern (R0-Resektion) erreicht werden. Falls diese nach Komplettierung des Stagings ohne relevante funktionelle Beeinträchtigung erreichbar scheint, entspricht die Resektion der Therapie der ersten Wahl. Auch im Falle einer ungeplanten Resektion sollte unter der Verdachtsdiagnose einer gutartigen Läsion eine Nachresektion erfolgen, um eine lokale Tumorkontrolle zu erreichen [1].

Der Tumor sollte en bloc reseziert und der Biopsiezugang mit entfernt werden. Das Ausmaß der Resektion richtet sich nach der anatomischen Lage und der etwaigen Beteiligung benachbarter Strukturen bzw. Organe. So unterscheiden sich die genauen Resektionsrichtlinien und auch die Definition des Resektionsabstandes in Abhängigkeit davon, ob es sich um ein Sarkom der Extremitäten, des Körperstammes oder des Retroperitoneums handelt.

Grundsätzlich wird nach Enneking zwischen intraläsionalen (R2) bzw. marginalen (R1) Resektionen, einer weiten Resektion und der Kompartmentresektion unterschieden [7]. Eine radikale Resektion bzw. vollständige Kompartmentresektion ist nur in Einzelfällen notwendig und sollte vor allem bei Sarkomen der Extremitäten immer gegen den Funktionserhalt abgewogen werden [8]. Oft kann durch eine neoadjuvante Behandlung (Systemtherapie +/- Hyperthermie, Radiatio, isolierte hypertherme Extremitätenperfusion) eine mutilierende Operation bzw. bei Sarkomen der Extremitäten eine Amputation vermieden werden [9]. Insgesamt ist lediglich bei ca. 10% der Patient:innen mit einem Sarkom der Extremitäten eine Amputation notwendig [10], [11].

1.1.2.2 Strahlentherapie, hypertherme Verfahren

Das Ziel der Strahlentherapie ist eine Verbesserung des Gesamtüberlebens [12]. Sie wird generell für alle high grade Weichgewebssarkome empfohlen und sollte insbesondere auch bei Patient:innen mit Sarkomen im Bereich der Extremitäten und des Körperstammes in Betracht gezogen werden [1], [13]–[15].

Im Gegensatz zur Ansprache auf die Systemtherapie scheint es bezüglich der Radiatio lediglich für MPNST, Synovialsarkome sowie myxoide Liposarkome subtypenspezifischen Unterschiede zu geben [1]. Eine prä- oder postoperative Strahlentherapie wird insbesondere bei hochgradigen (G2/G3) Weichgewebssarkomen empfohlen [16].

Optimalerweise erfolgt die Durchführung neoadjuvant, vor allem weil dann eine geringere Größe der Strahlenfelder gewählt werden kann [17], [18].

Die präoperativ applizierte Dosis beträgt in der Regel 45-50 Gy (25 Fraktionen, Einzeldosis 1,8-2,0 Gy), bei absehbar positiven Resektionsrändern kann ergänzend ein intraoperativer Boost mit 10-15 Gy appliziert werden [12], [19]. Neben normofraktionierten Schemata wird zunehmend auch eine hypofraktionierte Applikation evaluiert [20].

Die neoadjuvante Strahlentherapie ist jedoch nicht für alle Patient:innen bzw. Lokalisationen zu empfehlen, wie unter anderem auch in der randomisierten Phase III EORTC-62092 (STRASS)- Studie für retroperitoneale Sarkome gezeigt werden konnte. Hier war das abdominale rezidivfreie Überleben bei den Patient:innen, die zusätzlich bestrahlt worden waren, sogar 6 Monate kürzer [13].

Bei postoperativer Durchführung sollte die Radiatio innerhalb von 3-6 Wochen begonnen werden [1]. Hier werden 66 Gy aufgeteilt in 33 Fraktionen verabreicht.

Zusätzlich kann z.B. bei Vorhandensein eines durch den:die jeweilige:n Operateur:in definierten Hochrisiko-Resektionsrandes im Bereich des Retroperitoneums ein simultaner integrierter Boost (SIB) appliziert werden [21].

Zur kombinierten Radiochemotherapie im Kontext der Weichgewebssarkome gibt es bei Fehlen großer randomisierter Studien mit direktem Vergleich zur alleinigen Radiatio bzw. Systemtherapie bisher keine einheitlichen Empfehlungen.

In einer Studie zu high grade STS der Extremitäten konnte durch eine kombinierte Radiochemotherapie verglichen mit alleiniger Radiatio das Gesamtüberleben (*overall survival*, OS), das Ereignisfreie Überleben (*event-free survival*, EFS) und auch die lokale Kontrollrate (*local control rate*, LCR) verbessert werden [22].

Randomisierte Daten zur Radiochemotherapie im Vergleich zur alleinigen Chemotherapie sind nicht verfügbar. Grundsätzlich ist die Toxizität bei Kombination beider Modalitäten höher. Auch bleibt unklar, welche Substanz am geeignetsten ist. Bisher wurden hierfür diverse Substanzen (z.B. Doxorubicin, Ifosfamid, Gemcitabin, Hafniumoxid, Trabectedin) oder ein sequentielles Vorgehen gewählt .

Im Rahmen der klinischen Routineversorgung ist die kombinierte Radiochemotherapie außer bei spezifischen Sarkomsubtypen wie u.a. Ewing- oder Rhabdomyosarkomen bisher nicht als Standard etabliert und basiert in der Regel auf der Präferenz bzw. Expertise der jeweiligen therapieführenden Institution [1].

Neben der konventionellen Strahlentherapie können in ausgewählten Fällen auch hypertherme Therapieverfahren wie u.a. die isolierte hypertherme Extremitätenperfusion (engl. *isolated limb perfusion, ILP*) oder eine regionale Tiefenhyperthermie (RHT) zum Einsatz kommen.

Bei der ILP handelt es sich um eine für Sarkome im Bereich der Extremitäten zugelassene Standardtherapie. Sie kann bei lokal fortgeschrittenen Primärtumoren oder Lokalrezidiven zur lokalen Tumorkontrolle präoperativ oder als palliative Maßnahme eingesetzt werden. Hierbei wird mittels gefäßchirurgischer Technik ein gesonderter Kreislauf für die betroffene Extremität hergestellt und eine Hyperthermie von 38-39,5° C etabliert [23]. In diesen separaten Perfusionskreislauf werden Melphalan und rekombinanter humaner Tumornekrosefaktor α-1a (engl. *recombinant human necrosis factor α-1a*, rhTNFα-1a) appliziert [24].

Die RHT umfasst eine durch elektromagnetische Wellen herbeigeführte Erwärmung des Tumors und des umgebenden Gewebes auf 40-43° C, welche eine chemo- und radiosensibilisierende Wirkung haben soll. Im Rahmen einer Phase III Studie konnte die

RHT in Kombination mit Systemtherapie das Progressionsfreie Überleben (*progression-free survival*, PFS) und EFS positiv beeinflussen [25].

1.1.2.3 Medikamentöse Tumortherapie

Als Standard für die Behandlung von Weichgewebssarkomen hat sich in den letzten Jahrzehnten die Anthrazyklin-basierte Behandlung etabliert [1]. Bei Fehlen von Kontraindikationen und einem ausreichenden Allgemeinzustand wird dieses in Kombination mit Ifosfamid oder Dacarbazin/DTIC gegeben [26]–[28],

Für einzelne Subentitäten stehen zusätzlich teilweise gleichwertige Substanzen für die Erstlinientherapie zur Verfügung, so z.B. Taxane bei Angiosarkomen oder Larotrectinib bzw. Entrectinib bei Nachweis bei Fusionen der Neurotrophen Tyrosin-Rezeptor Kinase (NTRK).

In den letzten Jahren gab es diverse Versuche, das mediane OS von knapp zwei Jahren bzw. das mediane PFS von 7 Monaten durch eine Intensivierung der Systemtherapie zu optimieren. Ein Beispiel hierfür ist die französische LMS-04 Studie [29]. Eingeschlossen wurden Patient:innen mit lokal fortgeschrittenem und/oder metastasiertem Leiomyosarkom. Diese erhielten in der Erstlinie Doxorubicin alleine oder in Kombination mit Trabectedin sowie ggf. dann noch eine Erhaltungstherapie mit Trabectedin. Durch die kombinierte Gabe des Anthrazyklins mit dem Tetrahydroisochinolin-Alkaloid Trabectedin konnte eine signifikante Verlängerung des PFS sowie ein Vorteil bezogen auf das mediane OS und die Gesamtansprechrate (*Overall response rate,* ORR) erreicht werden [30].

Der Nutzen der Systemtherapie in der adjuvanten Situation konnte bei Weichteilsarkomen bisher nur für bestimmte Subgruppen nachgewiesen werden. So zeigt sich insbesondere für Entitäten wie Angiosarkome, high grade Liposarkome, Leiomyosarkome sowie undifferenzierte pleomorphe Sarkome ein Überlebensvorteil [28]. Allgemeine Risikofaktoren sind wie oben bereits genannt die Größe des Primärtumors, das Grading und die Lokalisation [1].

Für die systemische Zweitlinientherapie der metastasierten und/oder lokal fortgeschrittenen Erkrankung stehen verschiedene äquieffektive Substanzen zur Verfügung.

Die Auswahl des jeweiligen Regimes sollte individuell in Abhängigkeit des Behandlungsdrucks, des histologischen Subtyps und des Patient:innenwunsches getroffen werden.

Bei leitliniengerecht mit einem Anthrazyklin vorbehandelten Patient:innen kann die Folgetherapie mit Pazopanib (außer bei Liposarkomen), Trabectedin (insbesondere bei L-Sarkomen), Paclitaxel (bei Angiosarkomen) oder Eribulin (nur bei Liposarkomen) erfolgen. Alternativ kann Gemcitabin als Monotherapie oder in Kombination mit Docetaxel oder Dacarbazin/DTIC eingesetzt werden [1], [28].

1.1.2.4 Therapiestragien in Abhängigkeit des Erkrankungsstadiums

Lokalisierte Tumoren

Im lokalisierten Stadium kann mittels chirurgischer Resektion in der Regel eine Heilung erreicht werden.

Low grade (G1-) Sarkome werden primär chirurgisch therapiert [1]. Nur bei Vorliegen bestimmter Risikofaktoren wird eine adjuvante Therapie im Sinne einer Bestrahlung empfohlen [31].

Mittel- bis hochgradige (G2, G3) lokalisierte Sarkome werden dagegen in der Regel lokal und/oder systemisch vorbehandelt, um die Wahrscheinlichkeit einer R0-Resektion zu erhöhen und eine potentielle Mikrometastasierung zu verhindern [32]. Bei entsprechendem Risikoprofil wird ggf. zusätzlich eine adjuvante Therapie empfohlen.

Die neoadjuvante Therapie kann aus einer Bestrahlung ggf. mit ergänzender Chemotherapie, einer Kombination aus Chemotherapie und Hyperthermie oder einer alleinigen Systemtherapie bestehen [1]. Wann immer es die anatomische Lage und der Allgemeinzustand des:der Patient:in zulassen, werden mehrere Modalitäten kombiniert.

Lokal fortgeschrittenes und/oder metastasiertes Stadium

Im Vordergrund steht hier die Systemtherapie, nur in Einzelfällen können auch zusätzlich lokale, d.h. chirurgische und/oder strahlentherapeutische Maßnahmen zum Einsatz kommen [1]. Dies umfasst u.a. die Reevaluation einer chirurgischen Therapieoption nach Durchführung einer pseudoneoadjuvanten Systemtherapie bei lokal fortgeschrittenen Tumoren oder die Resektion singulärer Metastasen falls hierdurch eine vollständige Remission erreicht werden kann. Grundsätzlich sollten solche individuellen Entscheidungen immer im Rahmen des spezialisierten interdisziplinären Tumorboards diskutiert werden.

Bei lokalisierten primär irresektablen Läsionen im Bereich des Stammes und der Extremitäten wird zunächst eine neoadjuvant intendierte Therapie empfohlen [31]. Im Verlauf bzw. nach Gabe von 3 bis 4 Behandlungszyklen wird dann erneut die Möglichkeit einer Operation evaluiert.

Im Falle einer oligometastasierten Erkrankung, bei welcher eine vollständige Resektion aller Läsionen möglich erscheint, kann diese ggf. mit ergänzender Induktions- und/oder Post-Induktionstherapie versucht werden [1]. Bei inoperabler und/oder metastasierter Erkrankung wird eine palliative Systemtherapie durchgeführt.

Therapie bei refraktärer Erkrankung und/oder Rezidiv

Für die Behandlung der refraktären Erkrankung sowie im Rezidiv stehen bisher wenige Daten aus randomisierten Studien zur Verfügung, so dass die Therapie oftmals individualisiert auf Basis der interdisziplinären Falldiskussion im Sarkom-Tumorboard erfolgt.

Bei isolierten pulmonalen Metastasen wird im Falle eines erkrankungsfreien Intervalls >12 Monate eine primär chirurgische Resektion empfohlen, sofern diese möglich erscheint [28].

Strategien in fortgeschrittenen Tumorstadien

Bei lokal inoperablen und/oder fortgeschrittenen Sarkomen steht die palliative Systemtherapie im Vordergrund [28]. Lokale Behandlungsoptionen werden hier in der Regel nur zur Symptomlinderung und/oder zur Vermeidung von Komplikationen eingesetzt.

1.2 Familie der Ewingsarkome

1.2.1 Epidemiologie und Basisinformationen

Die Familie der Ewingsarkome (*Ewing Family of Tumors*, EFT) umfasst aggressive Knochen- und Weichgewebsneoplasien, welche mit einer jährlichen Inzidenz von 0,15/100 000 Personen am häufigsten bei Kindern und jungen Erwachsenen auftreten [33], [34]. Ewingsarkome sind per definition high grade Tumore und weisen charakteristische balancierte Translokationen auf, welche Gene der *Ten eleven translocation* (TET)- Familie (*Ewing Sarcoma breakpoint region 1*, EWSR1; *FUS gene*, FUS) und der *erythroblast transformation-specific* (ETS)-Familie (*Friend leukemia integration 1 transcription factor*, FLI1; *transcriptional regulator ERG*, ERG; *ETS translocation variant 4*, ETV4; *fifth Ewing variant*, FEV) betreffen. In der aktuellen WHO Klassifikation von 2020 wurden weitere klein- und rundzellige Sarkome des Knochens und des Weichgewebes mit anderen Translokationen neu definiert, welche derzeit aber noch analog der Ewingsarkome multimodal therapiert werden [3], [33]. EFT können in jeglicher Körperregion auftreten, meistens sind sie jedoch im Bereich

des Beckens und der proximalen Röhrenknochen lokalisiert [35]. Bei Erwachsenen sind extraossäre Manifestationen häufiger als bei Kindern [36], [37].

1.2.2 Aktuelle Therapiestandards

1.2.2.1 Erstlinientherapie

Die Therapie dieser seltenen Erkrankung orientiert sich an seit den 1970ern in den USA und Europa durchgeführten multizentrischen Studien, in welchen vorwiegend Kombinationen aus Vincristin, Actinomycin D, Cyclophosphamid, Doxorubicin sowie Ifosfamid und Etoposid evaluiert wurden [38]. Die aktuellsten Daten stammen aus der EWING2012-Studie, in welcher sich bei Vergleich von VIDE mit dem VDC/IE Schema sowohl eine Verbesserung des Ereignisfreien Überleben (EFS) als auch des Gesamtüberlebens ergab. Aus diesem Grund wird das komprimierte VDC/IE-Regime nun als Standard empfohlen [39].

Die Therapie sollte immer multimodal sein und gliedert sich in eine Induktionsphase, auf welche dann eine Resektion und ggf. eine lokale Radiatio folgt, falls dies klinisch realisierbar ist. Abschließend wird eine konsolidierende Chemotherapie gegeben [40].

1.2.2.2 Therapie bei refraktärer Erkrankung und/oder Rezidiv

Bezüglich des Vorgehens in der Rezidivsituation war die Datenlage bisher spärlich. Mit Auswertung der sogenannten rEECur-Studie, einer großen internationalen Untersuchung zur Behandlung von rezidivierten Ewingsarkom-Erkrankungen, liegen nun jedoch aktuelle Daten vor [41]. Im Vergleich mit den Kombinationen Gemcitabin plus Docetaxel bzw. Irinotecan plus Temozolomid zeigten sich Topotecan plus Cyclophosphamid sowie insbesondere hochdosiertes Ifosfamid sowohl bezogen auf das EFS und das OS deutlich überlegen.

1.3 Zukünftige Perspektiven: Zielgerichtete Moleküle und Immuntherapie

Die Durchführung großer randomisierter Studien ist im Kontext der Knochen- und Weichgewebssarkome aufgrund der Seltenheit und der Heterogenität der über 70 verschiedenen Subtypen nur sehr eingeschränkt möglich. Darüber hinaus treten Sarkome vor allem im jungen Alter und teilweise auch im Zusammenhang mit erblichen Erkrankungen (u.a. Li-Fraumeni-Syndrom, Neurofibromatose 1) auf [1].

Angesichts der begrenzten Auswahl effektiver konventioneller Zytostatika stellen individualisierte, idealerweise auf den jeweiligen molekulargenetischen Subtyp abgestimmte Therapieansätze einen wichtigen Bestandteil der Behandlung dar. Als

Voraussetzung dafür ist neben der Durchführung kommerziell erhältlicher oder an den Zentren individuell etablierter diagnostischer Gen-Panels beispielsweise auch ein Einschluss von Sarkom-Patient:innen jeden Alters in das *Molecularly Aided Stratification for Tumor Eradication* (MASTER-) Programm des Deutschen Krebsforschungszentrums (DKFZ), des Nationalen Centrums für Tumorerkrankungen (NCT) sowie des Deutschen Konsortiums für Translationale Krebsforschung (DKTK) möglich [42]. Im Rahmen dieser Plattform erfolgt eine umfassende genetische Charakterisierung mittels Exom- und Genom-Analyse, RNA-Sequenzierung sowie ggf. auch eine Keimbahndiagnostik. In Einzelfällen ergibt sich hierdurch die Option einer molekular stratifizierten Therapie. Für Tumore mit seltenen EWSR1-Fusionspartnern (*rare fusion partners*, RFP) konnte zum Beispiel kürzlich gezeigt werden, dass diese häufiger Angriffspunkte für zielgerichtete Therapien aufweisen [43].

Darüber hinaus sind für ausgewählte Subentitäten bereits zielgerichtete Therapien verfügbar: Neben dem anti- *Vascular Endothelial Growth Factor Receptor* (VEGFR)-Tyrosinkinase-Inhibitor Pazopanib, welcher für vorbehandelte Weichgewebssarkome zugelassen ist, stehen weitere Tyrosinkinaseinhibitoren zur Verfügung [44]. Darunter u.a. Sorafenib für Desmoidtumore, Sunitinib für Solitär Fibröse Tumore (SFT) und Alveoläre Weichgewebssarkome (*alveolar soft part sarcoma*, ASPS), Pexidartinib für Tenosynoviale Riesenzelltumore sowie Crizotinib für Inflammatorische myofibroblastische Tumore (IMT) mit Aktivierung des *Anaplastic lymphoma kinase* (ALK)-Gens [45]–[49]. Bei ASPS ist darüber hinaus oftmals Cediranib, ein weiterer VEGFR-Inhibitor wirksam [50].

Für epitheloide Sarkome wurde Tazemetostat, ein selektiver Inhibitor von *enhancer of zeste 2 polycomb repressive complex 2 subunit* (EZH2), in den USA bereits durch die FDA zugelassen [51].

Am innovativsten ist der Einsatz von *Murine double minute 2* (MDM2)- Inhibitoren: hier sind verschiedene Substanzen im Rahmen von Phase III- Studien verfügbar, u.a. Brigimadlin und Milademetan [52], [53]. Die MDM2-Inhibition erscheint insbesondere bei hoch- und dedifferenzierten Liposarkomen sowie Intimasarkomen aussichtsreich, da bei diesen in ca. 95% bzw. 70% der Fälle eine MDM2-Amplifikation vorliegt [54], [55].

Ein weiterer Angriffspunkt ist die Hemmung der *Cyclin-dependent kinase 4/6* (CDK4/6) z.B. mit Palbociclib, welche bei vorbehandelten fortgeschrittenen Sarkomen vielversprechende Ergebnisse erzielt hat [56].

NTRK-Fusionen können bei <1% der Sarkome nachgewiesen werden [57], [58]. In diesen Fällen sollte Entitätsunabhängig Larotrectinib oder Entrectinib eingesetzt werden [59], [60].

Auch die Immuntherapie gewinnt für die Behandlung von Sarkomen zunehmend an Bedeutung. Die im Kontext verschiedener solider Tumoren etablierten prädiktiven Marker wie eine hohe Tumormutationslast (*Tumor mutational burden*, TMB) oder eine Mismatch-Reparatur (MMR)-Defizienz liegen bei Sarkomerkrankungen jedoch nur in sehr wenigen Fällen vor [61]. Eine Ausnahme bilden Angiosarkome, hier werden z.B. Immuncheckpointinhibitoren (*Programmed cell death protein 1, PD1; Programmed cell death 1 ligand* 1, PD-L1) bereits erfolgreich eingesetzt [62]–[64]. Eine duale Checkpointblockade mit Nivolumab und Ipilimumab erscheint nicht nur bei Angiosarkomen sondern auch bei undifferenzierten pleomorphen Sarkomen und dedifferenzierten Liposarkomen vielversprechend [65], [66].

Tumor-assoziierte Antigene bzw. Tumor/Testis Antigene (*Cancer testis antigens*, CTA) können mittels zielgerichteter Immuntherapien adressiert werden. Hierzu zählen chimäre Antigenrezeptor-T (CAR-T)-Zell-Konstrukte sowie Tumorvakzinen, welche derzeit im Rahmen klinischer Studien untersucht werden [67], [68]. Für Weichgewebssarkome kommen u.a. *New York esophageal squamous cell carcinoma*-1 (NY-ESO 1), *Melanoma antigen gene* (MAGE) und *Preferentially expressed antigen in melanoma* (PRAME) als Zielstrukturen infrage [61].

Zielsetzung der im folgenden zusammengefassten Originalarbeiten war die Optimierung der Behandlung von Sarkomen, welche durch eine insgesamt limitierte Auswahl an Behandlungsoptionen mit einer vergleichsweise schlechten Prognose einhergehen [2].

Neben dem medizinischen und technischen Fortschritt ist auch die Etablierung prognostischer und prädiktiver Marker notwendig, um für den:die Patient:in jeweils individualisierte Behandlungskonzepte zu ermöglichen.

Mit diesem Thema befassen sich Publikation 2.1 bzw. 2.2, hier geht es um den Stellenwert von in der klinischen Routine einfach zu erfassenden Charakteristika: der prognostische Einfluss von Komorbiditäten bei älteren Patient:innen mit EFT bzw. die Aussagekraft von etablierten Sepsis- und Performance-Scores bei intensivmedizinisch betreuten Sarkompatient:innen.

2 Originalarbeiten

2.1 Comorbidities rather than older age define outcome in adult patients with tumors of the Ewing sarcoma family

Striefler JK, Schmiester M, Brandes F, Dörr A, Pahl S, Kaul D, Rau D, Dobrindt EM, Koulaxouzidis G, Bullinger L, Märdian S, Flörcken A.
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Tumore der Ewingsarkom-Familie treten im Erwachsenenalter nur sehr selten auf [2]. Demzufolge sind lediglich sehr limitierte Daten zum klinischen Verlauf sowie der Prognose dieser Patient:innengruppe verfügbar. Die in Publikation 2.1 beschriebene retrospektive Analyse soll zur Optimierung der Therapie bei erwachsenen Patient:innen mit EFT beitragen.

Insgesamt konnten 71 Patient:innen, welche von 2002 bis 2020 am Campus Virchow Klinikum der Charité behandelt wurden, identifiziert werden. Davon waren 58 für die Auswertung geeignet. Das mediane Patient:innenalter lag bei 31 Jahren (range 18-90). Eine extraskelettale Primärmanifestation war häufiger als eine skelettale (n=32 bzw. n=26). In n=20 Fällen war der Tumor ≥8 cm. Bei n=19 lag bereits bei Erstdiagnose ein metastasiertes Stadium vor.

Zwischen den verschiedenen Altersgruppen (≤25 vs. 26–40 vs. ≥41 Jahre) fanden sich Unterschiede bezogen auf den *Charlson comorbidity index* (CCI; 2 vs. ≥3; p=0.003), den Tumorursprung (extraskelettal vs. skelettal; p<0.001) und die Anzahl der Therapiezyklen (≤6 vs. >6; p=0.013).

Bezüglich der Toxizitäten und der Notwendigkeit von Dosismodifikationen zeigten sich keine relevanten altersabhängigen Unterschiede. Das mediane OS betrug 79 Monate (95% *confidence interval*, CI; 28.5–131.4) und das mediane PFS 34 Monate (95% CI; 21.4–45.8). Bei Patient:innen ≤25 Jahre zeigte sich eine Tendenz zu einem längeren OS und PFS, auch wenn diese Unterschiede nicht signifikant waren (medianes PFS: ≥41 Jahre: 22 Monate vs. 26– 40 Jahre: 30 Monate vs. ≤25 Jahre: 80 Monate; medianes OS: ≥41 Jahre: 59 Monate vs. 26–40 Jahre: 92 Monate vs. ≤25 Jahre: nicht erreicht).

Ein CCI ≥3 hatte dagegen eine signifikante Verkürzung des medianen PFS zur Folge (21,7 vs. 79,9 Monate, *hazard ratio*, HR, 0.334, p=0.006). Gleiches gilt für das metastasierte Tumorstadium (19,3 vs. 79,9 Monate, HR 0.403, p=0.021).

In der untersuchten Kohorte fanden sich in den verschiedenen Altersgruppen signifikante Unterschiede bezogen auf die Komorbiditäten, den Tumorursprung und die Anzahl der Therapiezyklen. Einen prognostischen Einfluss auf das mediane PFS hatten

die Komorbiditäten sowie das Tumorstadium, jedoch nicht das vorliegende chronologische Alter.

Zwischen den drei Altersgruppen fanden sich entgegen unserer Erwartungen keine signifikanten Unterschiede bezogen auf die Therapieintensität und die Notwendigkeit von Dosismodifikationen. Dies ist möglicherweise auch ein Grund für das Fehlen altersabhängiger Überlebensunterschiede und lässt indirekte Rückschlüsse auf die Bedeutung einer Durchführung auch intensiver Behandlungsstrategien bei älteren Patient:innen mit EFT zur Verbesserung der Prognose nahe.

Angesichts der kleinen Fallzahl unserer Kohorte sind weitere größere Untersuchungen zur Validierung der Ergebnisse notwendig.

In der nachfolgend zusammengefassten Publikation 2.2 werden weitere allgemeine klinische Charakteristika und etablierte intensivmedizinische Sepsis- und Performance-Scores bezüglich ihrer prognostischen Aussagekraft bei Sarkomerkrankungen untersucht. Hier geht es jedoch im Besonderen um das Überleben während bzw. nach einer stationären intensivmedizinischen Behandlung.

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RESEARCH ARTICLE

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Comorbidities rather than older age define outcome in adult patients with tumors of the Ewing sarcoma family

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Abstract

Background: Ewing family of tumors (EFT) is rarely diagnosed in patients (pts) over the age of 18 years (years), and data on the clinical course and the outcome of adult EFT pts is sparse.

Methods: In this retrospective analysis, we summarize our experience with adult EFT pts. From 2002 to 2020, we identified 71 pts of whom 58 were evaluable for the final analysis.

Results: Median age was 31 years (18–90 years). Pts presented with skeletal (n = 26), and extra-skeletal primary disease (n =32). Tumor size was ≥8 cm in 20 pts and 19 pts were metastasized at first diagnosis. Between the age groups (≤25 vs. 26–40 vs. ≥41 years) we observed differences of Charlson comorbidity index (CCI), tumor origin, as well as type and number of therapy cycles. Overall, median overall survival (OS) was 79 months (95% confidence interval, CI; 28.5–131.4 months), and median progression-free survival (PFS) 34 months (95% CI; 21.4–45.8 months). We observed a poorer outcome (OS, PFS) in older pts. This could be in part due to differences in treatment intensity and the CCI (<3 vs. ≥3; hazard ratio, HR 0.334, 95% CI 0.15–0.72, $p = 0.006$). In addition, tumor stage had

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a significant impact on PFS (localized vs. metastasized stage: HR 0.403, 95% CI 0.18–0.87, $p = 0.021$).

Conclusions: Our data confirms the feasibility of intensive treatment regimens in adult EFT pts. While in our cohort outcome was influenced by age, due to differences in treatment intensity, CCI, and tumor stage, larger studies are warranted to further explore optimized treatment protocols in adult EFT pts.

KEYWORDS

adult patients, Charlson comorbidity index, chemotherapy, Ewing's sarcoma, sarcoma

1 | INTRODUCTION

Although a rare disease, the Ewing family of tumors (EFT) is the second most common primary malignancy originating from bone. In addition to the histologic entities of Ewing sarcoma (ES) and primitive neuroectodermal tumor, EFT also includes extra-skeletal ES, malignant small round cell tumors of the thoracopulmonary region (Askin tumor), and atypical ES.[1] Overall, EFT is a rare cancer entity, mainly occurring in younger patients, especially in young adolescents between 10 and 15 years of age. In Germany, the annual incidence is 2.4 per 1 million adolescents and young adults, respectively.[2] In adults, EFT are even rarer. Published data suggest a rate of only <20% of all ES occurring over the age of 40.[3] Furthermore, there is evidence that ES in patients ≥41 years tend to be more aggressive as patients may be more likely to show extra-skeletal and metastatic disease. Additionally, the survival rate in older patients seems to be generally lower.[4]

At the genomic level, EFT is characterized by chromosomal aberrations involving the *Ewing Sarcoma breakpoint region 1* (*EWSR1*) gene on chromosome 22 resulting in hybrid proteins involved in tumorigenesis. Multiple different gene fusions have been reported, which may influence the course of disease and the outcome.[5–7] In accordance, the revised WHO classification of tumors of soft tissue and bone 2020 defines new subgroups of molecular tumors formerly belonging to the EFT group. For instance, CIC-fused and BCOR-rearranged sarcomas are now considered as a separate entity (Ewing-like sarcoma, ELS).[8–10]

During the last decades, multimodal therapeutic approaches have improved the survival of young adolescent patients with EFT. The overall 5-year-survival rates range from 40 to 60% in patients with localized as well as metastatic disease at first presentation. In spite of no existing international consensus concerning a standardized prognostic score, there are some established risk factors such as metastatic disease, tumor localization, LDH level, age >15 years, tumor size ≥8 cm, and response to neoadjuvant therapy.[11,12] Furthermore, the body mass index (BMI) and the presence of comorbidities might impact EFT patient outcome.[13,14]

In general, the multimodal therapy approach spans a time of 8–12 months and consists of neoadjuvant chemotherapy, local therapy (surgery and/or radiation), and adjuvant chemotherapy. Treatment standards have only been established for younger patients and rely on results of international trials of which the Ewing 2008 trial has defined the chemotherapeutic standard.[11] In this trial, in the neoadjuvant setting patients received six cycles of vincristine, ifosfamide, doxorubicin and etoposide (VIDE). After surgery and/or local radiation, patients either received eight cycles of adjuvant chemotherapy with vincristine, actinomycin D, and ifosfamide (VAI) (males) or eight cycles of vincristine, actinomycin D, and cyclophosphamide, (VAC) (females). Recently, the European Ewing 2012 trial (ISRCTN92192408) demonstrated superiority of an induction therapy of vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE) improving both event free survival and overall survival (OS),[15] and thus resulting in a refined treatment standard.

Until now, there is only sparse data for the optimal treatment of adults with EFT. The therapeutic approach is most often less intense than respective pediatric therapy protocols. Even with some evidence for the benefit of a very aggressive treatment, practice-defining studies are still lacking, but there is some data available regarding the feasibility of standard dose intense therapy in the adult patient population.[16–18] Usually, VDC/IE is given to patients with localized disease. In the metastasized situation, vincristine, doxorubicin, actinomycin D, and cyclophosphamide are commonly used.[14–16,19]

For relapsed and/or refractory disease, there are two equally effective therapeutic options, topotecan/cyclophosphamide or high-dose ifosfamide. The combinations of gemcitabine/docetaxel or irinotecan/temozolomide are alternative options, but of inferior efficacy as shown in the rEECur trial.[20,21] Furthermore, there is emerging data on targeted therapies in EFT,[22] and relevant effort is put into personalizing therapeutic

strategies based on underlying molecular aberrations identified via sequencing individual tumors in scientific programs. One example hereof is the molecularly aided stratification for tumor eradication (MASTER) Program led by the National Center for Tumor Diseases (NCT) in Heidelberg within the German Cancer Consortium (DKTK).[23] It comprises a central rapid-turnaround molecular profiling and streamlined data acquisition and analysis of rare cancers, including EFT.

In summary, there is a high unmet medical need to further optimize the treatment of EFT in adult patients, but this can only be done based on an improved understanding of the treatment outcome with current treatment strategies. In accordance, we present here our specialized center experience in adult patients with this rare entity.

2 | MATERIAL AND METHODS

2.1 | Patients

In total, 68 EFT and three ELS patients ≥18 years who were newly diagnosed and/or treated at Charité-Universitätsmedizin Berlin between 2002 and 2020 were identified, of whom 58 were eligible for this analysis. Data were retrospectively extracted from archived patient records.

2.2 | Treatment

Patients with an adequate performance status (ECOG 0–2) were treated within or on the basis of the Euro EWING 99 and 2008 trials.[11] Dose adjustments were done on an individual basis, but in-line with standardized protocols. Patients gave written consent according to institutional and national guidelines. Local treatment consisted of surgery and/or radiotherapy and was individually planned for each patient.

2.3 | Statistical analysis

OS and progression-free survival (PFS) were calculated from the date of diagnosis to death or to first event of progression, respectively. For PFS, an event was defined as distant relapse, local relapse, or death, whichever came first. OS and PFS curves were calculated using the Kaplan–Meier method and compared using the log-rank test and Cox regression with hazard ratios (HR) and 95% confidence intervals (95% CI) as indicated. Chi-square tests were used to examine associations between categorical variables. A $p \leq 0.05$ was considered significant. Data analysis was performed using the IBM SPSS Statistics (version 25) software.

3 | RESULTS

3.1 | Patient characteristics

Thirty-three (57%) female and 25 (43%) male patients were included. Median age of the overall cohort at diagnosis was 31 years (range 18–90 years) with 17 (29%) patients being ≥41 years. Median Charlson comorbidity index (CCI)[24] was 2 (range 2–7), whereas the median BMI was 24.7 (range 16.1–43.4). Median follow-up was 23 months (range 1–219 months) from diagnosis. Baseline patient characteristics are provided in Table 1.

3.2 | Tumor localization and size

In our patient cohort, $n = 26$ patients (45%) had a skeletal and $n = 32$ (55%) had an extra-skeletal primary tumor, respectively (see Table 2). At the time of diagnosis $n = 19$ (33%) had metastatic and $n = 39$ (67%) localized disease. In male patients, appendicular skeleton localization was most common (40%), followed by non-pelvic (28%), pelvic (24%), and axial (8%) tumor sites. In contrast, non-pelvic (33%) and axial (30%) localization was most frequent in female patients, followed by appendicular (27%) and pelvic (10%) tumors. An extra-skeletal primary tumor was less common in male than in female patients (40% vs. 67%), whereas a skeletal origin was more frequent in males than females (60% vs. 33%).

TABLE 1 Baseline patient characteristics

Characteristic	All	≤25 years	26–40 years	≥41 years	*p* value
Age, *n* (%)	58	21 (36)	20 (34)	17 (29)	
Sex, *n* (%)					0.168
Male	25 (43)	8 (38)	12 (60)	5 (29)	
Female	33 (57)	13 (62)	8 (40)	12 (71)	
CCI at diagnosis, *n* (%)					0.003
2	34 (59)	15 (71)	15 (75)	4 (24)	
≥3	24 (41)	6 (29)	5 (25)	13 (76)	
BMI, *n* (%)					0.280
<25	37 (64)	15 (71)	10 (50)	12 (71)	
≥25	21 (36)	6 (39)	10 (50)	5 (29)	

Note: Shown are the baseline patient characteristics of all patients as well as of the three different age groups (≤25 years vs. 26–40 years vs. ≥41 years).

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index.

TABLE 2 Baseline tumor characteristics

Characteristic	All	≤25 years	26–40 years	≥41 years	*p* value
Primary tumor site, *n* (%)					0.882
Pelvic	9 (15)	5 (24)	3 (15)	1 (6)	
Non-pelvic	18 (31)	2 (10)	9 (45)	7 (41)	
Axial	12 (21)	4 (19)	3 (15)	5 (29)	
Appendicular	19 (33)	10 (47)	5 (25)	4 (24)	
Tissue origin, *n* (%)					<0.001
Skeletal	26 (45)	15 (71)	10 (55)	2 (12)	
Extra-skeletal	32 (55)	6 (29)	8 (45)	15 (88)	
Stage, *n* (%)					0.106
Localized	39 (67)	15 (71)	13 (65)	11 (65)	
Distant metastases	19 (33)	6 (29)	5 (35)	6 (35)	
Size, *n* (%)					0.376
<8 cm	15 (43)	7 (54)	4 (29)	4 (50)	
≥8 cm	20 (57)	6 (46)	10 (71)	4 (50)	
Translocation, *n* (%)					0.025
EWSR1 translocation, not further described (EWSR1-unknown)	21 (55)	11 (86)	4 (27)	6 (60)	
EWSR1-FLI1	12 (32)	1 (7)	8 (53)	3 (30)	
EWSR1-ERG	2 (5)	1 (7)	1 (7)	0 (0)	
CIC-DUX4	3 (8)	0 (0)	2 (13)	1 (10)	

Note: Shown are the baseline tumor characteristics of all patients as well as of the three different age groups (≤25 years vs. 26–40 years vs. ≥41 years).

Abbreviations: CIC-DUX4, Capicua–double homeobox 4; ERG, transcriptional regulator ERG; EWSR1, Ewing sarcoma breakpoint region 1; EWSR1-FLI1, EWSR1/FLI1 fusion protein type 1.

In patients ≥41 years, a non-pelvic tumor localization was most commonly seen (41%), followed by an axial (29%), an appendicular (24%), and a pelvic primary (6%). There was a significant association of an extra-skeletal primary tumor with age ≥41 years (88%; $p < 0.001$). In patients aged 26–40 years, the most common primary tumor site was also non-pelvic (45%), followed by an appendicular localization (25%). The remaining patients (30%) distributed equally to a pelvic and an axial localization, respectively. Half of the patients (55%) showed a skeletal origin, whereas the other half (45%) had an extra-skeletal primary. In younger patients (≤25 years), an appendicular localization was most commonly seen (47%), followed by a pelvic (24%), an axial (19%), and a non-pelvic (10%) primary. A skeletal primary was more common than an extra-skeletal origin (71% vs. 29%).

Exact tumor size was documented in $n = 35$ cases (60%). Among these, $n = 20$ (57%) were measured ≥8 cm and $n = 15$ (43%) <8 cm. Relating to tumor size, no significant differences between the three age groups were observed. Patients ≥41 years distributed equally to a tumor size ≥8 and <8 cm (50%). For patients in the 26–40 years age group, tumor size was more often ≥8 (71%) than <8 cm (29%). In younger patients (≤25 years), tumor size was more often <8 cm (54%) than ≥8 cm (46%).

3.3 | Molecular evaluation

Data of molecular diagnostics of the ES gene were available for $n = 38$ patients (66%). Fluorescence in situ hybridization (FISH) was used in 19 patients (51%), and RT-PCR in $n = 12$ (33%), whereas a combination of both FISH and RT-PCR was performed in six patients (16%) (for one patient no information concerning the performed analysis was documented). In half of the patients ($n = 21$, 55%), an aberration of EWSR1 with unknown translocation partner (EWSR1-unknown) was detected. Identification of the translocation partner was possible in the other half ($n = 17$, 45%): EWSR1-FLI1 ($n = 12$, 32%), CIC-DUX4 ($n = 3$, 8%), and EWSR1-ERG ($n = 2$, 5%).

There were no significant differences referring to molecular tumor characteristics between the three age

groups. In patients ≥41 years, we predominantly found EWSR1-unknown translocations (60%). Furthermore, translocations of EWSR1-FLI1 (30%), as well as CIC-DUX4 (10%) were detected. Half of the patients in the 26–40 years age group showed EWSR1-FLI1 translocations (53%), followed by EWSR1-unknown (27%), CIC-DUX4 (13%), and EWSR1-ERG (7%). In patients ≤25 years, there was no CIC-DUX4 translocation detected. Most common was EWSR1-unknown (86%), whereas the remaining patients (14%) distributed equally to tumors with translocations of EWSR1-ERG and EWSR1-FLI1 (Table 2).

Two patients were also included in the aforementioned MASTER program of the NCT/DKTK for further molecular profiling, and one additional patient was screened for targeted therapy options within the local Charité molecular tumor board program. In one patient we identified an alteration of the CDKN2A gene, as well as mutations in SMARCA2 and ARID1A. In the other two cases BRCAness and amplifications of MYC and CCND1 were found, respectively.

3.4 | Comorbidities

In our cohort of patients, a significant association between the age at diagnosis and the CCI was observed ($p = 0.003$). In detail, the median CCI was four in the age group ≥41 years, whereas the median CCI was two in patients ≤40 years. However, a higher CCI was not associated with the frequency of chemotherapy dose modifications due to toxicities.

The median BMI of 24.7 observed in the entire cohort had no relevant impact on the outcome. Interestingly, in patients with a BMI <25 a R0 resection was significantly more frequently achieved than in patients with a higher BMI (66% vs. 27%; $p = 0.031$).

3.5 | First-line treatment

3.5.1 | Neoadjuvant chemotherapy

In general, patients with a tumor size ≥8 cm more frequently received a preoperative chemotherapy than those with smaller lesions (79% vs. 21%, $p = 0.008$). Altogether, in $n = 31$ patients (53%) of the overall cohort a neoadjuvant chemotherapy was performed. In patients ≥41 years of age, preoperative treatment was realized in $n = 5$ cases (29%), whereas $n = 12$ patients (71%) received no neoadjuvant chemotherapy. Half of the patients ($n = 8$, 47%) received a primary resection allowing both histologic diagnosis and therapy, simultaneously. In the other patients, emergency surgery and/or radiation or palliative treatment were primarily performed. In the younger patients of 26–40 years and ≤25 of age, neoadjuvant therapy was also frequently realized ($n = 10$, 53% and $n = 16$, 76%, respectively).

Overall, the most frequently applied regimen in the neoadjuvant setting was VIDE ($n = 27$, 87%), but in patients ≥41 years, the percentage of patients receiving VIDE was somewhat lower (60%) compared to 90% and 94% in the age groups 26–40 and ≤25 years, respectively. Alternatively, few patients received either VDC/IE or doxorubicin/ifosfamide. With a median of six cycles throughout the entire patient population, there was no statistically significant difference in the number of applied cycles between the age groups, but patients ≥41 years received only two to six cycles, whereas in patients ≤40 years, a maximum of nine cycles was given and the majority of patients received six cycles (Table 3).

3.5.2 | Local treatment strategies

Altogether, $n = 55$ patients (95%) received local therapy of their primary tumor. In $n = 34$ patients (62%) surgery as well as radiation therapy was performed. In $n = 21$ (38%) either surgery ($n = 17$, 31%) or radiation only ($n = 4$, 7%) was implemented into the therapeutic algorithm. There were no significant differences between the three age groups referring to the choice of the local treatment strategy (Table 3).

3.5.3 | Adjuvant therapy

Of the overall cohort, $n = 41$ patients (71%) received adjuvant chemotherapy such as VAI ($n = 14$, 34%), followed by VAC ($n = 9$, 22%), VIDE ($n = 9$, 22%), alternating VAC/VAI ($n = 3$, 7%), and VDC/IE ($n = 3$, 7%) or individual

TABLE 3 Baseline therapeutic data

Characteristic	All	≤25 years	26–40 years	≥41 years	p value
Radiation, *n* (%)					0.099
Yes	41 (77)	11 (56)	14 (70)	16 (94)	
No	12 (23)	5 (44)	6 (30)	1 (6)	
No of cycles first-line chemotherapy, *n* (%)					0.013
<6	10 (21)	1 (7)	2 (11)	7 (44)	
≥6	38 (79)	13 (93)	16 (89)	9 (56)	

Note: Shown are the baseline therapeutic data of all patients as well as of the three different age groups (≤25 years vs. 26–40 years vs. ≥41 years).

concepts such as VCDE, and combination of ifosfamide and doxorubicin or etoposide.

There were significant differences between the age cohorts concerning the choice of the adjuvant regimen ($p = 0.004$). The majority of patients ≥41 years received VIDE (31%), followed by alternating VAC/VAI (23%) and VAI (15%). In the remaining patients in this age cohort (31%) VAC, VCDE, or doxorubicin/ifosfamide was applied. In patients of 26–40 years, VAI was the most common regimen (40%), followed by VIDE (33%), VDC/IE (13%), and ifosfamide/etoposide or VAC (each 7%). In contrast, the younger patients (≤25 years), received either VAC or VAI (each 50%).

The number of adjuvant chemotherapy cycles given was also significantly different relating to the three age groups ($p = 0.017$). The majority of patients ≥41 and 26–40 years received six cycles (≥41 years: median 6, range 2–8 cycles; 26–40 years: median 6, range 1–9 cycles). In contrast, in the age group ≤25 years the majority of patients received eight cycles (≤25 years: median 8, range 1–8).

3.6 | Consolidating therapy

Fourteen patients (24%) obtained consolidating chemotherapy subsequent to the first-line treatment. Of those, $n = 8$ (57%) received VAI, $n = 4$ (29%) VAC and $n = 1$ (7%) VIDE and VAC/VAI, respectively. The median number of cycles were five (range 1–8). Moreover, seven patients (12%) received high-dose chemotherapy with autologous stem cell support as consolidating therapy in a curative intention (≥41 years: $n = 1$; 26–40 years: $n = 5$; ≤25: $n = 1$).

3.7 | Treatment of recurrent disease

In our cohort, $n = 26$ patients (45%) showed relapse and/or refractory disease.

3.7.1 | Systemic therapy

Data on palliative chemotherapy applied in this situation were available for $n = 21$ patients (81%). The first-line treatment at relapse most often consisted of temozolomide/irinotecan ($n = 8$, 38%), followed by topotecan/cyclophosphamide ($n = 7$, 33%), and patient-individual concepts such as topotecan- or ifosfamide-based combinations, as well as DTIC or alternating VAC/VAI. Patients ≥41 years ($n = 7$) received temozolomide/irinotecan ($n = 4$), followed by dacarbazine, cyclophosphamide/topotecan, and vincristine/ifosfamide ($n = 1$ each). Patients aged 26–40 years ($n = 11$) often received cyclophosphamide/topotecan ($n = 5$), temozolomide/irinotecan ($n = 3$), and topotecan- or ifosfamide-based combinations, as well as alternating VAC/VAI ($n = 1$ each). In patients ≤25 years ($n = 3$), temozolomide/irinotecan, ifosfamide, and cyclophosphamide/topotecan was given ($n = 1$ each). The median number of cycles differed among the three age groups (≥41 years: 1, range 0–2; 26–40 years: 2, range 2–10; ≤25 years: 8, range 1–8; see Figure 1 and Table 3).

Second-line palliative chemotherapy in relapse was applied in $n = 15$ patients (26%) of the overall cohort. Many received cyclophosphamide/topotecan (≥41 years: $n = 2$; 26–40 years: $n = 3$; ≤25 years: $n = 2$), whereas in patients aged 26–40 years temozolomide/irinotecan was also commonly given ($n = 5$; Figure 1).

3.7.2 | Local treatment strategies

Altogether, $n = 13$ patients (22%) received radiation therapy in recurrent disease only, whereas in $n = 4$ patients (7%), local irradiation was also performed in the later course of the disease in addition to the prior curatively intended treatment (see Table 3).

3.8 | Treatment of special cases

In four patients the malignant disease was initially not classified as an EFT, but as a neuroendocrine tumor, a neuroendocrine carcinoma, or an olfactorius neuroblastoma, respectively. In all of those patients, the tumor was primarily resected at an external site. In the majority of cases, the diagnosis was revised in the event of relapse or refractory disease by referral pathology. For instance, systemic therapy consisted of streptozotocin/5-fluorouracil, as well as folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX regimen) combined with radiation therapy.

In addition to the standard molecular diagnostics in EFT, three patients were screened for targeted therapy options within the MASTER program of the NCT/DKTK, and the local Charité molecular tumor board program, respectively. An alteration of the CDKN2A gene was identified, as well as mutations in SMARCA2 and ARID1A. Thus, CDK4/6 inhibition and BET or EZH2 inhibition was recommended. In the other two cases BRCAness and amplifications of MYC and CCND1 were found, respectively. Both patients died due to progressive disease before targeted therapy could be initiated.

3.9 | Toxicity

Dose modification due to toxicity was performed in $n = 36$ patients (62%) of the overall study population at any time

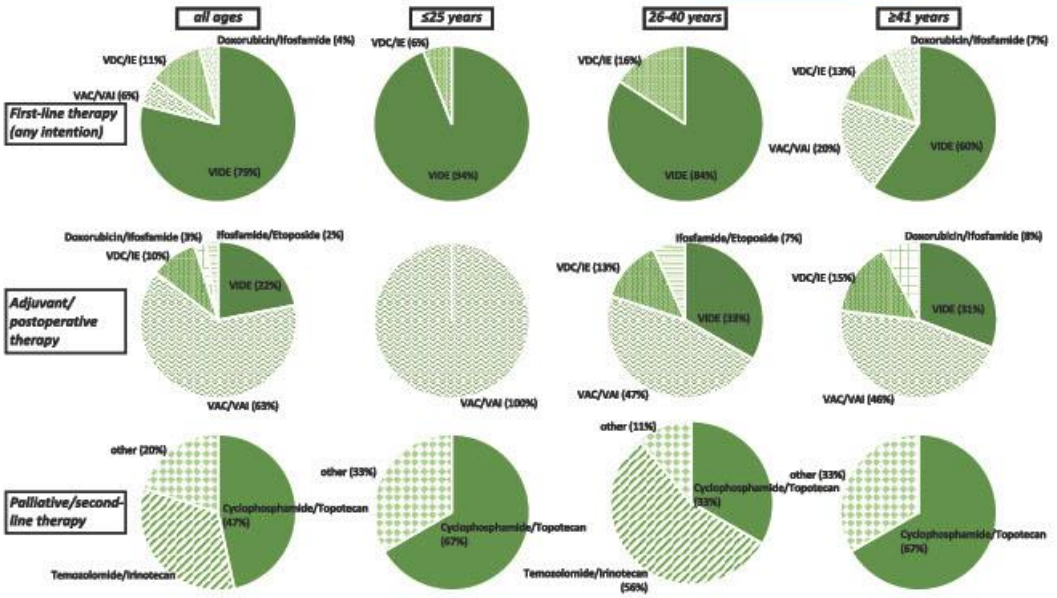

FIGURE 1 Therapeutic regimen. VAC, vincristine, actinomycin D, and cyclophosphamide; VAI, vincristine, actinomycin D, and Ifosfamide; VDC/IE, vincristine, doxorubicin, cyclophosphamide, and etoposide/ifosfamide; VIDE, vincristine, ifosfamide, dacarbazine, and etoposide. Shown are the applied therapeutic regimen within all patients as well as of the three different age groups (≤25 years vs. 26–40 years vs. ≥41 years) as first-line, adjuvant/postoperative, and palliative/second-line therapy, respectively

point. The most common reason was the occurrence of both clinical neutropenia and polyneuropathy (n = 8, 22%), followed by neutropenia and polyneuropathy as sole symptoms (n = 6, 17% each). The combination of both neutropenia and mucositis led to dose reductions in n = 4 patients (11%). The remaining dose modifications were due to age >67 years (n = 3, 8%), mucositis (n = 2, 5%), psychotic symptoms, and/or nephrotoxicity.

During the course of first-line chemotherapy, a dose modification was observed in 32 patients (55%). Among the three age groups (≥41 vs. 26–40 vs. ≤25 years), no significant difference in the rate of dose modification was found (76% vs. 60% vs. 33%, respectively; p = 0.028).

In the palliative therapy setting, dose modifications were documented in n = 19 patients (33%). Referring to the frequency of dose reduction, there were no significant differences between the three age groups (≥41: 47% vs. 26–40: 25% vs. ≤25 years: 19).

3.10 | Outcome

3.10.1 | Neoadjuvant therapy

Thirty-one patients (53%) received neoadjuvant treatment, of whom data on outcome was available for n = 28 (90%). In n = 18 a CR was detected, whereas n = 8 patients achieved PR, and n = 2 SD. During neoadjuvant treatment, there was no PD observed. Relating to the different age groups, therapeutic outcome was as follows: ≥41 years: n = 3 CR, n = 2 PR, n = 0 SD; 26–40 years: n = 4 CR, n = 4 PR, n = 2 SD; ≤25 years: n = 11 CR, n = 2 PR. There were no significant age-dependent differences.

3.10.2 | Postoperative results

Histological evaluation after neoadjuvant therapy and resection was realized in n = 21 (36%) of the overall patient population. In the majority of cases (n = 15, 71%), a regression grade I according to Salzer–Kuntschik was observed. Two patients had a regression grade II, n = 2 grade III, n = 1 grade IV, and n = 1 grade V after completion of neoadjuvant treatment. Referring to the efficacy of neoadjuvant treatment, there were no significant differences between the three age groups. Data on resection status were available for 42 patients (72%). In n = 24 (57%) of these, R0 resection was achieved. R1 resection was documented in n = 4 (10%), R2 in n = 5 (12%), and Rx in n = 9 (21%) cases, respectively. There were no significant differences relating to resection status between the three age groups. Many patients with R0 resection status (n = 14, 58%)

received local radiation therapy in addition to resection of the primary tumor. There were no significant differences of frequency of adjuvant irradiation referring to resection status. As mentioned above, R0 resection was more frequently observed in patients with a BMI <25 compared to those with a higher BMI ($p = 0.031$).

3.10.3 | Completion of first-line therapy

Altogether, $n = 41$ patients (71%) received adjuvant treatment. Data on outcome after completion of multimodal first-line therapy were available for 39 patients (67%). In these patients, the clinical staging showed CR in $n = 29$ cases (74%), followed by PD in six patients (15%). In contrast, PR and SD were achieved in $n = 2$ (5%) each. Referring to the three age groups, there were no significant age-dependent differences observed. The therapeutic outcome was as follows: ≥41 years ($n = 11$): $n = 7$ CR, $n = 2$ PR, $n = 2$ PD; 26–40 years ($n = 15$): $n = 11$ CR, $n = 2$ SD, $n = 2$ PD; ≤25 years ($n = 13$): $n = 11$ CR, $n = 2$ PD. BMI as well as CCI did not have any relevant influence. In patients with a R0 resection as well as with EWSR1-unknown status CR was more common than in the remaining cases (R0 vs. ≥R0: 62% vs. 38%; $p = 0.018$, and EWSR1-unknown vs. other translocation: 59% vs. 41%, $p = 0.005$, respectively).

3.10.4 | Relapse

Altogether, $n = 26$ patients (45%) showed a relapse of the EFT. Regarding the different age groups, there were no significant age-dependent differences found. The majority showed further disease progression ($n = 11$, 52%), $n = 5$ (24%) achieved partial remission, $n = 3$ stable disease (14%), and $n = 2$ complete remission (10%), respectively. In detail, the therapeutic outcome was as follows: ≥41 years ($n = 7$): no CR, $n = 2$ PR, $n = 1$ SD, $n = 4$ PD; 26–40 years ($n = 11$): $n = 2$ CR, $n = 2$ PR, $n = 1$ SD, $n = 6$ PD; ≤25 years ($n = 3$): no CR, $n = 1$ PR, $n = 1$ SD, $n = 1$ PD.

Fifteen patients received second-line palliative treatment ($n = 1$ CR, $n = 4$ SD, and $n = 10$ PD), and $n = 5$ received third-line palliative treatment ($n = 2$ SD, $n = 3$ PD).

3.11 | Survival data

Survival parameters (OS, PFS) were evaluable in $n = 38$ (66%) patients. Median OS was 79 months (95% CI 29–131), median progression free survival (PFS) 34 months (95% CI 21–46; see Figure 2).

There was a trend to longer survival in younger patients even if it was not statistically significant neither for PFS nor for OS (median PFS: ≥41 years: 22 months, 26–40 years: 30 months, and ≤25 years: 80 months; median OS: ≥41 years: 59 months, 26–40 years: 92 months, and ≤25 years: not reached), please refer to Figure 3A,B.

Likewise, we observed no significant differences of survival in the curative setting referring to gender and BMI ≥25.

In contrast, univariable analysis showed a relevant influence of CCI on survival. A CCI ≥3 was associated with an impaired OS (HR, 0.429; 95% CI, 0.16–1.10; $p = 0.080$) and PFS (HR, 0.334; 95% CI, 0.15–0.72; $p = 0.006$; see Figure 3C,D).

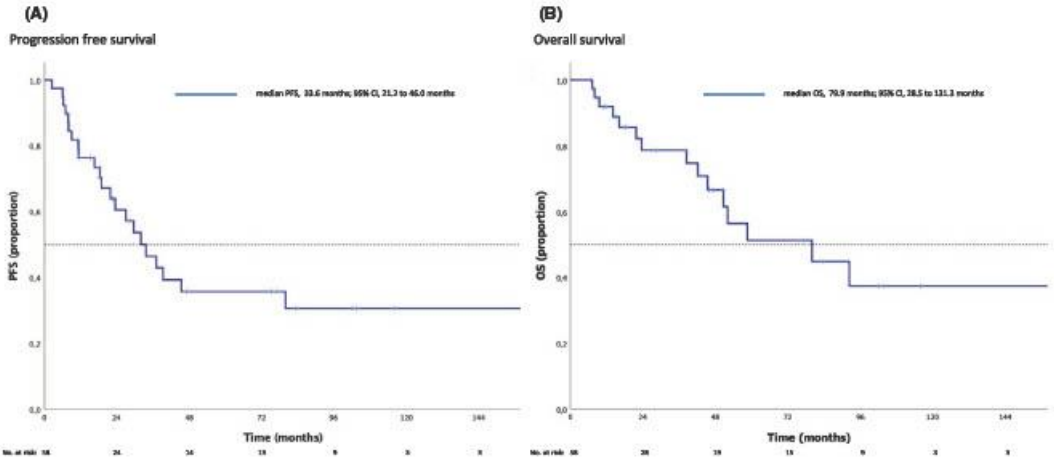

FIGURE 2 Survival estimates of the overall patient population. Shown are Kaplan–Meier estimates for (A) progression-free survival, PFS, and (B) overall survival, OS. Median follow-up of 23 months (range 1–219 months) from diagnosis

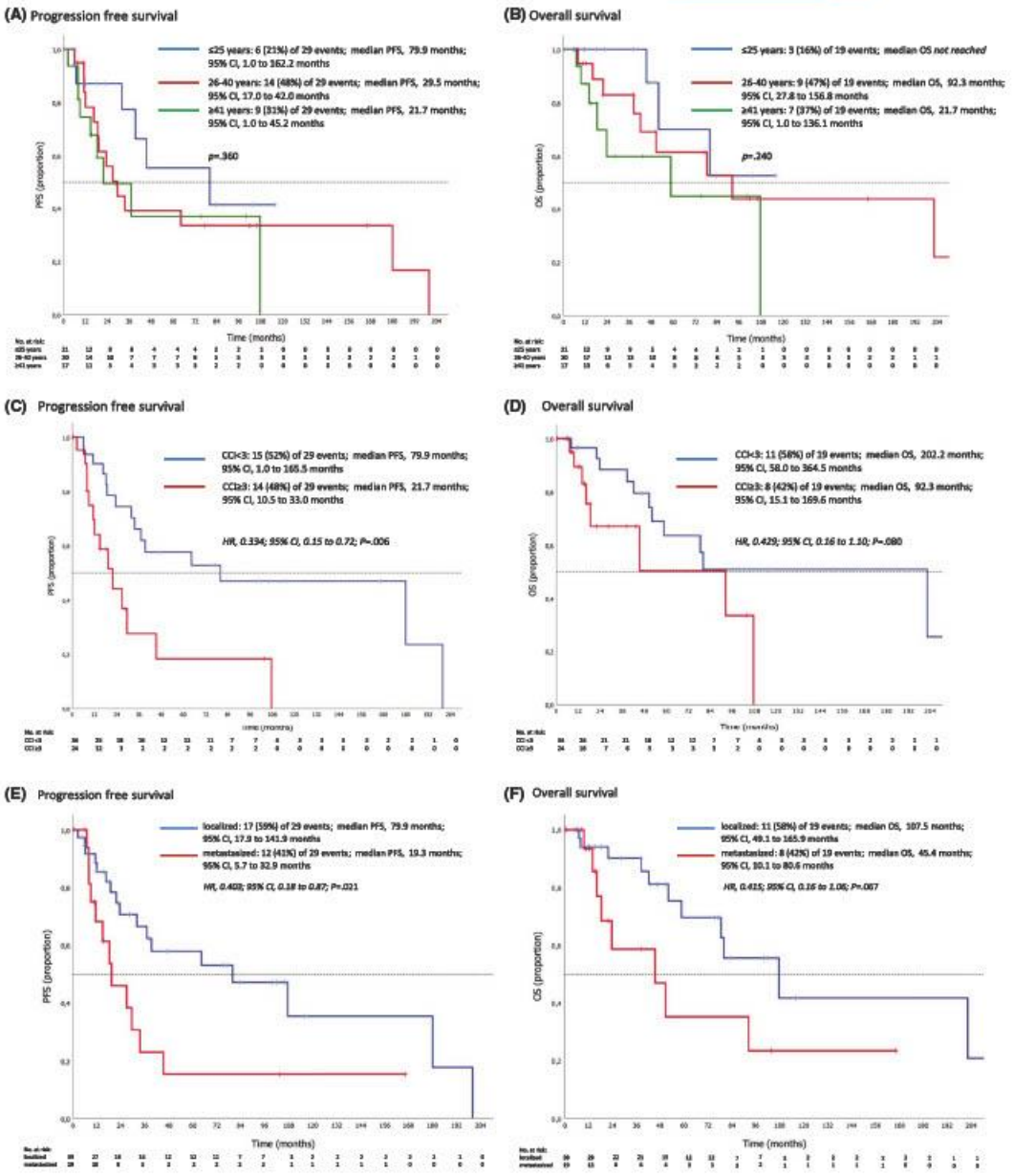

FIGURE 3 Kaplan-Meier estimates for progression-free survival, PFS, and overall survival, OS. (A and B) Age at diagnosis (≤25 years vs. 26–40 years vs. ≥41 years); (C and D) Charlson comorbidity Index, CCI (CCI <3 vs. CCI ≥3); (E and F) Stage at diagnosis (localized vs. metastasized). Shown are Kaplan–Meier estimates for (left) progression-free survival, PFS, and (right) overall survival, OS. Hazard ratios (HR) derived from univariable Cox regression testing. *p* values derived from log-rank test. Median follow-up of 23 months (range 1–219 months) from diagnosis

Tumor stage (localized vs. metastasized) at first diagnosis had a relevant impact on median PFS as well as OS in the curative setting (PFS, HR 0.403, 95% CI 0.18–0.87, $p = 0.021$; OS, HR 0.415, 95% CI 0.16–1.06, $p = 0.067$; see Figure 3E,F). Referring to primary tumor site (pelvic, non-pelvic, axial, and appendicular) as well as to origin (extra-skeletal vs. skeletal) there was no relevant difference in survival in the course of first-line therapy. The diverse genetic aberrations (EWSR1-unknown, EWSR1-FLI1, CIC-DUX, and EWS-ERG) and tumor size ≥8 cm were not found to impact OS or PFS.

Similarly, for first-line and/or curative therapy, there were no significant differences in PFS or OS observed relating to the respective regimen, regression grade or resection status as well as to the number of chemotherapy cycles and modalities of local therapy applied.

For second-line therapy, survival parameters (OS2, PFS2) were evaluable in 20 patients (34%). Median overall survival (OS2) from relapse/progression to death was 17 months (95% CI 7–27), median progression-free survival (PFS2) calculated from first relapse/progression to second relapse/progression was 8 months (95% CI 3–12). There was no significant difference in PFS2 and OS2, respectively, between the three age groups (≤25 vs. 26–40 vs. ≥41 years). Twenty patients (34%) died due to progression of EFT. There was no therapy-associated death. A BMI ≥25 had a significant impact on median OS2 (BMI ≥25 vs. BMI <25: 63 vs. 6 months, $p = 0.013$). Other patient characteristics such as age, gender, and comorbidities did not have any significant influence neither on PFS2 nor on OS2. Referring to the tumor characteristics, in particular tumor size, location, as well as tumor stage at first diagnosis, there was no relevant impact on survival in the context of advanced disease and/or palliative therapy observed.

The number of conducted chemotherapy cycles and the regression grade achieved by neoadjuvant treatment significantly influenced PFS2 and/or OS2. In general, median PFS2 was significantly longer in patients receiving more cycles of any first-line therapy (neoadjuvant, adjuvant, or palliative) than in those who got a smaller number of treatment cycles ($p = 0.002$). In detail, the number of cycles in the neoadjuvant as well as in the adjuvant setting significantly influenced median PFS2: 1 versus 8 months (neoadjuvant therapy: five vs. six cycles; $p = 0.016$), and one versus 10 months (adjuvant therapy: one vs. eight cycles; $p < 0.001$). In addition, the number of adjuvant therapy cycles had a significant impact on median OS2: 5 versus 19 months (one vs. eight cycles; $p = 0.024$). The regression grade according to Salzer–Kuntschik was inversely correlated with the OS2: 5 versus 17 months (regression grade 4 vs. 1; $p < 0.001$). Due to the small sample size, an assessment of the influence of the chemotherapeutic regimen, the resection status as well as of the local therapy on survival was not realizable.

4 | DISCUSSION

EFT sarcomas are very rare in adult age, therefore most of the literature refers to pediatric patient populations. Thus, our aim was to underline the feasibility of comparatively intense chemotherapeutic regimen in adult patients as well as to examine outcome parameters in our selected single center cohort. In-line with recently published data, our patient population showed no inferior survival in adult patients in general. However, although not statistically significant, we did observe poorer outcome in patients ≥41 years compared to ≤25 years. In part this can be explained by the comorbidities, which had a relevant influence on outcome. A higher CCI ≥3 was associated with a significant shorter OS and even PFS. This observation is in-line with previous studies suggesting an adverse effect of comorbidity on survival of sarcoma patients.[25–27] In addition, in accordance with previously published case series, we found a significant higher frequency of extra-skeletal primary tumors in the older patient which could also explain part of our observation.[3,28]

Furthermore, as expected, patients with metastatic disease had a significantly shorter OS and PFS than those with localized disease. The prominent role of stage in our cohort is consistent with previous analyses in adult patients with EFT and even was described as the sole predictor of survival by Martin II et al.[29–32] In addition, some adult patient populations have linked tumor size, gender, and non-extremity bone location as well as the differing treatment regimen to impact outcome.[29,31] In contrast, we did not observe respective significant differences related to these specific patient and tumor characteristics. While our study comprised only a small cohort of cases, many of the meta-analysis or registry data sets might also be biased and this indicates that additional studies need to be performed for patients above the age of 18 years.

For instance, contrary to our expectations a high BMI (≥25) had no impact on any clinical aspect other than survival following relapse and/or progression (OS2). Although Goldstein et al. could show a better survival and an increase of tumor necrosis in their pediatric population with EFT and a normal BMI, we found no significant difference of OS or PFS in our adult cohort depending on body weight.[14] In general, data on the negative effect of a high BMI on cancer survival is heterogeneous and is not applicable on all cancer types and patient characteristics.[33] Nevertheless, the comparatively high BMI in our cohort might reflect a selection bias in our patient population or could be indicative that obesity, which has been linked to cancer, might even increase the risk for EFT.

While EFT often present as very aggressive and advanced/metastasized disease, therapeutic concepts are multimodal, combining chemotherapy, surgery, and local

radiation ideally. The recent results of the EWING 2012 trial showing a superiority of VDC/IE induction in patients of 5–50 years of age might change the therapeutic approach in EFT.[15] As previously shown by Lu et al., it is also feasible in the adult EFT patient,[32] and our data would also support this, as we did not see a general correlation of age with a higher therapy- associated toxicity. Of course, based on the long time period of data collection in our study, diagnostic procedures and treatment sequences were heterogeneous, especially in the older patient population, in whom VIDE was less frequently used as primary therapy. This could of course also explain why in general toxicity did not differ among the age groups. Unfortunately, due to the limited quality of the retrospectively acquired data were not able to analyze treatment delays. This important issue might be integrated in subsequent studies.

Interestingly, we also found an association of the number of cycles of any first-line therapy with the outcome in the relapsed situation (OS2 and PFS2). Patients who received a larger number (≥6) of first-line treatment cycles showed significantly longer OS2 and PFS2 than those receiving a smaller number (<6). Presumably, the number of cycles of first-line therapy given might primarily reflect the performance status and/or frailty of the respective patient which both significantly influence the therapeutic possibilities at the time of relapse. On the other hand, this could also be due to a more effective control of minimal residual disease following more treatment cycles. In accordance, there is some evidence for the improvement of survival by use of a high-dose chemotherapy in selected patients with EFT,[11,34,35] which could also result in deeper remissions. Patients above the age of 40 might also benefit from this therapeutic approach but are rarely included in the respective trials.

In summary, our study shows the feasibility of an intensive treatment in EFT patients of adult age. In future trials, multimodal treatment approaches will have to be more individually adapted to patient and tumor characteristics. Definition of new molecular subgroups might be the first step on the way to targeted therapeutic strategies. For example, CIC-fused and BCOR-rearranged sarcomas are now considered as a separate entity (ELS).[8–10] Whereas, given the absence of a significant impact on survival relating to molecular genetic aberrations as well as the lack of a specific therapeutic strategy for those patients we decided to include them in our analysis.

In the era of increasing availability of molecular genetic diagnostics, a more individualized therapy or even targeting EWSR1-FLI1 translocations will hopefully be enabled soon.[19]

Additionally, conventional multimodal therapeutic approaches with an optimized therapy intensity and toxicity profile for each patient should also be envisioned. Evidently, there is an urgent medical need to optimize the assessment of elderly patients regarding the increasing gap between chronological and physiological age. Presumably, frailty rather than age might serve as predictor of chemo-associated toxicity. However, even though a multitude of geriatric assessment tools were developed during the last years, none are routinely integrated into the clinical routine or validated by randomized controlled trials, yet.[36–38]

In the absence of a standardized geriatric assessment, decision-making about the intensity of a multimodal therapy might be based on physiological rather than chronological age taking into account the respective bone marrow reserve, for example. Accordingly, our data suggest that an outcome comparable to younger age groups can also be achieved in older patients.

However, with increasing numbers of long-term survivors, not only long-term toxicity, but also the occurrence of secondary neoplasms will have to be taken into account. Thus, as we have already learned from clinical trials in the context of soft tissue sarcoma, we need to move forward from a one-for-all strategy toward precision medicine approaches in EFT.

5 | CONCLUSIONS

With our retrospective analysis, we could confirm a manageable toxicity in adult patients with EFT treated with multimodal therapies. Due to significant differences in the applied first-line and neo–/adjuvant chemotherapeutic regimen, we could see differences in OS and PFS in the older age group (≥41 years) compared to younger adults (≤25 years). This warrants further exploration, as novel treatment protocols for an optimized multimodal management of patients should be adjusted to the individual age cohorts to ensure the possibility of intensive treatment in all patient groups. This is of great importance, especially as our data demonstrate the influence of comorbidity on outcome, which often might prevent intensive therapy. Furthermore, novel options are needed for advanced tumor stages that have also poor impact on prognosis in EFT. Therefore, therapeutic decisions should not only be based on chronological age, but also on a thorough individual assessment of the patient. Given the rarity of EFT in adults, additional prospective data sets need to be collected in larger cooperative group to allow for further optimization of diagnostic approaches. For example, comprehensive molecular EFT profiling might be a prerequisite for a better understanding of the molecular mechanisms underlying the EFT subgroups with aggressive behavior.

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CONFLICT OF INTEREST

There is no conflict of interest to declare for the author as well as for the coauthors.

AUTHOR CONTRIBUTIONS

Jana Käthe Striefler had full access to all of the data in the study and took responsibility for the integration of the data and the accuracy of the data analysis. Concept and design: Jana Käthe Striefler and Anne Flörcken. Acquisition, analysis, or interpretation of data: Jana Käthe Striefler, Lars Bullinger, and Anne Flörcken. Drafting of the manuscript: Jana Käthe Striefler, Lars Bullinger, and Anne Flörcken. Critical revision of the manuscript for important intellectual content: Jana Käthe Striefler, Maren Schmiester, Franziska Brandes, Anne Dörr, Stefan Pahl, David Kaul, Daniel Rau, Eva-Maria Dobrindt, Georgios Koulaxouzidis, Lars Bullinger, Sven Märdian, and Anne Flörcken. Statistical analysis: Jana Käthe Striefler and Anne Flörcken. Administrative, technical, or material support: Jana Käthe Striefler, Lars Bullinger, and Anne Flörcken. All authors have read and approved the manuscript.

CONSENT FOR PUBLICATION

Not Applicable.

ETHICS STATEMENT

Our study involving human subjects has been performed with institutional ethical review board approval of Charité's Ethics Committee (Approval Number EA2/240/20) and appropriate participants' written informed consent in compliance with the Helsinki Declaration.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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2.2 Sarcoma patients admitted to the intensive care unit (ICU): predictive relevance of common sepsis and performance parameters

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Die Behandlung von Patient:innen mit Sarkomerkrankung konnte infolge des zunehmenden Verständnisses der Krankheitsentstehung durch die Entdeckung neuer therapeutischer Ansätze bereits verbessert werden [69]. Nichtsdestotrotz bleibt die intensive konventionelle medikamentöse Therapie ein integraler Bestandteil der Behandlung. Diese birgt aufgrund ihrer Toxizität das Risiko schwerwiegender Nebenwirkungen, welche eine intensivmedizinische Behandlung notwendig machen können. Zu den Charakteristika der betroffenen Sarkompatient:innen sowie den Folgen einer Behandlung auf der Intensivstation (*intensive care unit*, ICU) liegen bisher nur wenige Daten vor. Die in Publikation 2.2 beschriebene retrospektive Analyse umfasst die von 2005 bis 2022 am Charité Campus Virchow Klinikum behandelten erwachsenen Patient:innen mit histologisch nachgewiesener Sarkomerkrankung, welche im Verlauf eine intensivmedizinische Betreuung erhalten haben. Neben allgemeinen Patient:innen- und Tumorcharakteristika wurden auch die in der Intensivmedizin etablierten Sepsis- und Performance-Scores in die Analyse miteinbezogen: *Simplified Acute Physiologic Score II*, SAPS II bzw. *Sequential Organ Failure Assessment*, SOFA und *Acute Physiology and Chronic Health Evaluation*, APACHE). Insgesamt konnten die Daten von 66 Patient:innen analysiert werden. Das mediane Alter war 57 Jahre (range 40-69), das Geschlechterverhältnis (weiblich bzw. männlich) ausgeglichen (n=34, 52% bzw. n=32, 48%). Die häufigsten Subentitäten waren L-Sarkome (n=19, 29%) und Osteosarkome (n=15, 23%). In 54% handelte es sich dabei um high grade Tumore. Der Primarius befand sich am häufigsten im Bereich der Extremitäten (n=27, 41%), gefolgt von Abdomen/Becken (n=25, 38%), Thorax (n=10, 15%) und dem Kopf-Hals-Bereich (n=4, 6%).

Bei der Mehrzahl der Patient:innen (n=55, 83%) lag ein metastasiertes Erkrankungsstadium vor, davon befanden sich 60% (n=33) im Bereich der Lunge.

Korrespondierend zu dem hohen Anteil von Fällen mit metastasierter Situation wurde in 82% (n=54) ein palliatives Konzept verfolgt. Die aktuelle Therapie war in 58% (n=38) medikamentös, in 49% (n=32) handelte es sich dabei um die Erstlinientherapie. Diese war bei 24% (n=16) Anthrazyklin-basiert. In 62% (n=41) der Fälle war bereits ein Progress der Sarkomerkrankung aufgetreten. Der mediane SAPS II war in der gesamten Kohorte 43 (range 30-64), der mediane Wert für das SOFA lag bei 3 (range 0-8). Das mediane OS der Gesamtpopulation lag bei 7,1 Monaten (95% CI, 0-30.6), in der Gruppe der ICU Überlebenden (*ICU survivors*, IC surv) wurde das OS nicht erreicht, in der Gruppe der Patient:innen die während der intensivmedizinischen Behandlung verstarben (*ICU non-survivors*, IC non-surv) war das mediane OS sechs Tage (95% CI, 4.2-7.7).

Von den untersuchten Charakteristika hatten folgende einen signifikanten Einfluss auf das mediane OS: Geschlecht (weiblich vs. männlich, 36 vs. 1 Monate; HR, 0.54; p= 0.46), Tumorlokalisation (Extremität vs. andere, nicht erreicht vs. 30 Tage; HR, 0.61; p=0.02), Therapieintention (kurativ vs. palliativ, nicht erreicht vs. 1,6 Monate; HR, 0.16; p=0.005), sowie SAPS II (≤50 vs. >50, 36 vs. 0,5 Monate; HR, 0.85; p=0.25) und SOFA (≤5 vs. >5, 36 Monate vs. 6 Tage; HR, 0.51; p=0.010). Diese Ergebnisse bestätigen die prognostische Relevanz der etablierten intensivmedizinischen Scores SAPS II bzw. SOFA auch für das Kollektiv der Sarkompatient:innen.

Um die Versorgung von Patient:innen mit Sarkomerkrankungen zu verbessern spielt neben der Identifizierung potentieller Biomarker auch die Weiterentwicklung der Behandlung selbst eine wichtige Rolle. Diese ist Thema der drei nachfolgenden Publikationen. Zunächst geht es in Publikation 2.3 um die Ergänzung der medikamentösen Tumortherapie um zielgerichtete und immuntherapeutische Strategien. Hier werden die Ergebnisse einer retrospektiven Auswertung eines solchen Ansatzes beschrieben im Rahmen dessen die konventionelle Chemotherapie mit einem gegen *platelet-derived growth factor receptor α* (PDGFRα) gerichteten monoklonalen Antikörper kombiniert wurde.

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ORIGINAL RESEARCH

Sarcoma Patients Admitted to the Intensive Care Unit (ICU): Predictive Relevance of Common Sepsis and Performance Parameters

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Purpose: Prognosis of sarcoma patients is improving, with a better understanding of sarcomagenesis revealing novel therapeutic targets. However, aggressive chemotherapy remains an essential part of treatment, bearing the risk of severe side effects that require intensive medical treatment. Available data on the characteristics and clinical outcome of sarcoma patients admitted to intensive care units (ICU) are sparse.

Patients and Methods: We performed a retrospective analysis of sarcoma patients admitted to the ICU from 2005 to 2022. Patients ≥18 years with histologically proven sarcoma were included in our study.

Results: Sixty-six patients were eligible for analysis. The following characteristics had significant impact on overall survival: sex (p=0.046), tumour localization (p=0.02), therapeutic intention (p=0.02), line of chemotherapy (p<0.001), SAPS II score (p=0.03) and SOFA score (p=0.02).

Conclusion: Our study confirms the predictive relevance of established sepsis and performance scores in sarcoma patients. For overall survival, common clinical characteristics are also of significant value. Further investigation is needed to optimize ICU treatment of sarcoma patients.

Keywords: soft tissue sarcoma, intensive care unit, sepsis and performance scores, SOFA, SAPS II, ICU-specific survival

Introduction

With an incidence rate of about 1.8–5.0 per 100,000 per year worldwide, soft-tissue sarcomas (STS) represent about 1% of the malignancies in adults.[1,2] The 5-year survival rate of these rare mesenchymal neoplasms is about 60% across all disease stages in Europe.[2,3] With over 70 different histopathologically defined subtypes, it remains difficult to establish a common therapeutic standard.[4] Diagnosed at an early stage, many STS can be cured by surgery alone. Local recurrence and metastatic disease, however, continue to be a therapeutic challenge especially

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in high-grade STS, often requiring multimodal approaches. To date, the standard of care for the majority of advanced STS remains doxorubicin, either as single-agent therapy or in combination with other substances.[5] Whenever possible, therapy should include multiple modalities, eg, local irradiation and/or chemotherapy combined with surgery.[5]

The therapeutic regimen utilized in the LMS 04 trial illustrates a trend towards intensified perioperative therapy in STS: combination treatment with doxorubicin and trabectedin enhances therapeutic efficacy but is accompanied by relevant toxicity, such as significantly more febrile neutropenia (24% vs 11%), thrombocytopenia (20% vs 0%) and gastrointestinal toxicity (12% vs 1%).[6] Thus, intensive treatment strategies may lead to a rising demand for intensive care, especially in older patients.

Until recently, there were no established guidelines regarding the selection of oncologic patients for intensive care unit admission.[7] In 2018, a consensus statement was published concluding the necessity to assess tumour patients like other severely ill non-oncologic patients.[8]

In a work by Biskup et al, the authors showed that the main reasons for admission of cancer patients to the ICU are hypotension, acute respiratory failure, sepsis, acute kidney injury, and bleeding. The indications for ICU admission are rarely related to the underlying malignancy.[7]

Analyses on the outcome of oncologic patients after intensive care treatment are sparse. A critical illness requiring ICU admission occurs in about 5% during the course of malignant disease. Overall, cancer patients account for about 15% of all intensive care treatments.[8–10]

A French single-centre analysis comparing ICU admission data from the years 2007–2008 and 2017–2018 showed an increase in patients with metastatic disease and of patients admitted for drug- or procedure-related adverse events. Interestingly, the overall ICU survival rate of about 77% and the 1-year survival rate of 33% did not change significantly during the specified periods.[11]

For critically ill oncologic patients, no sarcoma specific scoring system predicting clinical outcome is available.[7] It has been shown, however, that mortality rates and clinical prognosis depend on the number of organ failures, the need of mechanical ventilation, vasopressors, and preceding therapies.[7]

The Acute Physiology and Chronic Health Evaluation (APACHE) score and the Sequential Organ Failure Assessment (SOFA) score are most commonly used to estimate ICU mortality.[7]

To date, APACHE exists in four versions (I–IV). To derive a severity score able to predict hospital mortality and sometimes even the length of stay, the input of several clinical variables is required.[12,13] APACHE II consists of three different parts: an acute physiological score, age, and chronic health points. The parameters are evaluated within the first 24 hours after admission to intensive care, the maximum score is 71 points.[14] Mortality increases in parallel with the respective score level.[15]

The Simplified Acute Physiologic Score (SAPS), on the other hand, is based on dichotomous and continuous variables. Severity is calculated based on the worst values measured within the first 24 hours after admission to the intensive care unit. The number of variables is 14 and thus smaller than those included in the APACHE score.[16–18] The maximum score is 163 points. Patients with the highest score have the worst prognosis.[19]

In cancer patients, older age, number of organ system failures, respiratory failure, and requirement of vasopressors as well as isolated lung injury influence mortality. Notably, the type of tumour has not been shown to be prognostic for ICU survival.[7] No such surrogate parameters indicating prognosis have been defined for sarcoma patients as of yet.

Our analysis aims to optimize the selection of sarcoma patients for ICU admission and to improve intensive care algorithms for this group of patients.

Materials and Methods

This retrospective analysis comprises patients ≥18 years treated at Charité-Universitätsmedizin Berlin from 2005 to 2022. We included all patients with histologically proven sarcoma who had been admitted to the ICU during this period. We excluded patients with oncological neoplasms other than STS. In addition, patients who were only

monitored perioperatively in the ICU were also excluded. In total, 66 of 834 screened patients were eligible for analysis.

Informed consent following institutional guidelines was obtained from all patients. Data was retrospectively extracted from archived patient records with approval of the local ethical review committee of Charité-Universitätsmedizin Berlin (EA2/240/20) and in accordance with the Declaration of Helsinki.

This study aimed to characterize sarcoma patients admitted to the ICU by means of explorative, descriptive statistics. Factors influencing the survival of these patients were analysed. Laboratory analysis was performed within the first 24 hours after admission to the ICU. Primary endpoint was the ICU mortality, and secondary endpoints were the in-hospital survival and the overall survival. The in-hospital survival comprised the percentage of patients who survived the ICU treatment, but died during the same hospital stay. The overall survival was defined as the time from ICU admission to death or if survival status was unknown, to last contact. The Kaplan–Meier method with Log rank tests was used for univariable survival analyses.

To evaluate and examine the ICU scores, we calculated the median scores of all patients admitted, of the ICU-survivors and of ICU non-survivors. The interquartile range (IQR) containing the second and third quartile of the ICU scores was used to show the range of our data.

In general, p-values <0.05 (calculated 2-sided) were considered significant.

Data analysis was performed using SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp).

Results

Patient and Treatment Characteristics

Overall Study Population

The characteristics of 66 included patients are shown in Table 1. The vast majority of patients (71.2%) had distant metastases at the time of ICU admission. The lung was the main location of these metastases.

More than half of the patients (62%) had progressive disease during the course of a mainly palliative treatment concept (83%). They were often (56%) multimodally pre-treated. Most commonly, the current therapy was a systemic treatment (58%) with an anthracycline-based combination chemotherapy (27%). In the majority of cases, it was the first-line treatment (56%). For details, please refer to Table 1.

ICU Survivors/Surv versus ICU Non-Survivors/Non-Surv

Altogether, 17 patients died during ICU treatment. The median age was 59 years, and 53% of those patients were female. Undifferentiated, high-grade sarcoma and "other" sarcoma was the most common histologic subtype (each 24%). In the majority of cases, the primary location of the sarcoma was the abdomen/pelvis (ICU non-survivors 47% vs ICU survivors 35%). Most of the patients had multiple distant metastases (82%). Almost all non-survivors (94%) were treated in palliative intention. The current chemotherapy was primarily an anthracycline-based combination chemotherapy or trabectedin (31%). Infection was the most common reason for ICU admission (77%). ICU non-survivors were also more likely to receive vasopressor therapy (71% vs 35%), invasive ventilation (53% vs 18%) and renal replacement therapy (35% vs 6%). For details, please refer to Table 2 as well as Table 3.

Both groups also showed major differences in the common sepsis and performance scores: The group of ICU non-survivors showed higher median scores in all reviewed ICU-scoring systems. For details, please refer to Table 4.

Survival Analysis

Overall Survival

Survival data was available in n=66 patients (100%). In the overall study population, median OS was 7 months 95% CI, 0 to 30.6 months (Figure 1A). Median OS in the ICU surv population was not reached (Figure 1B). The median survival in the ICU non-surv study population was 6 days (Figure 1C).

Table 1 General Patient Characteristics

	All Patients (n=66)	ICU Surv (n=49)	ICU Non-Surv (n=17)
Age			
Years (median (IQR))	57 (40–69)	57 (40–69)	59 (45–69)
Sex			
Female	34 (53%)	25 (51%)	9 (53%)
Male	32 (49%)	24 (49%)	8 (47%)
Histology			
Bone sarcoma (incl. osteo, chondro, and EFT)	15 (23%)	12 (24%)	3 (18%)
GIST	2 (3%)	2 (4%)	-
Leiomyosarcoma	8 (12%)	6 (12%)	2 (12%)
Liposarcoma	11 (17%)	9 (18%)	2 (12%)
Myxofibrosarcoma	5 (%)	3 (6%)	2 (12%)
Solitary fibrous tumor	2 (3%)	1 (2%)	1 (6%)
Synovial sarcoma	3 (8%)	3 (6%)	-
Undifferentiated pleomorphic sarcoma (UPS)	5 (7%)	4 (8%)	1 (6%)
Undifferentiated, high-grade	4 (6%)	2 (4%)	2 (12%)
Vascular	3 (5%)	2 (4%)	1 (6%)
Other	8 (12%)	5 (10%)	3 (18%)
Grading			
None	24 (36%)	18 (37%)	6 (35%)
Low grade	6 (9%)	5 (10%)	1 (6%)
High grade	36 (54%)	26 (53%)	10 (59%)
Primary tumor location			
Extremity	27 (41%)	22 (45%)	5 (29%)
Abdomen/pelvis	25 (38%)	17 (35%)	8 (47%)
Thorax	10 (15%)	7 (14%)	3 (18%)
Head/neck	4 (6%)	3 (6%)	1 (6%)
Pulmonary metastases			
Not present	33 (50%)	27 (55%)	6 (35%)
Present	33 (50%)	22 (45%)	11 (65%)
Metastatic status			
None	10 (15%)	8 (16%)	2 (12%)
Localized	8 (12%)	7 (14%)	1 (6%)
Multiple	47 (71%)	32 (67%)	14 (82%)
Unknown	1 (2%)	1 (2%)	-

Abbreviations: Chondro, chondrosarcoma; EFT, Ewing family of tumors; GIST, gastrointestinal stromal tumor; ICU, intensive care unit; IQR, interquartile range; surv, survival; non-surv, non-survival; osteo, osteosarcoma.

Role of Therapy

For ICU-survival, Kaplan–Meier analysis showed significant differences regarding the current chemotherapy ($p=0.02$) and the chemotherapy line ($p<0.01$). Univariate analysis showed a better clinical outcome for patients receiving a first-line chemotherapy than for those who received a chemotherapy regimen for relapse or progression. The median ICU-survival for a first-line chemotherapy was 19 days compared to 2 days for a fourth line chemotherapy. Median time from last chemotherapy to admission to the ICU was 11 days (range 1–27 days).

For the overall survival, univariate analysis showed significant differences regarding the intention of therapy ($p=0.05$) (Figure 2). Line of therapy also had a significant impact on OS of the overall patient population ($p<0.001$) and on OS of the non-surv population ($p<0.001$). There was a trend towards improved overall survival depending of disease status: first diagnosis/progressive disease vs stable disease/partial/complete remission ($p=0.039$) and towards the current chemotherapeutic regimen: anthracycline-based vs gemcitabine-based regimen vs trabectedin vs taxan vs Ewing sarcoma regimen vs other ($p=0.034$). Neither previous nor current therapy (chemotherapy vs resection vs multimodal vs none) significantly influenced prognosis.

Table 2 ICU-Related Characteristics

	All Patients (n=66)	ICU Surv (n=49)	ICU Non-Surv (n=17)
Clinical symptom at ICU admission			
Infection	32 (49%)	19 (39%)	13 (77%)
Cardiac	4 (6%)	3 (6%)	1 (6%)
Respiratory	9 (14%)	7 (14%)	2 (12%)
Neurological	5 (8%)	5 (10%)	-
Other	16 (24%)	15 (31%)	1 (6%)
Reason for ICU admission			
Therapy-related	33 (50%)	21 (43%)	12 (71%)
Tumor-related	23 (35%)	19 (39%)	4 (24%)
Therapy- and tumor-related	10 (15%)	9 (18%)	1 (6%)
Leucopenia prior to ICU admission			
Present	18 (27%)	13 (27%)	5 (29%)
Not present	40 (61%)	29 (59%)	11 (65%)
Vasopressor therapy			
Present	29 (44%)	17 (35%)	12 (71%)
Not present	37 (56%)	32 (65%)	5 (29%)
Ventilation			
Oxygen/non-invasive	41 (62%)	33 (67%)	8 (47%)
Invasive	18 (27%)	9 (18%)	9 (53%)
None	7 (11%)	7 (14%)	-
Renal replacement therapy			
Present	9 (14%)	3 (6%)	6 (35%)
Not present	57 (86%)	46 (94%)	11 (65%)
Blood transfusions			
Present	34 (52%)	23 (47%)	11 (65%)
Not present	32 (49%)	26 (53%)	6 (35%)
Location of infection			
Abdominal	3 (5%)	3 (6%)	-
Catheter-associated	3 (5%)	4 (8%)	-
Fever of unknown origin	4 (6%)	4 (8%)	-
Lung	16 (24%)	8 (16%)	8 (47%)
Urogenital	3 (5%)	3 (6%)	-
Other	2 (3%)	1 (4%)	1 (6%)
None	35 (52%)	27 (55%)	8 (47%)

Abbreviations: ICU, intensive care unit; surv, survival; non-surv, non-survival.

Laboratory results

As stated before, systemically pre-treated patients had a shorter ICU-survival, as did those with an elevated potassium >5 mmol/l (p=0.001) and a decreased haemoglobin <9 mg/dl (p=0.04). Median ICU-survival for patients with normokalaemia was 19 days vs 4 days for patients with hyperkalaemia. Patients with a haemoglobin <9 mg/dl had a mean ICU-survival of 19 days vs 25 days with a haemoglobin >9 mg/dl.

Elevated potassium levels >5 mmol/l (p=0.011) as well as hyperuricemia >50 mg/dl (p<0.001) significantly influenced overall survival. Furthermore, liver parameters such as an elevated alkaline phosphatase >90 U/I (p=0.02) and an elevated bilirubin >1,2 mg/dl (p=0.01) were significantly associated with a reduced OS.

Haematological parameters such as anaemia, thrombopenia and leukopenia had no relevant impact on overall survival, whereas a pronounced anaemia adversely influenced ICU-surv.

Table 3 Treatment Characteristics

	All Patients (n=66)	ICU Surv (n=49)	ICU Non-Surv (n=17)
Disease status			
Treatment-naïve/first cycles	11 (17%)	8 (17%)	3 (18%)
Progressive disease	41 (62%)	31 (65%)	10 (59%)
Stable disease	8 (12%)	5 (10%)	3 (18%)
Partial remission	5 (8%)	4 (8%)	1 (6%)
Treatment concept			
Curative	11 (17%)	10 (21%)	1 (6%)
Palliative	54 (82%)	38 (79%)	16 (94%)
Previous treatment modality			
Chemotherapy	9 (14%)	7 (14%)	2 (12%)
Resection	8 (12%)	6 (12%)	2 (12%)
Multimodal	37 (56%)	27 (55%)	10 (59%)
None	12 (18%)	9 (18%)	3 (18%)
Current treatment modality			
Chemotherapy	38 (58%)	26 (53%)	12 (71%)
Resection	3 (5%)	3 (6%)	-
Radiation	4 (6%)	2 (4%)	2 (12%)
Multimodal	7 (11%)	6 (12%)	1 (6%)
None	14 (21%)	12 (25%)	2 (12%)
Current chemotherapy			
Anthracycline ± olaratumab	5 (8%)	5 (10%)	-
Anthracycline-based combination	11 (17%)	7 (14%)	4 (24%)
Trabectedin	8 (12%)	4 (8%)	4 (24%)
Ewing sarcoma regimen	5 (8%)	5 (10%)	-
Taxan	1 (2%)	-	1 (14%)
Gemcitabine-based regimen	3 (5%)	2 (4%)	1 (14%)
Other	5 (8%)	6 (12%)	3 (18%)
Chemotherapy line			
First-line	32 (49%)	26 (53%)	6 (35%)
Second-line	17 (26%)	11 (22%)	6 (35%)
Third-line	6 (9%)	5 (10%)	1 (6%)
Fourth-line	2 (3%)	-	2 (12%)
Duration of ICU treatment			
Median days (IQR)	3 (1–7)	3 (1–7)	6 (1.5–10.5)
Duration of hospitalization			
Median days (IQR)	17 (11–29.5)	17.5 (13.3–30)	12 (6–39)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; surv, survival; non-surv, non-survival.

Table 4 ICU-Scores

	All Patients (n=66)	ICU Surv (n=49)	ICU Non-Surv (n=17)
APACHE II			
Median (IQR)	15.5 (10–26.3)	15 (10–22)	26 (11.5–36.5)
SAPS II			
Median (IQR)	43 (30.8–64.3)	36 (30–48.5)	65 (47–78)
SOFA			
Median (IQR)	3 (0–8)	2 (0–4)	9 (6.3–14.3)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IQR, interquartile range; SAPS, Simplified Acute Physiologic Score; SOFA: Sequential Organ Failure Assessment; surv, survival; non-surv, non-survival.

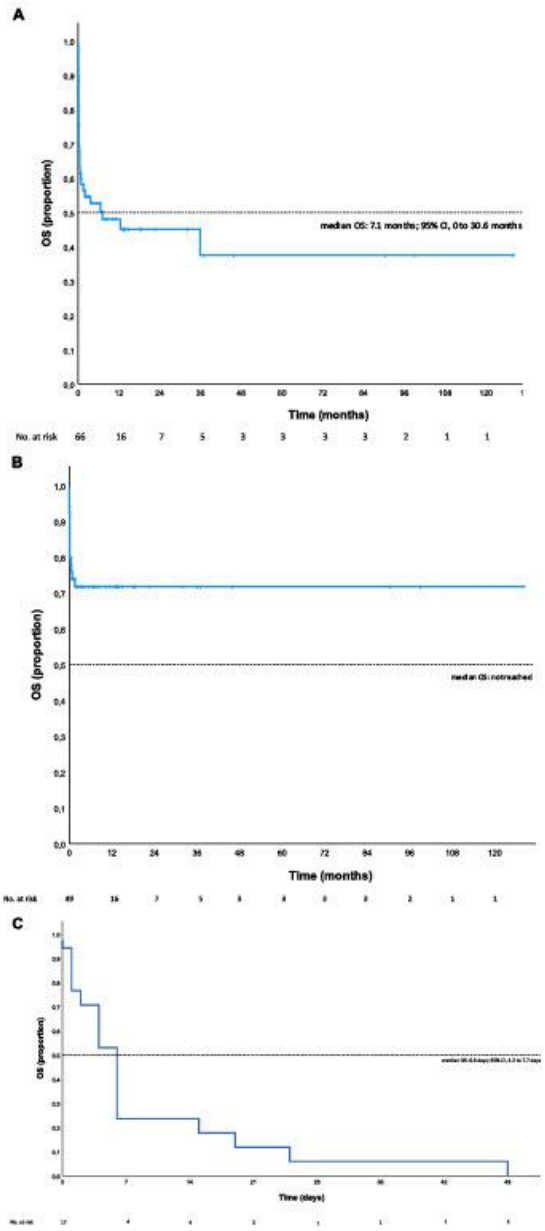

Figure 1 **(A)** Survival estimates of the overall patient population. **(B)** Survival estimates of the ICU surv patient population. **(C)** Survival estimates of the ICU non-surv patient population.

Abbreviations: CI, confidence interval; no., number; OS, overall survival; ICU, intensive care unit; surv, survival; non-surv, non-survival.

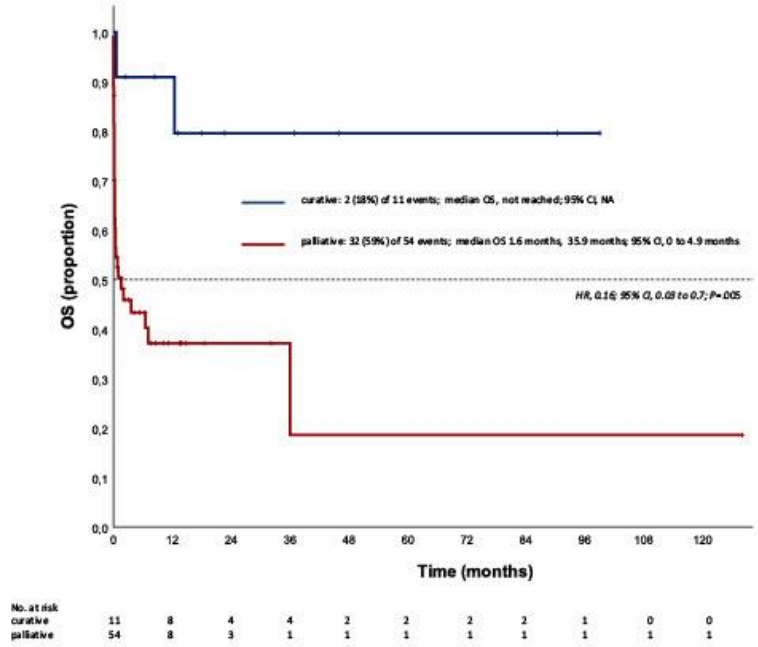

Figure 2 Kaplan–Meier estimates for OS with respect to the therapeutic intention (curative vs palliative).
Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable; no., number; OS, overall survival.

Patient and Tumour Characteristics

Female patients showed better overall survival than male patients, see Figure 3A. Primary tumours located at the extremity were associated with an improved prognosis compared to tumours of other locations, see Figure 3B. Comorbidities such as cardiovascular, renal or metabolic disorders did not relevantly influence survival.

ICU Scores and Treatment

Regarding the ICU-scoring systems, we identified a SOFA score >5 (p=0.004) and a SAPS II score >50 (p=0.007) as predictive for ICU survival and for OS. For the latter, refer to Figure 4A and to Figure 4B. By contrast, APACHE II did not predict survival. Patients of the non-surv population who needed vasopressors or renal replacement therapy showed worse survival (p=0.016 and p=0.006, respectively). The use of non-/invasive ventilation had no relevant impact on prognosis.

Discussion

Sarcomas are rare neoplasms, and data regarding intensive care mortality, survival, and prognostic factors in this specific patient population are sparse, with only one other published analysis regarding sarcoma patients treated in the ICU.[20] Therefore, our data contribute to further improve intensive care treatment of this specific population.

Overall, ICU-survival of sarcoma patients appears to be comparable to those of patients with other solid cancer types.[21–24] By contrast, ICU mortality in case of haematological disease is relevantly higher.[23,25,26]

We were able to confirm the value of common sepsis and performance scores (SOFA and SAPS II) to grade disease severity and to estimate ICU-related survival through the objective classification of organ dysfunction in sarcoma patients. Patients with a relevant organ dysfunction and a higher risk score showed a relevant increase in ICU-related

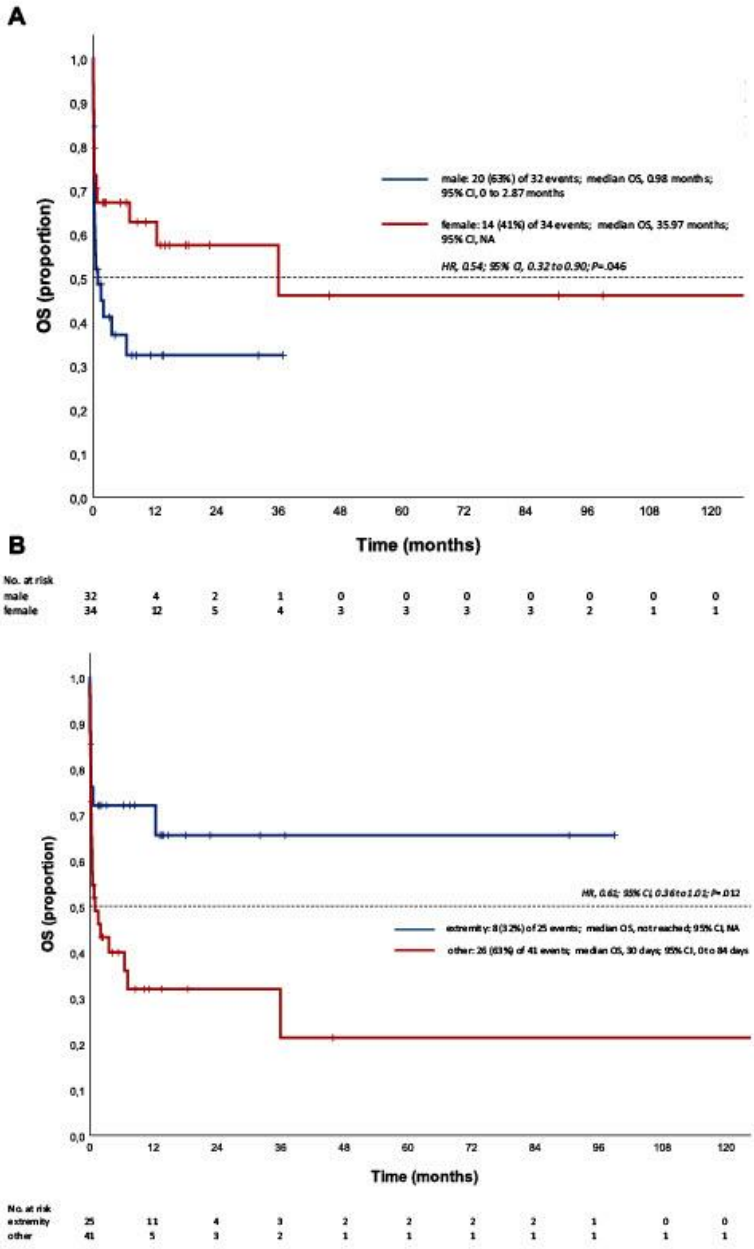

Figure 3 (**A**) Kaplan–Meier estimates for OS with respect to sex (male vs female). (**B**) Kaplan–Meier estimates for OS with respect to primary tumor location (extremity vs other).
Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable; no., number; vs, versus.

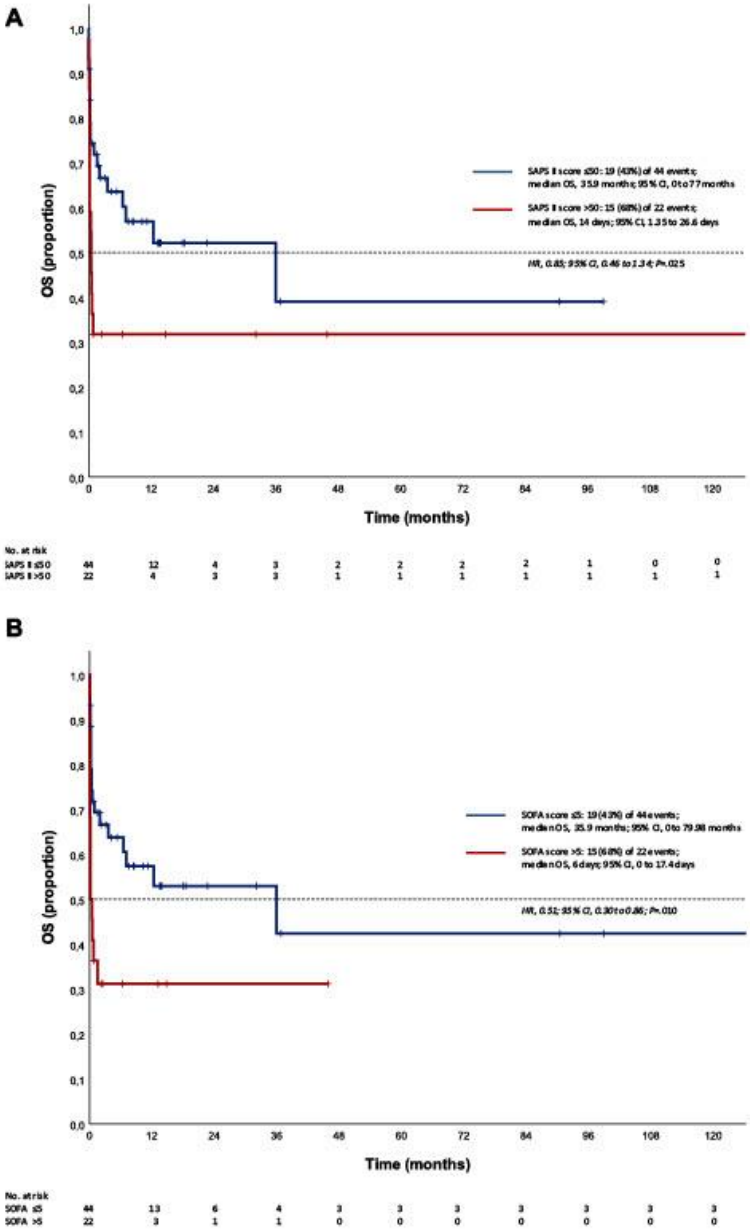

Figure 4 (**A**) Kaplan–Meier estimates for OS with respect to the SAPS II score. (**B**) Kaplan–Meier estimates for OS with respect to the SOFA score.
Abbreviations: CI, confidence interval; HR, hazard ratio; no., number; OS, overall survival; SAPS, Simplified Acute Physiologic Score; SOFA, Sequential Organ Failure Assessment.

mortality. The same applies to heavily chemotherapy pre-treated patients. As previously stated, ICU-related survival in the course of first-line tumour therapy was slightly better than in subsequent lines.

In addition, there was a significant impact of individual clinical characteristics such as sex and primary tumour location on OS.

In general, the investigated cohort is comparable to other sarcoma patient populations.[1] The sex ratio is well balanced, the majority of primary tumours was located at the extremity, and pulmonary metastases were the most common. Regarding STS, leiomyosarcoma as well as liposarcoma were the predominant histologic sub entities.

In accordance with prior publications, the most common indication for admittance to intensive care in our cohort were infectious complications (49%), followed by neurologic disturbances (14%). In total, 50% of the admissions were therapy-related, 35% tumour-associated, and 15% both therapy- and tumour-related. This is in line with previous analyses of oncologic patients requiring intensive care, with sepsis or septic shock being the most common reason for ICU treatment.[27] In contrast to Torres et al, we did not observe a negative impact of tumour-related critical illness compared to therapy-associated or other reasons on overall prognosis.[28]

As shown before in patients with lung cancer, those patients who died in the ICU received significantly vasopressors, invasive ventilation, and haemodialysis significantly more often, reflecting the respective severity of sepsis.[27,29,30]

In the ICU, prognostic scores are usually used to assess survival probability and severity of illness. Thus, we included APACHE II, SAPS II as well as SOFA score into our analysis. We did not find any significant impact of APACHE II. However, there was a significant association between a high SAPS II and SOFA score at admission and both ICU mortality and median ICU survival. Our results are thus in accordance with Gupta et al.[20]

In general, a higher grade of organ dysfunction might represent an important risk factor for ICU mortality.[31] Consistent with this observation, results of laboratory chemistry indicating organ failure are different in the cohort of patients who died in the ICU. To some extent, the relevant parameters are already part of the respective scoring systems, which might explain the applicability of these scores. Accordingly, in univariate analysis, we observed a worse ICU-survival in patients with a high SOFA score.

Patients receiving first-line chemotherapy at admission to intensive care showed a slightly better ICU survival than those receiving a later line of therapy. As anthracycline-based combination therapy still represents the first-line therapeutic standard in soft tissue sarcoma, patients receiving trabectedin or any other second- or further line treatment had worse outcomes than those receiving the former.[32,33] Hypothetically, accumulated therapy-associated toxicity in pre-treated patients might also contribute to the poor prognosis of this specific population. Additionally, in the situation of progressive disease, tumour-associated complications are more common.[33] In univariate analysis, female sex had a positive impact on overall survival. This survival advantage in malignant disease was shown before in diverse entities.[34–37] To date, a multifactorial cause such as gender-specific, biological and socio-cultural features is assumed.[34]

In addition, location of the primary tumour might have an influence on prognosis. In our cohort, patients with extremity tumour had a better OS than those with tumours of other locations. Tumours of the extremity are likely to be diagnosed at an early stage of disease due to a more rapid onset of symptoms. In addition, they are more accessible to surgery and/or radiation therapy.

In our study, disease stage as well as the respective therapeutic concept had an impact on OS. Thus, we were able to confirm previous analyses showing a negative prognostic role of progressive disease and of a palliative situation.[20]

In the analysed cohort, ICU mortality was 25.8%, whereas overall in-hospital mortality was 43.4%. ICU survival of sarcoma patients was therefore comparable to previously published results.[20] In contrast, in-hospital mortality was higher than observed before (42 vs 30%). This might be explained by a relevantly higher proportion of patients with progressive disease (63 vs 34%) and thus a lower percentage of stable disease as well as partial remission (20 vs 38%) in our cohort. However, the ICU-mortality rate found in this analysis was lower than the one observed for oncologic patients admitted to intensive care at tertiary institutions in previous publications by other authors.[27,30]

Median OS in our cohort was 7 months, which is relatively short compared to oncologic patients with other carcinomas treated at the ICU.[38] A potential reason is the heterogeneity as well as the limited efficacy of chemotherapeutic substances in soft tissue and bone sarcomas.

There are some limitations regarding our trial. First of all, it is a monocentric retrospective study with only a limited number of patients included. Multicentric, prospective analyses are desirable to minimize selection bias. Our analysis was realised in a high-volume university hospital setting; thus, data can only partially be compared to smaller non-academic institutions.

Additionally, sarcomas are a very heterogeneous tumour entity and conclusions are not easily generalisable. Therefore, subsequent studies might further distinguish between histologic sub entities and collect additional data regarding quality of life or other long-term information. We did not analyse a control group, eg, sarcoma patients with critical illness who were managed outside of the ICU or even patients with other cancer types needing intensive care treatment. Moreover, due to the limited number of patients, we were not able to perform multivariate statistics to eliminate confounding factors.

However, despite the rarity of sarcomas, we were able to analyse a relevant number of cases reflecting the real-life care of patients treated at a high-volume university hospital.

Conclusion

So far, there is only one other published monocentric analysis evaluating intensive care outcomes in sarcoma patients. To the best of our knowledge, this trial represents the first retrospective analysis of this specific patient population in Europe. Given the diverse scoring systems utilized in the intensive care setting, we analysed not only the SOFA score but also SAPS II and APACHE II. These scoring systems are well established in intensive care medicine. Patients with a relevant organ dysfunction and a higher risk score showed a relevant increase in ICU-related mortality.

Our analysis can contribute to optimising clinical decision-making based on objective data as well as individual patient characteristics. To date, there are no defined criteria for triaging in this distinct patient population. Of significant importance might be the definition of clear goals for each individual patient.

In a palliative setting, ICU admittance of patients for tumour-related reasons and with progressive disease should be reconsidered carefully as the clinical benefit in this constellation might be limited. Further investigation is necessary to enable an optimisation of the ICU treatment of sarcoma patients.

Abbreviations

APACHE, Acute Physiology and Chronic Health Evaluation; chondro, chondrosarcoma; CI, confidence interval; dl, decilitre; eg, exempli gratia; EFT, Ewing family of tumours; GIST, gastrointestinal stromal tumour; HR, hazard ratio; ICU, intensive care unit; incl, inclusive; IQR, interquartile range; l, litre; mg, milligram; NA, not applicable; no., number; non-surv, non-survival; NR, not reached; OS, overall survival; osteo, osteosarcoma; SAPS, Simplified Acute Physiologic Score; SOFA, Sequential Organ Failure Assessment; STS, soft tissue sarcoma; surv, survival; U, unit; vs, versus.

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Disclosure

Prof. Dr Lars Bullinger reports personal fees from AbbVie, Bristol-Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Hexal, Janssen, Jazz Pharmaceuticals, Menarini, Novartis, Pfizer; grants from Bayer, Jazz Pharmaceuticals, outside the submitted work. Prof. Dr Kai-Uwe Eckardt reports personal fees from Akebia, Astra Zeneka, Evotec, Fresenius, Otsuka, Sanofi; grants from Vifor, Amgen, Bayer, outside the submitted work. The authors report no other conflicts of interest in this work.

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2.3 Combination therapy with olaratumab/doxorubicin in advanced or metastatic soft tissue sarcoma -a single-Centre experience.

Striefler JK, Brandes F, Baur A, Pfitzner BM, Kaul D, Rau D, Dörr A, Schmiester M, Koulaouzidis G, Bullinger L, Märdian S, Flörcken A.
Combination therapy with Olaratumab/doxorubicin in advanced or metastatic soft tissue sarcoma -a single-Centre experience.
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Der PDGFRα- Antikörper Olaratumab wurde 2016 in Kombination mit Doxorubicin für metastasierte Weichgewebssarkome durch die US-amerikanische *Federal Drug Agency* (FDA) zugelassen. Grundlage hierfür waren vielversprechende Ergebnisse einer Phase Ib/II Studie, in welcher durch die kombinierte Gabe von Doxorubicin und Olaratumab sowohl eine Verbesserung der PFS als auch des OS erzielt worden war (6,6 vs 4,4 Monate bzw. 26,5 vs. 1,7 Monate)[70]. In der nachfolgenden Phase III ANNOUNCE Studie konnte dann jedoch der Zusatznutzen von Olaratumab nicht bestätigt werden, hier war das PFS bei den mit einer Doxorubicin-Monotherapie behandelten Patient:innen sogar besser als im Kombinationsarm, wohingegen sich keinen signifikanten Unterschiede bezogen auf das OS ergaben [71].

Um zum besseren Verständnis der Sarkomerkrankung beizutragen und mit dem Ziel der Identifikation von Subgruppen welche möglicherweise von der Gabe des Antikörpers profitieren, werteten wir unsere Erfahrungen mit Olaratumab und Doxorubicin systematisch aus. In Publikation 2.3 werden die Ergebnisse der retrospektiven Analyse von n= 32 Patient:innen, welche zwischen 2016 und 2019 am Campus Virchow Klinikum der Charité behandelt wurden, beschrieben.

Insgesamt wurden 66% (n= 21) männliche bzw. 34% (n=11) weibliche Patient:innen mit einem medianen Alter von 63 Jahren (range 44-81) eingeschlossen. In der Mehrzahl der Fälle (jeweils 69%) lag ein metastasiertes Erkrankungsstadium eines high-grade Sarkoms vor. Durchschnittlich wurden vier Therapiezyklen appliziert (range 1-8). In zwei Drittel der Fälle (n= 14) erfolgte zusätzlich zur medikamentösen Behandlung im Rahmen eines individuellen Vorgehens zusätzlich eine chirurgische Therapie (n= 9) bzw. eine regionale Tiefenhyperthermie (n= 5).

Das mediane PFS in der Gesamtkohorte war 3,1 Monate (range 0.6–16.2). Ein therapeutisches Ansprechen, definiert als komplette Remission (*complete remission*, CR), partielle Remission (*partial remission*, PR) oder eine Erkrankungsstabilisierung

(*stable disease*, SD) konnte in n = 11 (34%) Fällen erreicht werden. Bei n= 21 (66%) Patient:innen kam es dagegen zu einem Fortschreiten der Erkrankung (*progressive disease*, PD).

Übereinstimmend mit den Ergebnissen der o.g. Phase III Studie zeigte sich auch in unserem Kollektiv keine signifikante Verbesserung des Überlebens durch die Hinzunahme von Olaratumab. Drei der insgesamt fünf Patient:innen, welche ergänzende zur medikamentösen Therapie eine Hyperthermiebehandlung erhielten, zeigten eine PR (n= 2) bzw. SD (n= 1) und konnten bei lokalisierter Erkrankung nach Diskussion im interdisziplinären Tumorboard und entsprechender Empfehlung sekundär reseziert werden. Diese Fälle veranschaulichen die synergistische Wirkung von medikamentöser Tumortherapie mit strahlentherapeutischen bzw. Hyperthermieverfahren in Bezug auf die lokale Kontrolle. In der nachfolgenden Publikation 2.4 wird diese weiter untersucht: in einer retrospektiven Analyse wird die Effektivität einer alleinigen Radiatio mit einer kombinierten Radiochemotherapie verglichen.

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Combination therapy with Olaratumab/doxorubicin in advanced or metastatic soft tissue sarcoma -a single-Centre experience

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Abstract

Background: The antibody targeting platelet-derived growth factor receptor alpha (PDGFRA), olaratumab, was approved in 2016 for metastatic soft tissue sarcoma (STS) in combination with doxorubicin based on promising results of a phase Ib/II trial by the Food and Drug Administration (FDA). However, recently the phase III ANNOUNCE trial could not confirm the additional value of olaratumab in this context.

Methods: Here, in a retrospective analysis we share our single-centre experience with olaratumab/doxorubicin in STS by including $n = 32$ patients treated with olaratumab/doxorubicin between 2016 and 2019.

Results: Median progression-free survival (PFS) in the overall cohort was 3.1 months (range 0.6–16.2). A response [complete remission (CR), partial remission (PR) or stable disease (SD)] was seen in $n = 11$ (34%) cases, whereas $n = 21$ (66%) patients showed progressive disease (PD). In $n = 9$ patients surgery was performed subsequently in an individual therapeutic approach. Out of $n = 5$ patients receiving additional regional hyperthermia, $n = 3$ achieved PR or SD.

Conclusions: This single-centre experience does also not support the promising phase Ib/II results for olaratumab/doxorubicin in STS. However, our findings do not preclude that olaratumab combination therapy could be valuable in a neoadjuvant setting. This warrants further exploration also taking into account the heterogeneous nature of STS.

Keywords: Soft tissue sarcoma, Doxorubicin, Olaratumab, Platelet-derived growth factor receptor alpha (PDGFRA), Hyperthermia

Background

Soft-tissue sarcomas (STS) are a rare and heterogeneous group of neoplasms of mesenchymal origin, which represent about 1% of malignancies in adulthood with an annual incidence rate in Germany of about 6 per 100,000 [1]. With over 50 different histologic subtypes, it remains difficult to establish a therapeutic standard. While many STS can be cured by surgery alone at an early stage of the disease, locally relapsing and metastatic disease continues to be a challenge and often requires multi-modal therapeutic approaches, especially in high-grade STS. In a palliative setting, single agent doxorubicin or doxorubicin combinations remain the standard of care for the majority of histologic STS subtypes [2]. Nevertheless, there is a high-unmet medical demand for improved STS treatment and innovative effective chemotherapeutic agents are needed.

Olaratumab is a human recombinant monoclonal immunoglobulin G subclass (IgG1) antibody, which binds specifically to platelet-derived growth factor receptor alpha (PDGFRA) and consecutively blocks ligand binding. As PDGFR signalling is known to be relevant in mesenchymal biology [3], a lot of hope was inspired within the STS community based on the promising results of a phase Ib/II trial showing a median

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progression-free survival (PFS) of 6.6 months in the olaratumab/doxorubicin arm compared to 4.1 months in the doxorubicin monotherapy cohort [4]. In accordance, olaratumab was approved in combination with doxorubicin by the FDA in 2016, especially as there was also an improved overall survival (OS) and overall response rate (ORR), which so far had not been documented for any other novel STS treatment. Hoping that this new approach would be paradigm changing, it seems that many patients have benefitted from the combination treatment since the approval of the drug. Surprisingly, the additional value of olaratumab in combination with doxorubicin treatment could recently not be confirmed in the large randomized, double-blind phase III ANNOUNCE trial [5].

While we were awaiting the detailed results of the ANNOUNCE trial, we concluded that our experience at the Charité–Universitätsmedizin Berlin, a large sarcoma centre, could further contribute to the understanding of these unanticipated efficacy results of olaratumab in STS.

Methods

The aim of this retrospective analysis is to understand the real-world effectivity of the combination regimen of olaratumab/doxorubicin as measured by OS, PFS, and ORR (defined as the rate of patient achieving a CR, PR, or SD), and to evaluate the toxicity of the combination therapy.

We included a total of $n = 32$ STS patients who were all treated with olaratumab/doxorubicin at our institution between 2016 and 2019. Patients were included with institutional review board approval and patient informed consent in accordance with the local ethical guidelines. The majority of patients had either adipocytic sarcomas ($n = 8$), undifferentiated/unclassified sarcomas ($n = 9$), or smooth muscle tumours ($n = 5$). For detailed information about the histologic subtypes, see Fig. 1. The median patient age was 63 years (range 44–81) with $n = 21$ males and $n = 11$ females included. For detailed patients' characteristics, see Table 1.

Patients received olaratumab (15 mg/kg) intravenously on day 1 and day 8 plus doxorubicin (75 mg/m^2) on day 1 of each 21-day cycle. All patients received olaratumab/doxorubicin in a palliative setting. In $n = 25$ of the patients it was given as first line therapy, and in $n = 7$ in more advanced treatment lines following trabectedin, pazopanib, paclitaxel, or other combination regimens. In $n = 9$ patients the systemic therapy was followed by surgery as a patient-adapted individual therapeutic approach. For detailed information on the respective therapeutic sequences, see Fig. 2.

In patients without clinical evidence for progressive disease, tumour response assessment was performed after 4 treatment cycles based on imaging with computed tomography (CT) or magnetic resonance imaging (MRI) scans. Response was evaluated in analogy to the RECIST v1.1 criteria. Follow-up analyses were performed every 3–4 months at physicians' discretion. The median follow-up time in this analysis was 140 days (range 48–533). Toxicity was assessed according to the National Cancer Institute (NCI) criteria v5.0 at each visit.

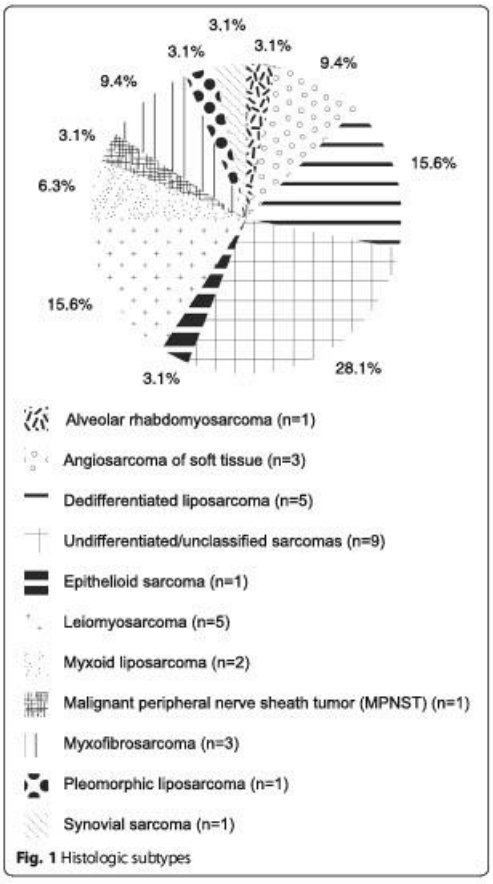

Fig. 1 Histologic subtypes

Results

Response to therapy

Of the $n = 32$ STS patients treated with olaratumab/doxorubicin at our institution, patients completed on average 4 cycles (range 1–8), while $n = 9$ (28%) patients completed 6–8 cycles (see Table 1). In $n = 5$ of the patients with localized primarily inoperable disease, as assessed by the interdisciplinary tumour board,

Table 1 Patients´ characteristics

Characteristic	n = 32
Sex n (%)	
male	21 (66)
female	11 (34)
Age (years)	
median	63
range	44–81
Stadium n (%)	
localized	10 (31)
metastasized	22 (69)
Grading n (%)	
G2, G3	22 (69)
G1	7 (22)
Gx[a]	3 (9)
Cycles of doxorubicin/olaratumab administered n (%)	
1 to 5	23 (72)
6 to 8	9 (28)
median no. of cycles	4
Exposure to doxorubicin	
median cumulative dose (mg/m²)	300
range (mg/m²)	75–600
Proportion of patients with delay of therapy due to toxicity/infection n (%)	4 (12,5)
Patients with previous treatment lines n (%)	
0	25 (78)
≥ 1	7 (32)
Response n (%)	
PR	4 (13)
SD	7 (22)
PD	21 (66)
Performance status (ECOG) n (%)	
0	14 (44)
1	16 (50)
2	2 (6)
Pattern of metastases n (%)	
lung only	3 (9)
multiple	6 (19)
Site of primary tumor n (%)	
extremity	8 (25)
retroperitoneum	8 (25)
trunc	14 (4)
head	1 (3)
uterus	1 (3)
Site of metastasis n (%)	
lung	6 (19)
liver	4 (13)
bone	2 (6)
other	7 (22)

PR partial remission; *SD* stable disease; *PR* progressive disease
[a]no formal grading available, but with clear histologic and radiologic features of high grade sarcoma

additional regional hyperthermia was given. This decision was made with the goal to possibly enable curative surgery in case of tumour response.

In our STS cohort, we observed a response in $n = 11$ (35%) cases (partial remission [PR] or stable disease [SD]). PR was seen in $n = 4$ patients (13%), $n = 7$ had SD (22%), whereas $n = 21$ had PD (66%) (see Table 2). The median progression-free survival (PFS) in the overall cohort was 3.1 months (range 0.6–16.2) and the median overall survival (OS) 4.6 months (range 1.6–17.5) (see Table 3).

A small number of n = 4 patients showed disease stabilization beyond 8 cycles of the combination regimen and received olaratumab maintenance therapy. In 3 out of 5 patients receiving additional regional hyperthermia a PR ($n = 2$), or SD ($n = 1$) was achieved.

Surgical intervention post olaratumab/doxorubicin treatment

A small subset of our cohort ($n = 9$) underwent surgery following olaratumab/doxorubicin treatment (see Table 2). The majority of these patients demonstrated PR or SD ($n = 6$) while the remaining patients ($n = 3$) underwent a palliative resection despite PD due to the absence of other reasonable therapeutic options.

In the cohort of patients undergoing surgery (n = 9) we could observe the following differences compared to the cohort without subsequent surgery ($n = 23$): these patients did slightly less frequently show high grade G3 sarcoma (44% vs. 48%) and were less often treated in a metastatic setting (33% vs. 83%). The median PFS of this cohort was 4.7 months (range 2.1–11.9) compared to 2.8 months (range 0.6–16.2) in the cases without surgery. Similarly, the median OS was 7.4 months (range 3.3–16.6) for operated STS vs. 3.9 months (range 1.6–17.5), respectively (see Table 3). The number of patients who completed 6 to 8 cycles of doxorubicin/olaratumab was also higher in the cohort with surgery (44% vs. 26%, respectively).

Treatment related toxicity

In our patient cohort, the combination treatment with olaratumab/doxorubicin was well tolerated and we did only observe few high-grade toxicities (grade 3 or higher). These consisted predominantly of hematologic

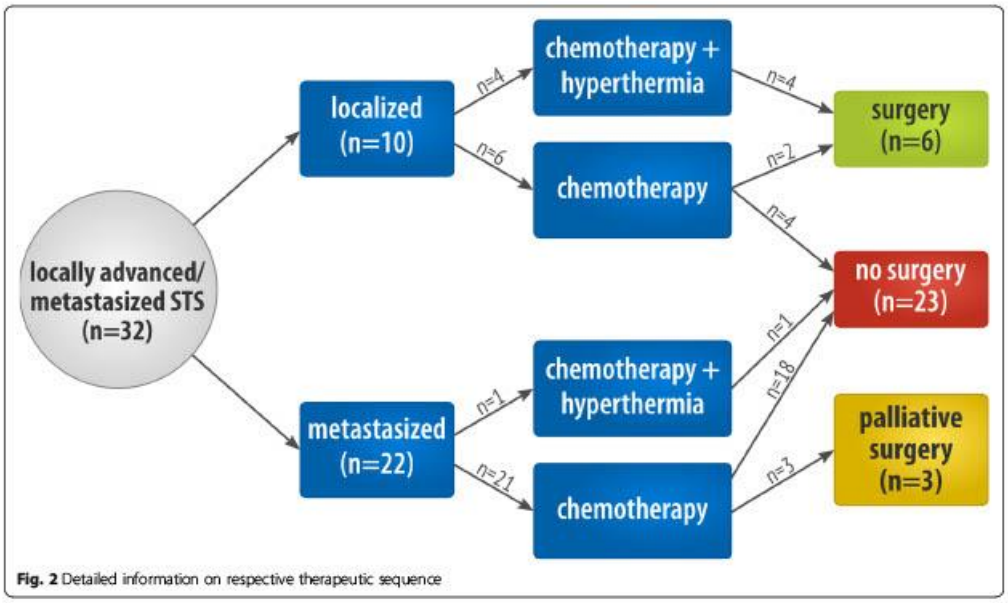

Fig. 2 Detailed information on respective therapeutic sequence

toxicity (e.g. anaemia in $n = 7$ [22%] cases and leukopenia in $n = 12$ [38%] cases). Grade 3 or 4 febrile neutropenia or other infections occurred in 9% or 13% of the patients, respectively. Treatment discontinuation due to toxicity was only necessary in $n = 1$ (3%) of the patients.

We observed the following grade 1/2 toxicities: anaemia ($n = 14$ [69%]), leukopenia ($n = 9$ [28%]), decreased appetite ($n = 10$ [31%]), constipation (n = 7 [22%]), diarrhea ($n = 2$ [6%]), infections/infestations ($n = 3$ [9%]), musculoskeletal pain (n = 2 [6%]), abdominal pain (n = 1 [3%]), febrile neutropenia (n = 1 [3%]), infusion-related reaction (n = 1 [3%]), and pyrexia (n = 1 [3%]).

No toxicity was documented that clearly related to olaratumab treatment. Apart from infusion-related reactions (IRR), no distinct olaratumab-associated adverse events are known. We did not observe any higher grade IRR in our cohort. For the detailed overview on the toxicities during olaratumab/doxorubicin combination treatment see Table 4.

Discussion

While the early results of the phase Ib/II trial with olaratumab/doxorubicin showed very promising clinical activity including a relevant improvement in OS [4], this could surprisingly not be confirmed in the large phase III ANNOUNCE trial [5].

In the phase Ib/II trial by Tap et al. the PFS and OS were considerably longer in the olaratumab/doxorubicin treated cohort compared to the monotherapy group (6.6 vs. 4.4 months and 26.5 vs. 14.7 months, respectively). Furthermore, the phase Ib/II study showed a disease control rate (CR, PR or SD) of 77.3% in the combination arm vs. 62.7% in the patients treated with single agent doxorubicin.

Astonishingly, the phase III ANNOUNCE trial presented at the ASCO annual meeting 2019 was not able to reproduce the additional therapeutic benefit of olaratumab in combination with doxorubicin. PFS in the doxorubicin plus placebo cohort was improved compared to the results of the combination arm, whereas concerning OS there was no difference shown between the two groups: 5.4 vs. 6.8 months and 19.7 vs. 20.4 months, respectively [5]. Disease control rate was also higher in patients receiving the monotherapy: 67.4% vs. 75.7%.

Similarly, our real-world data as well as a recently published Austrian analysis [6] did also not demonstrate the high disease stabilization rates seen in the phase Ib/II study, as SD was seen in only 22% of our cases compared to 59% of the phase Ib/II cohort and 54% in the ANNOUNCE trial. However, the rate of patients achieving a PR was similar with 13% compared to 15% in the phase Ib/II cohort and 13% in the ANNOUNCE trial, respectively.

The poorer disease stabilization and the shorter survival of our cohort may be caused by selection-bias. In our study, we mostly opted for olaratumab/doxorubicin

Table 2 Overall response

	all patients	patients receiving surgery
outcome	n = 32	n = 9
PD n (%)	21 (65.6)	3 (33.3)
PR n (%)	4 (12.5)	4 (44.4)
SD n (%)	7 (21.9)	2 (22.2)

PR partial response; *SD* stable disease; *PR* progressive disease
Response was assessed based on imaging (CT or MRI) scans in analogy to the RECIST v1.1. criteria

if the patient did not appear to have an adequate performance status for the combination of doxorubicin and ifosfamide.

Concerning the patient characteristics "sex", "age", and "number of previous therapies" our patient population was in some respect more alike to the one of the phase III ANNOUNCE trial than to the phase Ib/II cohort. Doxorubicin and olaratumab was the first systemic therapy for the majority of patients treated in our centre (78%) and also in the ANNOUNCE trial (74%), in the phase Ib/II trial there were only 41% patients without previous therapy included.

In our study, there was a predominance of male patients (66%) whereas there were less male patients included in the phase Ib/II (44%) and in the ANNOUNCE trial (42%), respectively. Male sex has been shown to be an adverse prognostic factor in different oncologic diseases concerning outcome and response to chemotherapy [7–10]. There also were more male patients in the doxorubicin mono group of the phase Ib/II trial included, but not in the ANNOUNCE trial as there were 39% vs. 44% male patients receiving single agent and combination therapy, respectively. In summary, gender does not really help to distinguish the differences between the different treatment groups in the previously published data, but could in part explain the dismal results in our limited patient population.

In line with the interpretation of the results of the ANNOUNCE trial, possibly the most important factor influencing the efficacy of STS treatment in general, is the exposure to a certain dosage of anthracyclines. Our patients received a median number of 4 cycles doxorubicin compared to 6 cycles in ANNOUNCE trial and 7 cycles

Table 3 Survival rates

	all patients	patients receiving systemic therapy only	patients receiving surgical intervention
	n = 32	*n* = 23	*n* = 9
PFS median (range)	3.1 (0.6–16.2)	2.8 (0.6–16.2)	4.7 (2.1–11.9)
OS median (range)	4.6 (1.6–17.5)	3.9 (1.6–17.5)	7.4 (3.3–16.6)

PFS progression free survival; *OS* overall survival

Table 4 Therapy-associated toxicity by grade per patient

Event	Any grade	Grade 3	Grade ≥ 4
Any toxicity n (%)			
Nausea Nausea	11 (34.4)	0 (0)	0 (0)
Fatigue	16 (50)	1 (3.1)	0 (0)
Neutropenia	15 (47)	2 (6.3)	10 (31.3)
Mucositis	6 (18.7)	1 (3.1)	0 (0)
Alopecia Alopecia	32 (100)	0 (0)	0 (0)
Vomiting	5 (15.6)	0 (0)	0 (0)
Anaemia Anaemia	29 (90.6)	7 (21.9)	0 (0)
Leukopenia Leukopenia	21 (65.6)	10 (31.3)	2 (6.3)
Constipation	7 (21.9)	0 (0)	0 (0)
Diarrhea Diarrhea	2 (6.3)	0 (0)	0 (0)
Decreased appetite Decreased appetite	10 (31.3)	0 (0)	0 (0)
Abdominal pain	3 (3.4)	1 (3.1)	1 (3.1)
Pyrexia	3 (9.4)	0 (0)	2 (6.3)
Musculoskeletal pain	2 (6.3)	0 (0)	0 (0)
Febrile neutropenia	4 (12.5)	1 (3.1)	2 (6.3)
Infections and infestations	7 (21.9)	1 (3.1)	3 (9.4)
Infusion-related reaction	1 (3.1)	0 (0)	0 (0)
Olaratumab-related toxicitiy	0 (0)	0 (0)	0 (0)
Toxicity leading to discontinuation	1 (3.1)	0 (0)	1 (3.1)
Cardiac dysfunction	0 (0)	0 (0)	0 (0)

Toxicity was assessed according to the National Cancer Institute (NCI) criteria v5.0

in the phase Ib/II trial. In our study, the combination regimen was well tolerated. We observed less toxicities than in the published data of the ANNOUNCE trial with only one exception: Hematologic toxicity (all grades) was more frequent in our cohort (anaemia 91% vs. 43% and leukopenia 66% vs. 32%, respectively) which could be due to the slightly older age of the patients included in our study (median 63 years vs. 57 years). In contrast to previously published results [4, 5], we did not notice any higher grade IRR, which is the most commonly described adverse treatment-related event of olaratumab. Additionally, there was no occurrence of therapy-limiting cardiac dysfunction, even though more than 25% of our patients completed 6 to 8 cycles of olaratumab/doxorubicin.

While our data do not support the initial enthusiasm on PDGFRA targeting, PDGFR signalling nevertheless plays a crucial role in oncogenesis as well as in angiogenesis and fibrogenesis [11–13]. As a result, this pathway has an impact on the tumour microenvironment, e.g. diffusion, and the growth of cancer cells [14]. Therefore, detailed efforts are undertaken to further

understand the anti-tumour activity of PDGFR antibodies such as olaratumab. In preclinical xenograft studies, olaratumab was effective to inhibit cancer cell growth [15]. Olaratumab showed an inhibition of interstitial pressure followed by a better delivery of cytotoxic substances. Most likely, PDGFRA inhibition is not the only mode of action of olaratumab. Additionally, there seems to be a pre-sensitizing effect on the tumour stroma, which allows an increased tumour cell permeability [16].

Except for one patient with leiomyosarcoma treated with olaratumab monotherapy [17], data derived from other advanced malignancies show that there is nearly no therapeutic efficacy by the antibody alone [15, 17]. Altogether, olaratumab only seems to be effective in combination with cytostatic chemotherapy. Luckily, the addition of olaratumab to chemotherapy does usually not increase side effects as also demonstrated in advanced ovarian cancer and metastatic prostate cancer [18, 19].

As there is also some preclinical data showing a synergistic effect of olaratumab combined with doxorubicin in xenograft models of human rhabdomyosarcoma, it seemed reasonable to combine the monoclonal antibody with this established effective substance in the context of STS [2, 20, 21].

As for other combinatorial treatment strategies, one might speculate that combination with radiotherapy and/or hyperthermia could be beneficial. Combining a PDGFRA antibody with radiotherapy in a murine model was not proven successful, as Song et al. could not show a significant effect of olaratumab as a radiosensitizer. However, they did find a decrease of pulmonary micro metastases in mice treated additionally with the monoclonal antibody, which however was not significant [21]. Because of the frequent use of radiation therapy in an adjuvant setting, this question could have been addressed further in case of continued olaratumab availability.

So far, there is also no published data for the combination of olaratumab/doxorubicin with hyperthermia. The use of hyperthermia in addition to radiation therapy or chemotherapy is well established for STS. In 2018, Issels et al. published the final results of a multinational phase III trial exploring in STS the use of hyperthermia in combination with chemotherapy in the neoadjuvant setting. They could show a significant effect of additional hyperthermia on local PFS, DFS, and OS with an improvement of overall survival and local progression-free survival [22]. A retrospective analysis of the radio-oncologic department at the Charité–Universitätsmedizin Berlin also demonstrated a comparable therapeutic response of hyperthermia and radiation therapy in STS in a neoadjuvant setting with a reduced rate of surgical complications in the former group [23]. For that reason, in selected patients we combined doxorubicin/olaratumab with regional hyperthermia in the cohort of patients with borderline resectable localized tumours. While our results are preliminary, the data from our limited single-centre cohort demonstrates feasibility of a combination of anthracycline/olaratumab-based combination chemotherapy with hyperthermia in a neo-adjuvant setting. As a clinical benefit was seen in 3 out of 5 patients receiving this multimodal combination treatment, the potential application of a respective strategy clearly warrants further investigation in larger patient cohorts and might be especially beneficial in a neoadjuvant setting.

Thus, we urgently have to develop more effective therapies for advanced and metastatic STS, in addition to more reliable biomarkers that are needed to better predict tumour response. While the combination of olaratumab and doxorubicin might not be beneficial in all STS cases, certain subgroups might well benefit from the treatment. Unfortunately, different efforts could not establish PDGFRA as a reliable marker, as it is heterogeneously expressed in the stromal component of the tumour microenvironment and the tumour itself [24]. For instance, the ANNOUNCE trial showed an improved OS in patients negative for PDGFRA compared to those with relevant PDGFRA expression [5]. For the definition of subgroups possibly benefiting from olaratumab, it is vital to further explore the role of predictive biomarkers besides PDGFRA expression, which so far has shown no robust predictive value.

Conclusions

The publication of the full results of the ANNOUNCE trial clearly demonstrate that we still do not fully understand the biology of STS and there remain many open questions. Our results from a single-centre cohort do also not support the high hopes that were put into an olaratumab/doxorubicin combination therapy based on the initial phase Ib/II trial data. While there may be an additional therapeutic effect of olaratumab for certain subgroups of patients with STS, e.g. in cases with less aggressive disease, we are convinced that one should also evaluate olaratumab/doxorubicin in the neoadjuvant setting in combination with hyperthermia. Additional real-world data would help to better understand the efficacy potential of olaratumab in different therapeutic settings in STS, and this could form the basis for additional studies even though the initial efforts have not been successful so far.

Abbreviations

ASCO: American Society of Clinical Oncology; CR: Complete remission; CT: Computed tomography; DFS: Disease free survival; FDA: Food and Drug Administration; IgG: Immunoglobulin G; IRR: Infusion-related reactions; MRI: Magnetic resonance imaging; NCI: National Cancer Institute; ORR: Overall response rate; OS: Overall survival; PD: Progressive disease;

PDGFRA: Platelet-derived growth factor receptor alpha; PFS: Progression-free survival; PR: Partial remission; SD: Stable disease; STS: Soft tissue sarcoma

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Authors' contributions
J.K.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: J.K.S. and A.F. Acquisition, analysis or interpretation of data: J.K.S. and A.F. Drafting of the manuscript: J.K.S, M.S., L.B. and A.F. Critical revision of the manuscript for important intellectual content: J.K.S, F.B., A.B, B.M.P., D.K, D.R, A.D., M.S., G.K, L.B, S.M. and A.F. Statistical analysis: J.K.S. and A.F. Administrative, technical or material support: J.K.S., M.S., L.B, and A.F. All authors have read and approved the manuscript.

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Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
Patients were included with institutional review board approval and written patient informed consent in accordance with the local ethical guidelines (Ethik-Kommission der Charité-Universitätsmedizin Berlin).

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interest.

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2.4 The role of neoadjuvant radiochemotherapy in the management of localized high-grade soft tissue sarcoma.

Kobus M, Roohani S, Ehret F, Flörcken A, **Striefler JK**, Brandes F, Märdian S, Rau D, Wittenberg S, Öllinger R, Kaul D. The role of neoadjuvant radiochemotherapy in the management of localized high-grade soft tissue sarcoma. Radiat Oncol. 2022 Aug 8;17(1):139. doi: 10.1186/s13014-022-02106-2. PMID: 35941656; PMCID: PMC9361547.

Im Mittelpunkt der Behandlung von lokalisierten high grade Weichgewebssarkomen steht die Extremitäten-erhaltende Chirurgie, welche durch prä- oder postoperative Strahlentherapie (RT) und/oder eine medikamentöse Therapie ergänzt wird. Die kombinierte Radiochemotherapie (RCT) ist aufgrund der bisher vorliegenden Daten kein Standard. Sie bleibt im Sinne eines individuellen Behandlungskonzeptes Patient:innen mit Hochrisiko-Konstellationen für Lokalrezidive, Fernmetastasen oder einem hohen Remissionsdruck vorbehalten.

Ziel der in Publikation 2.4 geschilderten Untersuchung war die Evaluierung von Prädiktoren bezüglich der lokalen Kontrolle (*local control*, LC), des Gesamtüberlebens (OS) sowie der Freiheit von Fernmetastasen (*freedom from distant metastases*, FFDM) bei Patient:innen mit lokalisierten high-grade Sarkomen (G2/3). Ein besonderer Fokus lag auf der Subgruppe mit kombinierter Radiochemotherapie.

Insgesamt konnten die Daten von 115 erwachsenen Patient:innen ausgewertet werden. Die Nachbeobachtungszeit betrug 34 Monate. Eine neoadjuvante RCT erhielten 20% (n= 23) der Patient:innen, in 80% (n= 92) wurde dagegen ein anderes Vorgehen gewählt: alleinige adjuvante RT (50%, n= 58); neoadjuvante Chemotherapie (CTX) + adjuvante RT (15%, n= 17); adjuvante RCT (9%, n= 10), alleinige neoadjuvante RT (6%, n = 7).

Für die Evaluierung der o.g Prädiktoren wurden univariate und multivariate Analysen durchgeführt (univariate (UVA) und multivariable (MVA) Cox proportional hazards Modelle).

In der UVA konnte eine signifikant bessere LC Rate für die Gruppe mit neoadjuvanter RCT (p= 0.025) nachgewiesen werden. Die 3-Jahres LC Rate lag bei 89,7% in der neoadjuvanten RCT Gruppe bzw. bei 75,6% in der "andere Therapien" Gruppe.

Die univariate Analyse zeigte zudem bessere OS Raten in der RCT Gruppe (p= 0.049), welche sich in der MVA jedoch nicht bestätigten (p= 0.205). Das 3-Jahres OS war 85,8% für Patient:innen mit neoadjuvanter RCT vs. 73,5% in der "andere Therapien" Gruppe.

Die UVA ergab eine signifikant bessere FFDM Rate ($p = 0.018$), in der MVA zeigte sich dagegen nur ein Trend zu einer besseren FFDM Rate ($p = 0.059$). Die 3-Jahres FFDM Rate lag in der Gruppe mit neoadjuvanter RCT bei 89,7%, in der "andere Therapien" Gruppe bei 65,9%. In der Subgruppe der Patient:innen mit G3 Weichgewebssarkom war die neoadjuvante RCT in der MVA ein signifikanter positiver Prädiktor für die LC bzw. FFDM ($p = 0.047$ bzw. $p = 0.027$), jedoch nicht für das OS. Unter der neoadjuvanten RCT traten signifikant häufiger Grad 3 und 4 Toxizitäten auf als bei anderen Therapien ($p = 0.019$; 73,9% vs. 38,0%).

Die Ergebnisse bestätigen die Relevanz der neoadjuvanten Radiochemotherapie für die Verbesserung der lokalen Kontrolle (LC Rate) und der Verhinderung von Fernmetastasen (FFDM Rate) bei Patient:innen mit lokalisiertem G3-Weichgewebssarkom. Diese muss jedoch gegen die erhöhte Rate an akuten Komplikationen abgewogen werden.

Die Therapie-assoziierte Toxizität ist auch ein Teilaspekt der nachfolgenden Publikation 2.5. Hier werden im Rahmen eines Reviews die Ergebnisse einer hypofraktionierten Durchführung der neoadjuvanten Bestrahlung untersucht.

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The role of neoadjuvant radiochemotherapy in the management of localized high-grade soft tissue sarcoma

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Abstract

Background: Standard treatment of soft tissue sarcoma (STS) of the extremities includes limb-sparing surgery combined with pre- or postoperative radiotherapy (RT). The role of perioperative chemotherapy (CTX) remains uncertain. STS patients with high-risk features for local recurrence, distant metastases, and increased mortality may require additional systemic therapy. The objective of this study was to evaluate predictors of outcome regarding local control (LC), overall survival (OS), and freedom from distant metastases (FFDM) in a large single-center cohort of patients suffering from localized high-grade STS (grade 2/3, G2/G3). Special emphasis was put on a subgroup of patients who received combined neoadjuvant radiochemotherapy (RCT).

Methods: Overall, 115 adult STS patients were included in this retrospective study. The median follow-up was 34 months. Twenty-three patients (20.0%) were treated with neoadjuvant RCT, 92 (80.0%) received other therapies (adjuvant RT alone (n = 58); neoadjuvant CTX + adjuvant RT (n = 17); adjuvant RCT (n = 10), neoadjuvant RT alone (n = 7)). To assess potential prognostic factors on LC, OS, and FFDM, univariate (UVA) and multivariable (MVA) Cox proportional hazards models were applied.

Results: UVA showed significantly better LC rates in the neoadjuvant RCT group (p = 0.025), with trends in MVA (p = 0.057). The 3-year LC rate was 89.7% in the neoadjuvant RCT group vs. 75.6% in the "other therapies" group. UVA also showed significantly better OS rates in the neoadjuvant RCT group (p = 0.049), however, this was not confirmed in MVA (p = 0.205), the 3-year OS rate was 85.8% for patients treated with neoadjuvant RCT compared to 73.5% in the "other therapies" group. UVA showed significantly better FFDM rates in (p = 0.018) and a trend towards better FFDM rates in MVA (p = 0.059). The 3-year FFDM rate was 89.7% for patients treated with neoadjuvant RCT compared to 65.9% in the "other therapies" group. In the subgroup of patients with G3 STS, neoadjuvant RCT was a significant positive predictor of LC and FFDM in MVA (p = 0.047, p = 0.027) but not for OS. Overall grade 3 and 4 toxicities were significantly higher (p = 0.019) in the neoadjuvant RCT group and occurred in 73.9% vs. 38.0% in patients receiving other therapies.

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Conclusions: The results suggest that neoadjuvant RCT might improve LC and FFDM in patients with localized G3 STS while also being associated with increased acute complication rates. Further prospective research is warranted to confirm these findings.

Keywords: Soft tissue sarcoma, High-grade soft tissue sarcoma, Localized sarcoma, Sarcoma, Neoadjuvant radiotherapy, Radiochemotherapy, Prognostic factors, Univariate analysis, Multivariable analysis, Retrospective study

Highlights

- Neoadjuvant radiochemotherapy may achieve better local control in high-grade (G3) soft tissue sarcoma than other therapies.
- Neoadjuvant radiochemotherapy may achieve better freedom from distant metastases in high-grade (G3) soft tissue sarcoma than other therapies.
- Neoadjuvant radiochemotherapy is associated with higher rates of acute major complications than other therapies.

Introduction

Soft tissue sarcomas (STS) are a rare and heterogeneous group of malignant tumors accounting for less than 1% of all solid malignancies in adults [1]. The diagnosis is challenging due to the histological heterogeneity—more than 100 subtypes of STS have been described [2]. Histological tumor grading is applied according to the National Cancer Institute or the French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) [3, 4]. While STS can arise in virtually all anatomic locations, the extremities are the most frequent (43%), followed by visceral (19%) and retroperitoneal sites (15%) [5].

Therapy of STS should preferably be carried out at specialized sarcoma centers [6–8]. The multimodal therapy of localized high-grade STS includes surgery and pre- or postoperative radiotherapy (RT) [9, 10]. The role of chemotherapy (CTX) and regional hyperthermia remains controversial [11]. Most patients with localized STS show good long-term outcomes with wide excision and RT [12, 13]. However, a large proportion of patients carry unfavorable features (high-risk features) for local recurrence (LR), including positive surgical margins, presentation with locally recurrent disease or older age [14, 15]. Moreover, high-risk features for distant metastases (DM) and shorter overall survival (OS) are high-grade STS, large tumor size, and certain histological subtypes [14, 16–18].

The significance of concomitant CTX added to neoadjuvant RT in the management of STS remains unclear. Combined neoadjuvant radiochemotherapy (RCT) may increase the local effect of RT through radiosensitization and provide control of potential micrometastases [19]. However, to date, no large, randomized trial has compared neoadjuvant RCT to RT alone. We evaluated predictors of outcome for local control (LC), OS, and freedom from distant metastases (FFDM) in a large single-center cohort of patients with the initial diagnosis of localized high-grade STS (grade 2/3, G2/G3). We put special emphasis on comparing the subgroup of patients who received neoadjuvant RCT.

Materials and methods

This single-center retrospective study included adult patients initially diagnosed with localized high-grade (G2/3) STS according to the FNCLCC between 2004 and 2020. The inclusion criteria were: primary diagnosis of histopathologically confirmed and resected high-grade STS, neoadjuvant or adjuvant RT, CTX or RCT of the STS, tumor located in the extremities, pelvis, head and neck, trunk wall, retroperitoneum or intraabdominally. Exclusion criteria were metastatic or recurrent disease at the time of diagnosis, age < 18 years, the most common STS of childhood and adolescence (rhabdomyosarcoma, Ewing sarcoma) and sarcoma-like lesions (desmoid fibromatosis or dermatofibrosarcoma protuberans).

We reviewed the medical records, pathological, and radiological reports of eligible patients. The study was approved by the institutional review board (EA1/163/21). Endpoints included LC, OS, FFDM, and acute toxicities. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events version 5.0 and classified as acute if it occurred within three months or late if it occurred after three months after treatment completion [20]. Major complications were defined as grade ≥ 3 [20].

The prescribed radiation dose for a large proportion of patients was 1.8 to 50.4 Gy with a simultaneous integrated boost (SIB) of 2.0 to 56 Gy. The planned target volume included the macroscopic tumor + 3 cm transversal and 5 cm longitudinal safety margins. The additional SIB dose of 2.0 to 56 Gy was applied to the macroscopic tumor volume alone visible on planning computed tomography and t2-weighted magnetic resonance imaging.

Statistical analysis was performed using IBM SPSS Statistics 27. T-tests were two-sided. A p-value of ≤ 0.05 was considered statistically significant. A p-value

of > 0.05–≤ 0.1 was considered a trend. Group comparisons of continuous variables were done using the t-test and the Mann–Whitney U test. Dichotomization of continuous variables (Karnofsky Performance Status (KPS), age, and tumor size) was done using the median of the respective variable. Group comparisons of categorical variables was made using the Chi-square test. For time-to-event variables, the Kaplan–Meier estimate was used. Univariate and multivariable Cox proportional hazards models were performed to analyze the influence of various factors on LC, OS, and FFDM. LC, OS, and FFDM were calculated from the date of initial surgery. We incorporated the variables with significant outcomes from univariate analysis (UVA) into the multivariable analysis (MVA). In LC and FFDM analysis, patients were censored on the date of death or last contact.

Results

Patients, tumor, and treatment characteristics

Patient', tumor-, and treatment characteristics are shown in Table 1. Out of 204 initially identified STS patients, 115 patients met the eligibility criteria and were retained for analysis. The median follow-up time was 34 months (range, 3–206 months).

Patients treated with neoadjuvant RCT were younger than patients who received other therapies (mean age 52.7 vs. 60.9 years) and had larger median tumor diameters (11.0 cm vs. 8.0cm in the "other therapies" group respectively). The mean total dose of RT was higher in the "other therapies" group than in the neoadjuvant RCT group with 59.5 Gy and 54.1 Gy, respectively.

In the neoadjuvant RCT group (n = 23), most patients (n = 21, 91.3%) received a combination of doxorubicin and ifosfamide. The most common regimen (n = 14, 60.9%) consisted of three initial cycles of doxorubicin (60 mg/m^2/d for d1–d2) plus ifosfamide (3000 mg/m^2/d for d1–d3) intravenously followed by RT (50.4/56 Gy in 1.8/2 Gy fractions with a SIB) and two concomitant cycles of ifosfamide, followed by a final cycle of doxorubicin and ifosfamide. Two patients from the neoadjuvant RCT group did not receive anthracyclines due to cardiac comorbidities. The 92 patients receiving other therapies can further be subdivided into adjuvant RT (n = 58), neoadjuvant CTX plus adjuvant RT (n = 17), adjuvant RCT (n = 10) and neoadjuvant RT (n = 7).

Oncological outcomes

R0 resection was achieved in 71 of 92 (77.2%) patients receiving other therapies and 21 of 23 (91.3%) patients from the RCT group, with no statistically significant difference (p = 0.317).

After neoadjuvant RCT and resection, histological assessment found seven of 23 (30.4%) patients to not have any viable appearing tumor cells. Three patients (13%) had single vital tumor cells or one vital cell cluster < 0.5 cm, five (21.7%) had vital tumor tissue of less than 10%, two (8.7%) had viable tumor tissue of between 10 and 50% and four (17.4%) had vital tumor tissue of more than 50% at the time of surgery. All patients treated with neoadjuvant RCT showed some degree of histological tumor cell death [21].

Local control

Table 2 shows the UVA and MVA for LC. Median time to recurrence in the overall cohort was 206 months, with a 3-year LC rate of 89.7% in the neoadjuvant RCT group versus 75.6% in the "other therapies" group. LC rates were significantly higher in the neoadjuvant RCT group in UVA and there was a trend towards higher rates on MVA (p = 0.025 and p = 0.057). In G3 STS, neoadjuvant RCT was a significant factor for LC in UVA and MVA (p = 0.022 and p = 0.047). In the entire cohort, negative surgical margins (p < 0.001 and p = 0.012 on UVA and MVA) and extremity location of the tumor (p = 0.001 and p = 0.007 on UVA and MVA) were associated with a better LC.

Overall survival

Table 3 shows the UVA and MVA for OS. The median OS was 113 months after diagnosis. In the neoadjuvant RCT group, the 3-year OS rates were 85.8% compared to 73.5% in the "other therapies" group. In UVA, OS differed significantly between both groups (p = 0.049), but the finding was not confirmed in MVA (p = 0.205). However, there was a trend towards a higher OS rate among patients with G3 STS treated with neoadjuvant RCT in MVA (p = 0.068). Although R0 resection margin did show a significantly increased survival rate in UVA compared to R1 or R2 (p = 0.008), MVA did not confirm this result (p = 0.092). KPS ≥ 90% was shown to be a positive predictor of survival in both UVA and MVA (p = 0.006 and p = 0.046). Moreover, the tumor location in the extremity also correlated with better OS in G2 STS (p = 0.015 and p = 0.029 in UVA and MVA). In an alternative analysis where only patients with neoadjuvant RCT vs. neoadjuvant RT were included, a significantly better OS in favor of neoadjuvant RCT was observed in UVA and MVA in G3 tumors (p = 0.001 and p = 0.010, Additional file 1: Table 1).

Freedom from distant metastases

Table 4 shows UVA and MVA for FFDM. The median time to metastasis was 105 months with a 3-year FFDM rate of 89.7% in the neoadjuvant RCT group compared to 65.9% in the "other therapies" group. In UVA of the entire cohort, FFDM differed significantly between the

Table 1 Baseline characteristics

Characteristic	Total (N = 115)	(%)	Neoadjuvant RCT (N = 23)	(%)	Other therapies (N = 92)	(%)
Sex						
Male	62	53.9	13	56.5	49	53.3
Female	53	46.1	10	43.5	43	46.7
Mean age, years (range)	59.27 (20–95)		52.7 (23–74)		60.91 (20–95)	
Karnofsky Performance Status						
40	1	0.9	0	0	1	1.1
50	0	0	0	0	0	0
60	4	3.5	0	0	4	4.3
70	4	3.5	0	0	4	4.3
80	36	31.3	5	21.7	31	33.7
90	56	48.7	13	56.5	43	46.7
100	13	11.3	5	21.7	8	8.7
n/a	1	0.9	0	0	1	1.1
Anatomic location						
Upper extremity	10	8.7	0	0	10	10.9
Lower extremity	66	57.4	18	78.3	48	52.2
Pelvis	6	5.2	3	13	3	3.3
Head/neck	6	5.2	0	0	6	6.5
Trunk wall	15	13	1	4.3	14	15.2
Retroperitoneal	8	7	1	4.3	7	7.6
Intra-abdominal	4	3.5	0	0	4	4.3
Sarcoma Subtype						
Liposarcoma/Myxoid Liposarcoma	25	21.7	1	4.3	24	26.1
Myxofibrosarcoma	26	22.6	6	26.1	20	21.7
Undifferentiated pleomorphic sarcoma	21	18.3	5	21.7	16	17.4
Synovial cell sarcoma	12	10.4	5	21.7	7	7.6
Malignant peripheral nerve sheath tumor	8	7	1	4.3	7	7.6
Leiomyosarcoma	9	7.8	1	4.3	8	8.7
Angiosarcoma	5	4.3	2	8.7	3	3.3
Spindle cell sarcoma	3	2.6	0	0	3	3.3
Fibrosarcoma	1	0.9	0	0	1	1.1
Giant cell sarcoma	1	0.9	0	0	1	1.1
Small cell/Clear cell sarcoma	2	1.7	1	4.3	1	1.1
Epitheloid sarcoma	1	0.9	1	4.3	0	0
Myxoinflammatory fibroblastic sarcoma	1	0.9	0	0	1	1.1
Mean tumor size, cm (range)	10.63 (1.5–41.6)		10.35 (3.5–16)		10.71 (1.5–41.6)	
Tumor depth						
Superficial	14	12.2	2	8.7	12	13
Deep	85	73.9	20	87	65	70.7
n/a	16	13.9	1	4.3	14	15.2
Grade						
G2	53	46.1	8	34.8	45	48.9
G3	62	53.9	15	65.2	47	51.1
Resection margin						
R0	92	80	21	91.3	71	77.2
R1	10	8.7	1	4.3	9	9.8
R2	2	1.7	0	0	2	2.2
n/a	11	9.6	1	4.3	10	10.9
Mean single radiation dose, Gy (range)	2.1 (1.2–5.0)		1.9 (1.6–2.15)		2.13 (1.2–5.0)	

Table 1 (continued)

Characteristic	Total (N = 115)	(%)	Neoadjuvant RCT (N = 23)	(%)	Other therapies (N = 92)	(%)
Mean total radiation dose, Gy (range)	58.4 (25.0–75.7)		54.1 (48.8–60.2)		59.5 (25.0–75.7)	
Targeted therapy	1	0.9	0	0	1	1.1
Hyperthermia	22	19.1	2	8.7	20	21.7
Local recurrence/progress	27	23.5	2	8.7	25	27.2
Therapy local recurrence						
Resection	20	17.4	2	8.7	18	19.6
Radiotherapy	4	3.5	0	0	5	5.4
Chemotherapy	11	9.6	0	0	11	12
Targeted Therapy	2	1.7	0	0	2	2.2
Hyperthermia	3	2.6	0	0	3	3.3
Distant metastases	42	36.5	6	26.1	36	39.1
Lungs	33	28.7	5	21.7	28	30.4
Bones	3	2.6	0	0	3	3.3
Liver	4	3.5	0	0	4	4.3
Lymph nodes	2	1.7	1	4.3	1	1.1
Other	7	6.1	0	0	7	7.6
Therapy distantmetastases						
Resection	20	17.4	5	21.7	15	16.3
Radiotherapy	9	7.8	1	4.3	8	8.7
Chemotherapy	16	13.9	1	4.3	15	16.3
Targeted Therapy	1	0.9	0	0	1	1.1
Hyperthermia	2	1.7	0	0	2	2.2
Death	37	32.2	6	26.1	31	33.7

n/a not available

neoadjuvant RCT and "other therapies" group in favor of neoadjuvant RCT ($p = 0.018$). In the MVA there was a trend towards higher FFDM rate among patients treated with neoadjuvant RCT ($p = 0.059$). Similar to the LC rates, the FFDM for the subgroup of G3 sarcomas again indicated a positive effect of neoadjuvant RCT with significant findings for both, UVA and MVA ($p = 0.002$ and $p = 0.027$). Moreover, a higher KPS was a positive prognostic factor for FFDM in UVA ($p = 0.021$) and showed a trend in MVA ($p = 0.088$). An alternative UVA and MVA comparing neoadjuvant RCT to neoadjuvant RT alone revealed a significant and favorable contribution of neoadjuvant RCT for the FFDM rate in G3 STS ($p < 0.001$ in both UVA and MVA, Additional file 2: Table 2).

Toxicity

Data on major acute toxicity (grade ≥ 3) are shown in Table 5. No treatment-related death was observed. Data for toxicity were missing for 16 (13.9%) patients. Data on late toxicity were only available in 21 (18.2%) patients. Therefore, no detailed analysis of late toxicity was performed. Overall, major toxicity (grade 3 or 4) was significantly higher with neoadjuvant RCT compared to other therapies (73.9% vs. 38.0%, $p = 0.019$) while major hematological toxicity occurred in 12 patients (52.2%) from the neoadjuvant RCT group vs. 17 patients (18.5%) from the "other therapies" group ($p < 0.001$). Moreover, the rate of grade 4 febrile neutropenia requiring hospitalization was significantly higher under neoadjuvant RCT compared to other therapies (39.1% vs. 6.5%, $p < 0.001$). Non-hematological toxicity was limited and without statistically significant differences among both groups. Local toxicity with major wound complications (grade 3 or 4) were seen in 26.1% and 16.3% of patients under neoadjuvant RCT and other therapies, respectively ($p = 0.50$).

Discussion

Herein, we report our single institutional experience on therapeutic outcomes of neoadjuvant RCT compared to other therapy modalities for localized high-grade STS.

Optimal management of localized high-grade STS is challenging and subject of ongoing debates. Standard treatment for localized G2 or G3 STS of the extremities includes wide excision and preoperative RT [9, 10, 22]. However, on the subject of adding systemic therapy for

Table 2 Univariate and multivariable analysis of LC

Variable	All (N = 115)				G2 sarcoma (N = 53)				G3 sarcoma (N = 62)			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age (in years)												
< 61	Ref				Ref				Ref			
≥ 61	.881 (.407–1.909)	.749			.584 (.155–2.202)	.427			1.069 (.380–3.009)	.899		
Sex												
Male	Ref				Ref				Ref			
Female	.888 (.407–1.934)	.764			.386 (.113–1.318)	.129			1.896 (.686–5.244)	.218		
KPS												
< 90	Ref				Ref				Ref		Ref	
≥ 90	.595 (.275–1.289)	.188			1.249 (.365–4.274)	.724			.330 (.112-.968)	.044*	.622 (.203–1.903)	.405
Location												
Other	Ref		Ref		Ref		Ref		Ref			
Extremity	.262 (.120-.572)	.001*	.300 (.124-.724)	.007*	.151 (.040-.576)	.006*	.293 (.066–1.302)	.107	.363 (.128–1.029)	.057		
Tumor size (in cm)												
< 8.8	Ref				Ref				Ref			
≥ 8.8	1.006 (.459–2.208)	.987			1.873 (.571–6.142)	.300			.580 (.201–1.675)	.314		
Resection margin												
R0	Ref		Ref		Ref		Ref		Ref			
R1/2	6.457 (2.738–15.228)	< .001*	3.303 (1.300–8.396)	.012*	13.434 (3.433–52.567)	< .001*	7.469 (1.649–33.828)	.009*	2.00 (.258–15.479)	.507		
n/a	1.017 (.234–4.426)	.982	.411 (.086–1.972)	.266	1.640 (.170–15.817)	.669	.950 (.090–10.006)	.966	1.133 (.148–8.685)	.905		
Therapy												
Other therapy	Ref		Ref		Ref				Ref		Ref	
Neoadjuvant RCT	.191 (.045-.815)	.025*	.236 (.053–1.044)	.057	.502 (.064–3.935)	.512			.091 (.012-.708)	.022*	.116 (.014-.974)	.047*
Hyperthermia												
No	Ref				Ref				Ref			
Yes	2.245 (.888–5.674)	.087			2.982 (.780–11.396)	.110			2.071 (.554–7.748)	.279		

n/a not available

Table 3 Univariate and multivariable analysis of OS

Variable	All (N = 115)				G2 sarcoma (N = 53)				G3 sarcoma (N = 62)			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age (in years)												
< 61	Ref				Ref				Ref			
≥ 61	1.951 (.991–3.842)	.053			2.482 (.807–7.636)	.113			1.446 (.617–3.387)	.396		
Sex												
Male	Ref				Ref	.303			Ref			
Female	.853 (.442–1.646)	.636			.563 (.189–1.680)				1.271 (.554–2.915)	.572		
KPS												
< 90	Ref		Ref		Ref				Ref		Ref	
≥ 90	.386 (.197-.756)	.006*	.485 (.238-.988)	.046*	.444 (.144–1.365)	.156			.372 (.162-.858)	.020*	.577 (.232–1.432)	.236
Location												
Other	Ref				Ref		Ref		Ref			
Extremity	.532 (.271–1.042)	.066			.244 (.078-.761)	.015*	.240 (.066-.867)	.029*	.774(.305–1.963)	.590		
Tumor size (in cm)												
< 8.8	Ref				Ref				Ref			
≥ 8.8	1.356 (.707–2.603)	.359			1.369 (.459–4.079)	.573			1.246 (.545–2.852)	.602		
Resection margin												
R0	Ref		Ref		Ref		Ref		Ref			
R1/2	3.090 (1.336–7.146)	.008*	2.114 (.884–5.058)	.092	4.648 (1.429–15.113)	.011*	2.252 (.620–8.186)	.218	2.137 (.480–9.512)	.319		
n/a	.577 (.137–2.424)	.453	.477 (.113–2.010)	.313	-	-			1.561 (.362–6.731)	.550		
Therapy												
Other therapy	Ref		Ref		Ref				Ref		Ref	
Neoadjuvant RCT	.405 (.165-.994)	.049*	.544 (.212–1.394)	.205	.830 (.182–3.793)	.810			.234 (.075-.729)	.012*	.318 (.093–1.090)	.068
Hyperthermia												
No	Ref				Ref				Ref			
Yes	1.130 (.433–2.946)	.803			1.353 (.295–6.194)	.697			1.029 (.296–3.573)	.965		

n/a not available

* = $p < 0.05$,statistically significant

Table 4 Univariate and multivariable analysis of FFDM

Variable	All (N = 115)				G2 sarcoma (N = 53)				G3 sarcoma (N = 62)			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age (in years)												
< 61	Ref				Ref				Ref			
≥ 61	1.137 (.614–2.105)	.683			.732 (.186–2.883)	.655			1.038 (.507–2.125)	.918		
Sex												
Male	Ref				Ref				Ref			
Female	.744 (.399–1.387)	.352			1.112 (.323–3.823)	.866			.885 (.406–1.926)	.757		
KPS												
< 90	Ref		Ref		Ref				Ref		Ref	
≥ 90	.476 (.253–.895)	.021*	.569 (.298–1.087)	.088	2.361 (.488–11.419)	.285			.306 (.143–.652)	.002*	.496 (.219–1.135)	.093
Location												
Other	Ref				Ref				Ref			
Extremity	.818 (.415–1.612)	.561			1.893 (.399–8.971)	.421			.535 (.250–1.143)	.106		
Tumor size (in cm)												
< 8.8	Ref				Ref				Ref			
≥ 8.8	1.282 (.686–2.394)	.436			.766 (.197–2.977)	.700			1.284 (.609–2.704)	.511		
Resection margin												
R0	Ref				Ref				Ref			
R1/2	1.443 (.510–4.086)	.489			2.092 (.417–10.490)	.370			1.780 (.415–7.644)	.438		
n/a	.624 (.188–2.072)	.441			-	-			1.724 (.519–5.727)	.374		
Therapy												
Other therapy	Ref		Ref		Ref				Ref		Ref	
Neoadjuvant RCT	.344 (.141-.836)	.018*	.415 (.166–1.036)	.059	.965 (.195–4.767)	.965			.182 (.061-.540)	.002*	.267 (.083-.862)	.027*
Hyperthermia												
No	Ref				Ref				Ref			
Yes	1.890 (.857–4.171	.115			2.510 (.514–12.258)	.256			1.800 (.714–4.541)	.213		

n/a **not available**

Table 5 Acute toxicity (greater than grade 2) according to the Common Terminology Criteria for Adverse Events version 5.0.

Toxicity	Neoadjuvant RCT n (%)		Other therapies n (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematological				
Anemia	4 (17.4)	0 (0)	9 (9.8)	1 (1.1)
Leukopenia	3 (13)	3 (13)	2 (2.2)	3 (3.3)
Lymphocytopenia	7 (30)	1 (4.3)	7 (7.6)	1 (1.1)
Neutropenia	0 (0)	9 (39.1)	1 (1.1)	6 (6.5)
Thrombocytopenia	3 (13)	1 (4.3)	1 (1.1)	1 (1.1)
Overall hematological	12 (52.2%) (Grade 3 + 4)		17 (18.5%) (Grade 3 + 4)	
Fatigue	3 (13)	0 (0)	4 (4.3)	0 (0)
Gastrointestinal				
Nausea	1 (4.3)	0 (0)	5 (5.4)	0 (0)
Dysgeusia	0 (0)	0 (0)	1 (1.1)	0 (0)
Dysphagia	0 (0)	0 (0)	1 (1.1)	0 (0)
Dermatological				
Erythema	0 (0)	0 (0)	3 (3.3)	0 (0)
Radiodermatitis	2 (8.7)	0 (0)	2 (2.2)	0 (0)
Hyperpigmentation	0 (0)	0 (0)	3 (3.3)	0 (0)
Epitheliolysis	0 (0)	0 (0)	2 (2.2)	0 (0)
Lymphedema	0 (0)	0 (0)	3 (3.3)	0 (0)
Inflammation				
Mucositis	1 (4.3)	0 (0)	1 (1.1)	1 (1.1)
Stomatitis	2 (8.7)	0 (0)	0 (0)	0 (0)
Neurological				
Psychosis	0 (0)	0 (0)	1 (1.1)	0 (0)
Wound complication	6 (26.1)	0 (0)	10 (10.9)	5 (5.4)
Other	1 (4.3)	0 (0)	1 (1.1)	1 (0)

No grade 5 toxicity was observed

patients with high-risk features guidelines still recommend individual assessment in multidisciplinary tumor boards due to a lack of phase III data comparing RCT to RT alone [9, 10, 14–18]. Taken together, patients with high-risk features constitute a substantial proportion of STS cases and therefore may require detailed prognostic evaluation and additional therapy [18, 23]. Although RCT is not considered standard of care, many rationales exist for adding CTX to RT for high-risk STS patients: intensification of treatment may decrease LR (1); lower risk of distant recurrence (DR) and improve OS (2); improve symptom control (pain relief) (3); therapeutic effects by CTX including radiosensitization allowing reduction of RT doses, thus lowering wound complication rates (4) [9, 10, 23–26].

Generally, our data support these rationales by showing favorable 3-year LC rates of 89.7% compared to 75.6% in the "other therapies" group. Particularly in patients with G3 sarcomas, RCT appears to have positive contributions. The high LC rates support previously published data including the pilot phase II study on neoadjuvant RCT by DeLaney et al. conducted at the Massachusetts General Hospital (MGH) in 2003 [19, 27–29]. With an RCT regimen consisting of 44 Gy of normofractionated preoperative RT with interdigitated CTX (mesna, Adriamycin (doxorubicin), ifosfamide and dacarbazine (MAID protocol)), the authors achieved remarkable LC rates in a total of 48 patients (5-year LC: 92%). One possible explanation for the better LC through neoadjuvant RCT in both, the present trial and the MGH trial, lies in the tendency of a higher rate of R0 resections observed in the neoadjuvant RCT groups (91.3% (n = 21) in the present trial and 85.4% (n = 41) in the MGH trial) compared to other therapies (77.2% in the present trial and 81.25% (n = 39) in the MGH trial), although the difference was not significant in the present trial [29]. A subsequent trial at MGH, also applying the MAID regimen, found comparable results [19]. Furthermore, a more recent retrospective single-center analysis on neoadjuvant RCT by Byun et al. observed similar results with successful resection rates (72.4% R0 (n = 21), 27.6% close margin (< 1 mm, n = 8), no cases of R1 resection) and subsequently good LC rates (86.7% at 5 years) [30]. Positive surgical margins are an established risk factor for LR and are therefore considered a high-risk feature [14, 15, 31–33]. Accordingly, R1 or R2 resection had a significant negative prognostic value on LC in the entire cohort in the present study (p = 0.012 in MVA). Moreover, once patients present with recurrent disease their mortality rates increase substantially [14, 34].

Our results confirm previous data and support the combination of CTX and RT in the preoperative setting to improve the chance of R0 resection, thereby lowering the risk of LR and mortality [23, 35]. However, conducting large, well-designed phase III randomized trials for rare malignancies remains challenging and cost-intensive.

With regards to survival, we found neoadjuvant RCT to be supportive by gaining 12.3% of OS at 3 years (85.8% compared to 73.5% with other therapies). A positive effect was also shown in UVA of predictive factors for OS in G3 sarcomas (p = 0.012) and showed a trend in MVA (p = 0.068). Similarly, DeLaney et al. found a substantial OS increase of 29% at 3-years in patients treated with neoadjuvant RCT compared to historical controls treated with RT and resection alone (87% vs. 58% (n = 48 in both groups), p = 0.0003). Even seven years after treatment, the survival benefit of the intensive RCT regimen in the MGH study sustained (36). The subsequent MGH trial applying the MAID regimen CTX together with preoperative RT confirmed the favorable results [19]. Interestingly, in the Radiation

Therapy Oncology Group (RTOG) 9514 trial, where a treatment regimen very similar to DeLaney et al. was used on 64 patients, the OS was poorer (3-year OS of 75.1%) [29, 36]. The median tumor size and histological subtypes were balanced in both trials [29, 36]. The increase in mortality compared to our study and the MGH trial was most likely associated with the higher proportion of G3 sarcomas (80% (n = 51) in RTOG9514 vs. 48% (n = 23) in the MGH trial vs. 65.2% (n = 15) in our study).

A different systemic approach to be mentioned is the addition of radiosensitizing agents to RT of STS such as the poly ADP ribose polymerase inhibitor olaparib. Preliminary data from an ongoing phase Ib trial testing olaparib with normofractionated external beam RT on a cohort of 41 unresectable STS have shown promising tumor responses with favorable toxicity profiles at the six months interim analysis [37]. Although these agents have been used for unresectable STS, the first results warrant further trials testing these agents [37, 38].

High histological grade and large tumor size are independent adverse prognostic factors for OS and may therefore also be considered high-risk features requiring additional measures such as adding CTX to RT to improve patients' outcomes [14, 18, 23, 39]. We found a promising 3-year FFDM rate of 89.7% in the neoadjuvant RCT group (vs. 65.9% by other therapies) with a significant finding in the UVA (p = 0.018) and a trend in MVA (p = 0.059) of the cox regression analysis. Particularly in the G3 sarcoma subgroup, neoadjuvant RCT significantly reduced the hazard ratio for distant metastasis (p = 0.002 in UVA, p = 0.027 in MVA). This data suggests promising effects of preoperative RCT and warrants further, comparative studies with a well-matched control arm treated with preoperative RT alone.

The foremost concerns of adding CTX to preoperative RT are increased systemic toxicity by CTX and higher wound complication rates.

After applying a median total dose of 56 Gy, in a mean single dose of 1.9 Gy/fraction in the RCT group and 60.2 Gy, 2 Gy/fraction in the "other therapies" group, we found no significant differences in wound complication rates among both groups (26.1% in preoperative RCT vs. 16.3% (p = 0.50) by other therapies) thereby affirming previous data on wound complications in preoperative RT [40]. Moreover, the use of SIB radiation did not lead to high rates of wound complications which was also observed in more recent retrospective data on localized extremity STS comparing sequential boost radiation to SIB radiation [41]. Although preoperative RT causes higher wound complication rates, postoperative RT leads to irreversible fibrosis-related toxicities adversely affecting patients' limb function, which caused an increasing notion of preferring pre-over postoperative RT among radiation oncologists [22, 40, 42–44].

While the threat of increased acute local RT-related toxicity was not confirmed in our trial, neoadjuvant RCT did correlate with a significant increase in overall acute major toxicity (73.9% vs. 38.9% in "other therapies", p = 0.019) and hematological toxicity (52.2% vs. 18.5% in "other therapies", p < 0.001). In the RTOG 9514 trial, a modified MAID regimen with higher ifosfamide dose (2500 mg/m^2 vs. 2000 mg/m^2 in the MGH trial) was applied, which caused higher overall and hematological toxicity compared to the MGH trial (e.g., grade 4 leukopenia: 73.4% versus 35.4% in RTOG9514 (28, 35)). Although the present trial applied even higher doses of ifosfamide (3000 mg/m^2) in the RCT group, grade 3 or 4 hematological toxicity of 52.2% were remarkably lower compared to 91% grade 3 or 4 hematological toxicity in the RTOG 9514 trial. The neoadjuvant RCT did cause higher rates of febrile neutropenia requiring hospitalization compared to the MGH trial (39.1% vs. 6.5% , respectively). However, no treatment-related deaths occurred (28). It is our impression that these differences in toxicity may be attributed to dacarbazine not being administered in our study. Apparently, not using dacarbazine did not negatively affect the outcome and may be the reason for the reduced toxicity when compared to the RTOG 9514 trial (35). Chowdhary et al. also noted a lower complication rate without dacarbazine (43).

Despite the existing toxicity, comprehensive trials investigating histology subtype-specific CTX regimens and an altered number of CTX cycles found three cycles of anthracycline/ifosfamide to remain the best option in terms of oncological outcomes for localized STS with high-risk features [39, 45–48]. Future trials comparing neoadjuvant RCT to RT alone in localized STS with high-risk features should therefore include three cycles of anthracycline/ifosfamide based CTX and standard preoperative RT regimen consisting of 1.8–2.0 Gy/fraction to a total dose of 50 to 50.4 Gy in 25–28 fractions delivered over 5–6 weeks [49].

Limitations

The current findings should be interpreted in light of the following limitations. Firstly, STS are a highly heterogeneous group of malignant tumors. This is a retrospective study conducted at a single institution and therefore prone to different types of bias (e.g. sampling bias). Moreover, our neoadjuvant RCT cohort's sample size was relatively small (n = 23, 20% of the entire cohort). In addition, the fact that patients treated with neoadjuvant RCT were fitter, yet had larger median (but not mean) tumor diameters than those who received other therapies, might have interfered with the interpretation of the therapy

outcomes of this study. Another important limitation is the heterogeneity of treatment regimens with SIBs in a large proportion of patients and the heterogeneity of the "other therapies" group. However, this does reflect the current diversity of perioperative treatment strategies for STS in everyday clinical setting.

Conclusions

The current retrospective study found significantly lower LR and DM rates in adult patients with localized G3 STS undergoing neoadjuvant RCT. Nevertheless, the significant increase in major complication rate remains an important concern in the implementation of neoadjuvant RCT as the standard perioperative management of STS. Further prospective and comparative studies are warranted to validate our findings.

Abbreviations

BIH: Berlin Institute of Health; CTX: Chemotherapy; DM: Distant metastases; FFDM: Freedom from distant metastases; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; KPS: Karnofsky Performance Status; LC: Local control; LR: Local recurrence; MAID: Mesna, Adriamycin (doxorubicin), ifosfamide and dacarbazine; MGH: Massachusetts General Hospital; MVA: Multivariable analysis; OS: Overall survival; RCT: Radiochemotherapy; RT: Radiotherapy; RTOG: Radiation Therapy Oncology Group; SIB: Simultaneous integrated boost; STS: Soft tissue sarcoma; UVA: Univariate analysis.

Supplementary Information

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Additional file 1. Supplementary table 1. Univariate and multivariable analysis of OS for G3 sarcoma. n/a (not available).

Additional file 2. Supplementary table 2. Univariate and multivariable analysis of FFDM for G3 sarcoma. n/a (not available).

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Authors' contributions

Conceptualization: MK, AF, SR and DK; investigation, data acquisition and analysis: MK and DK; writing—original draft preparation: MK, AF, SR, FE and DK; writing—review and editing: MK, SR, FE, AF, JKS, FB, SM, DR, SW, RÖ and DK; visualization, MK, AF, SR, FE and DK; supervision: DK. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

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Declarations

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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2.5 Preoperative hypofractionated radiotherapy for soft tissue sarcomas: a systematic review.

Roohani S, Ehret F, Kobus M, Flörcken A, Märdian S, **Striefler JK**, Rau D, Öllinger R, Jarosch A, Budach V, Kaul D. Preoperative hypofractionated radiotherapy for soft tissue sarcomas: a systematic review. Radiat Oncol. 2022 Sep 14;17(1):159. doi: 10.1186/s13014-022-02072-9. PMID: 36104789; PMCID: PMC9472188.

Weichgewebssarkome repräsentieren eine heterogene Gruppe seltener mesenchymaler Tumore. Die neoadjuvante Behandlung lokalisierter high-grade Sarkome umfasst in der Regel eine 5- bis 6-wöchige präoperative Strahlentherapie (Radiotherapie, RT) mit anschließender Resektion. Die Verkürzung der präoperativen Bestrahlungszyklen durch eine Hypofraktionierung scheint sich nach aktuellem Wissensstand bei anderen soliden Tumorerkrankungen jedoch weder negativ auf die Toxizität noch auf das onkologische Ergebnis auszuwirken[72], [73].

Stattdessen kann durch die Verkürzung der RT-Zyklen neben der Therapieadhärenz auch die Kosteneffektivität gesteigert und eine Erweiterung der Behandlungsoptionen erzielt werden. In Publikation 2.5 werden die vorliegende Evidenz für präoperative hypofraktionierte RT (HFRT) zusammengefasst und deren Einfluss auf das Behandlungsergebnis sowie die Toxizität im Vergleich zu einer normofraktionierten RT diskutiert.

Hierfür erfolgte unter Verwendung mehrerer klinischer Datenbanken (PubMed, Cochrane library, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Embase und Ovid Medline) eine systematische Analyse derjenigen klinischen Studien, welche das Outcome der neoadjuvanten HFRT beim Weichgewebssarkom beschreiben.

Insgesamt wurden 8 Phase II Studien und 5 retrospektive Analysen ausgewertet. Davon waren in insgesamt 8 Untersuchungen 5x5 Gy präoperativ bei Patient:innen mit high-grade Sarkomen appliziert worden.

Unter der HFRT zeigte sich im Vergleich mit historischen Kontrollen, in welchen eine normofraktionierte RT durchgeführt wurde, keine Erhöhung der Nebenwirkungsrate. Stattdessen war die Toxizität überwiegend ähnlich oder sogar niedriger als in den Studien mit normofraktionierter RT. Darüber hinaus konnte eine vergleichbare lokale Kontrolle (LC) bei insgesamt kürzerer Therapiedauer erzielt werden.

Zusammenfassend zeigen die analysierten retrospektiven Daten sowie die Phase II Studien, dass eine präoperative HFRT eine gute Behandlungsoption für diese Patient:innenpopulation ist. Sowohl das onkologische Ergebnis als auch das Toxizitätsprofil waren vorteilhaft. Bisher gibt es hierzu keine randomisierte Phase III

Studie, jedoch sind derzeit über 15 prospektive Studien zu HFRT + / – Chemotherapie aktiv, welche voraussichtlich weitere Erkenntnisse bezüglich akuter und später Toxizitäten erbringen werden.

In der o.g. Analyse wird die Hypofraktionierung nicht nur hinsichtlich ihrer therapeutischen Ergebnisse diskutiert. Ein weiterer und sehr wichtiger Aspekt ist die positive Auswirkung auf die Lebensqualität, da die Strahlentherapie ohne Erhöhung der Toxizität in kürzerer Zeit durchgeführt und abgeschlossen werden kann. Dies kann zu einer verbesserten Therapieadhärenz beitragen, welche die Effektivität der therapeutischen Bemühungen maßgeblich beeinflusst. So kann die Behandlung der Tumorerkrankung nur dann realisiert werden, wenn der:die Erkrankte sich in einem ausreichenden Allgemeinzustand befindet und aktiv dazu beiträgt. Das umfasst neben den regelmäßigen Aufenthalten in medizinischen Einrichtungen zur Therapiedurchführung auch die allgemeine Lebensführung. Noch viel zu selten liegt der Fokus neben der Kontrolle der Tumorerkrankung auf der jeweiligen Lebensqualität. Der Erhalt derselben ist aber für die Umsetzbarkeit der Therapiekonzepte von maßgeblicher Bedeutung. Hiermit beschäftigt sich Publikation 2.6, in welcher der Einfluss der Palliativ- bzw. Supportivtherapie auf den Erkrankungsverlauf untersucht wird.

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Radiation Oncology

REVIEW Open Access

Preoperative hypofractionated radiotherapy for soft tissue sarcomas: a systematic review

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Abstract

Background: Soft tissue sarcomas (STS) represent a diverse group of rare malignant tumors. Currently, five to six weeks of preoperative radiotherapy (RT) combined with surgery constitute the mainstay of therapy for localized high-grade sarcomas (G2–G3). Growing evidence suggests that shortening preoperative RT courses by hypofractionation neither increases toxicity rates nor impairs oncological outcomes. Instead, shortening RT courses may improve therapy adherence, raise cost-effectiveness, and provide more treatment opportunities for a wider range of patients. Presumed higher rates of adverse effects and worse outcomes are concerns about hypofractionated RT (HFRT) for STS. This systematic review summarizes the current evidence on preoperative HFRT for the treatment of STS and discusses toxicity and oncological outcomes compared to normofractionated RT.

Methods: We conducted a systematic review of clinical trials describing outcomes for preoperative HFRT in the management of STS using PubMed, the Cochrane library, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Embase, and Ovid Medline. We followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Trials on retroperitoneal sarcomas, postoperative RT, and hyperthermia were excluded. Articles published until November 30th, 2021, were included.

Results: Initial search yielded 94 articles. After removal of duplicate and ineligible articles, 13 articles qualified for analysis. Eight phase II trials and five retrospective analyses were reviewed. Most trials applied 5 × 5 Gy preoperatively in patients with high-grade STS. HFRT courses did not show increased rates of adverse events compared to historical trials of normofractionated RT. Toxicity rates were mostly comparable or lower than in trials of normofractionated RT. Moreover, HFRT achieved comparable local control rates with shorter duration of therapy. Currently, more than 15 prospective studies on HFRT +/− chemotherapy are ongoing.

Conclusions: Retrospective data and phase II trials suggest preoperative HFRT to be a reasonable treatment modality for STS. Oncological outcomes and toxicity profiles were favorable. To date, our knowledge is mostly derived from phase II data. No randomized phase III trial comparing normofractionated and HFRT in STS has been published yet. Multiple ongoing phase II trials applying HFRT to investigate acute and late toxicity will hopefully bring forth valuable findings.

Keywords: Soft tissue sarcoma, Sarcoma, Radiotherapy, Hypofractionation, Preoperative radiotherapy, Neoadjuvant radiotherapy, Toxicity, Wound complications

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Introduction

Soft tissue sarcomas (STS) are a heterogenous group of malignant tumors arising from mesenchymal tissue in virtually all anatomic locations and age groups [1, 2]. STS account for less than 1% of all tumor entities in adults and 7% in pediatric patients [3, 4]. The estimated incidence rate in Europe is 4–5 per 100 000 per year [5]. The World Health Organization applies two standard histopathological grading systems for STS based on histological, morphological and molecular characteristics [6–8]. This review will analyze data on adult patients with STS of the extremities and trunk and exclude retroperitoneal STS and trials on hyperthermia, which are discussed elsewhere [9, 10].

Owing to STS heterogeneity, the disease-associated morbidity and mortality are highly variable. Positive surgical margins, recurrent disease at presentation, histological grade, tumor depth, and previous local recurrences (LR) are independent risk factors for subsequent recurrences and mortality [11–14]. Moreover, specific histological subtypes, e.g., malignant peripheral nerve sheath tumors or myxofibrosarcomas, are associated with unfavorable clinical outcomes [11, 12, 15, 16]. In high-grade STS (G2-G3), current standard of care comprises surgery combined with preoperative conventionally fractionated RT, preferably carried out in sarcoma reference centers [17–19]. Preoperative (neoadjuvant) conventionally fractionated RT is applied over five to six weeks in daily fractions of 1.8–2.0 Gy to a total dose of 50–50.4 Gy [18, 20]. The role of perioperative chemotherapy remains controversial and depends on the above-mentioned risk factors [21]. Although preoperative RT causes higher wound complication rates, postoperative RT leads to irreversible fibrosis-related toxicities adversely affecting patients' function. This has caused an increasing notion of preferring pre- over postoperative RT among radiation oncologists [22–26].

In daily practice, single doses higher than 2.2 Gy are usually considered as hypofractionated radiotherapy (HFRT), although no exact definition exists. It has been hypothesized that increasing radiation doses per fraction would raise the toxicity rate in normal tissue [27, 28]. Therefore, HFRT was mainly applied in palliative settings where fast symptom relief (e.g., pain relief in bone metastases) and lower total doses than in definitive RT settings are required. However, within the last two decades, further evidence on the efficacy and safety of hypofractionated therapy regimens has come from RT trials of breast cancer, prostate cancer, and rectal cancer, where hypofractionation is now routinely applied [29–31].

When comparing outcomes of different clinical trials, it is essential to bear in mind that over the last decades, RT has been—and is to this date—subject to tremendous technological advances. Technical innovation in all sections of radiation oncology (imaging, treatment planning, linear accelerators) have remarkably improved radiation precision and tolerability [32–34]. In line with this, a more recent trial applying modern radiation techniques and image guidance has shed new light on RT in STS: By using advanced and more precise radiation techniques, the investigators were able to reduce toxicity rates in preoperative, normofractionated RT for STS (10.5% of at least one grade ≥ 2 toxicity at two years vs. 35% in the SR-2 trial) [35].

Another rationale in favor of hypofractionation is based on radiobiological observations in STS. STS like liposarcomas and rhabdomyosarcomas are likely to have lower α/β ratios (<10), making them rather sensitive to larger fraction sizes [36–38]. Rather interestingly, other tumor entities with similar α/β ratios of less than 10 (e.g., breast and rectal cancer) have shown similar local control (LC) rates after HFRT as compared to conventionally fractionated RT [39, 40].

Supporters of HFRT also argue with practical advantages of this therapy regimen. The treatment of STS at specialized, multidisciplinary sarcoma centers has shown beneficial outcomes for patients and improves overall survival (OS) [19, 41–43]. By shortening RT courses through hypofractionation without compromising patient outcomes, access to high-volume sarcoma centers can be particularly improved for immobile, frail, and elderly patients [44]. Shortening RT regimens is not only preferred by patients; it also reduces the economic burden on the health care system while increasing patient throughput at high-volume centers [45–49]. Especially during the COVID-19 pandemic, when medical care is less widely available, and patient contact is aimed to be reduced to a minimum, hypofractionation may constitute a preferred treatment modality [50].

To the best of our knowledge, no review has systematically analyzed the literature on preoperative HFRT regimens for STS treatment. To address this topic and give deeper insights into the advantages and drawbacks of hypofractionation, we conducted a systematic review of the literature to assess patient outcome parameters, toxicity rates, and feasibility. The current evidence and findings for preoperative HFRT in the treatment of STS in adults are summarized herein.

Materials and methods

A systematic review of the literature was performed in accordance to the guidelines of the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, PRISMA 2020 study protocol checklist, Additional file 1: The PRISMA 2020 checklist, supplementary materials) [51]. The databases

Table 1 Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Study design	Any except narrative reviews and systematic reviews	Systematic reviews Narrative reviews
Population	Age: ≥ 18 years	Pediatric patients (< 18 years)
	Sex: Any	Retroperitoneal sarcoma
	Race: Any	
	Disease: Soft tissue sarcomas located at the extremities and/or trunk	Other location than extremity or trunk
	Histological grade: Any	
	Stage: Localized	
Intervention	Hypofractionated RT (> 2.2 Gy/fraction/day) Neoadjuvant RT Neoadjuvant and/or adjuvant chemotherapy Surgical resection	Normofractionated RT (1.8–2.2 Gy/fraction) Hyperfractionated RT (< 1.8 Gy/fraction) Hyperthermia Postoperative RT (trials adding postoperative boost to preoperative RT were not excluded)
Outcomes	Acute toxicity including wound complications Late toxicity OS DFS LC LR LRFS	
Date range	Until November 30th, 2021	

DFS disease-free survival, *LC* local control, *LR* local recurrence, *LRFS* local recurrence-free survival, *OS* overall survival, *RT* radiotherapy

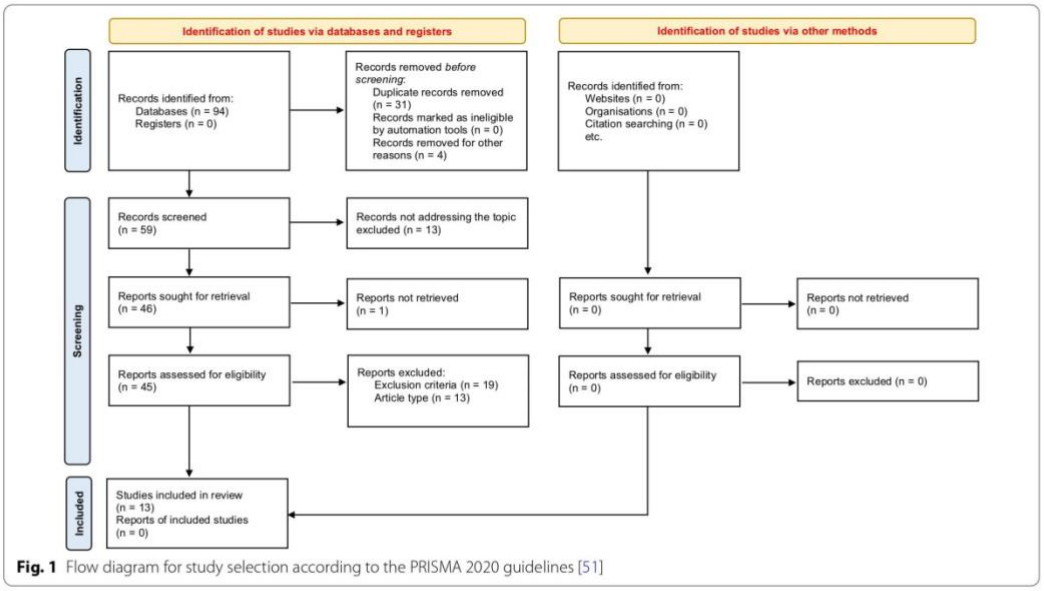

Fig. 1 Flow diagram for study selection according to the PRISMA 2020 guidelines [51]

PubMed, ClinicalTrials.gov, the Cochrane library and the Cochrane Central Register of Controlled Trials, Embase, and Ovid Medline were used. Variably combined search items included "hypofractionation", "soft tissue sarcoma", "radiotherapy", "trunk and extremity sarcoma", "neoadjuvant radiotherapy", "oncological outcomes", "wound complication", "toxicity", "safety", "feasibility" and "efficacy". For ongoing clinical trials,

the ClinicalTrials.gov webpage was used with the following search items: "soft tissue sarcoma", "hypofractionated radiotherapy" and "radiotherapy". Databases were searched on November 30th, 2021 (Table 1). No filters or limits were applied. All English studies published before November 30th, 2021, were included. The first reviewer (S.R.) excluded duplicates, trials on hyperthermia or postoperative RT (trials adding postoperative boost to preoperative RT were not excluded), trials not matching the search items and trials on retroperitoneal sarcomas (due to their profound differences regarding the clinical course, treatment, and histological subtypes). The following types of articles were included: randomized controlled trials, open-label trials, retrospective analyses, phase II and III clinical trials, as well as single and multicenter trials applying preoperative HFRT on adults (≥ 18 years) with STS. This review was not registered.

Data items

The data items extracted from all eligible studies were author list, publication date, number of patients, patient demographics, histological subtypes of STS, anatomical locations, median tumor size, dose per fraction, number of fractions, time from RT to surgery and from surgery to RT, chemotherapy regimens, median follow-up, overall survival, local control, local recurrence, local recurrence-free survival (LRFS), progression-free survival (PFS), disease-free survival (DFS), wound complication (WC)- and late toxicity rates. If an article lacked any data on the aforementioned items, the specific field was left blank in the summary table resulting in lower validity and comparability of the respective trial. After initial selection of data items by the first reviewer (S.R.), the second reviewer (D.K.) checked for suitability and accuracy.

Quality control and assessment

To ensure adequate quality standards for included articles, both the titles, abstracts, and full texts were thoroughly examined by the first reviewer. All resources obtained online were saved as PDF files in case the online record was edited or removed. Risk of bias was assessed individually for every study by using the Risk of Bias In Non-randomized Studies of Interventions tool (ROBINS-I) developed by the Cochrane Bias Methods Group [52] (Additional file 2: Risk of bias assessment according to ROBINS-I, Table 1). After initial evaluation by the first reviewer, the second reviewer then critically edited the bias assessment, list of results, data and added further articles, if required. In cases of uncertainty, the third reviewer (F.E.) gave critical input.

Results

The PRISMA flow diagram depicted in Fig. 1 shows all initial search results, excluded articles and the final number of articles meeting the inclusion criteria. Systemically reviewed studies on preoperative hypofractionated radiotherapy are summarized in Table 2; major studies on conventionally fractionated radiotherapy are summarized in Table 3.

Discussion

Herein, we review the current literature on preoperative HFRT in the management of STS. The most frequently voiced criticism of this treatment approach concerns the following points: (i) the possibilty of increased toxicity with pre- and postoperative complications; (ii) assumed worse oncological outcomes compared to standard fractionated RT; (iii) financial concerns due to the reduced number of therapy sessions in HFRT [72, 73]. From a logistical and health economic standpoint, HFRT is undoubtedly the preferred and better applicable treatment modality for all patients and age groups seeking care at sarcoma centers [41, 42, 44]. Regional hyperthermia has historically been used in combination with chemotherapy showing promising results for the treatment of STS [74–78]. Combined with neoadjuvant chemotherapy, regional hyperthermia improves OS and local progression-free survival for patients with localized high-grade STS [79, 80]. As part of a first study, hypofractionated radiotherapy was combined with hyperthermia on 30 patients with marginally or unresectable, mostly G1 STS. This phase II feasibility study from the Warsaw sarcoma center by Spałek et al. met its primary endpoint of testing feasibility as it was well tolerated and adherence to the therapy protocol was successful [81]. Due to the scope of the present review to describe and compare preoperative HFRT to current standard treatment (normo-fractionated RT), trials on regional hyperthermia were not included.

Acute and late toxicity

The first and foremost concern about increased early and late toxicity with HFRT cannot be confirmed based on the available data. Firstly, to define major WCs, most trials adopted their definition from the largest phase III trial (SR-2 trial) that compared toxicity rates in pre- vs. postoperative normofractionated RT. In this trial, a major WC was defined as a second surgery under general or regional anesthesia for wound repair up to four months after primary surgery. Additionally, aspiration of seromas, readmission for wound care such as intravenous antibiotics or persistent deep packing for 120 days or beyond were included in that definition [26]. Preoperative RT was

Table 2 Results. The table summarizes the current literature on preoperative hypofractionated RT for STS

Author	Year and country	Type of trial and inclusion criteria	N	Median age (years)	Sex ratio (♀:♂ in %)	Histologic grade	Location	Median tumor diameter	Fraction and dose; target Volume	EQD2/BEDα/β of 4 (Gy)
Kosela-Paterczyk et al. [53]	2021 Poland	Phase II single center trial Localized G2-G3 STS or G1 if >10cm	311	57	52 : 48	G1-2: 9.7% G3: 84.1% Unknown: 6.2%	LE: 72% UE: 16.7% Trunk: 11.3%	10 cm	5 x 5 Gy = 25 Gy CTV = GTV + 2cm transv.; + 4cm long. PTV = CTV + 0.7-1cm	37.5 Gy/ 56.3 Gy
Spalek et al. [54]	2021 Poland	Phase II single center trial Localized, marginally resectable G2-G3 STS	46	58	37 : 63	G2: 34.8% G3: 65.2%	LE: 63% UE: 15% Trunk: 22%	17.4 cm	5 x 5 Gy = 25 Gy CTV = GTV + 2cm transv.; + 4cm long. PTV = CTV + 0.7-1cm	37.5 Gy/ 56.3 Gy
Leite et al. [55]	2021 Brazil	Phase II single center trial Localized, extremity G2-G3 STS > 10 cm	25	42	44 : 56	G1-2: 21.7% G3: 78.3 %	LE: 60% UE: 40%	14 cm Pre-SBRT 10.5 cm Post-SBRT	5 x 8 Gy = 40 Gy CTV = GTV + 0.3-0.5 cm radial; + 2-3 cm long. PTV = CTV + 0.3cm	80 Gy/120 Gy
Potkrajcic et al. [56]	2021 Germany	Retrosp. Analysis Age >75 yrs., G2-G3 STS, localized on extremity/trunk	18	83.7	N/A	G2: 33.3% G3: 55.6% G2-3: 5.6% Unknown: 5.6%	LE: 55.6% UE: 27.8% Trunk: 16.6%	7.9 cm	5 x 5 Gy = 25 Gy CTV = GTV + 1.5cm radial; + 3cm long. PTV = CTV + 0.5-1 cm	37.5 Gy/ 56.3 Gy
Silva et al. [57]	2021 Brazil	Phase II single center trial Age 18-75, localized STS, not amenable to resection	18	53.5	56 : 44	G2: 11% G3: 89%	LE: 67% UE: 33%	8.9 cm	5 x 5 Gy = 25 Gy CTV = GTV + 1.5cm radial; + 4cm long. PTV = CTV + 1cm	37.5 Gy/ 56.3 Gy

Table 2 (continued)

RT modality	CTX	Time to surgery	Median FU (mths)	OS	LR	LC	LRFS	DFS	Acute toxicity	Late toxicity
3D-CRT: 95.8% IMRT: 3.9% VMAT: 0.3 % IGRT: 100%	30.2 % pre-OP AI or doxo/DTIC	2-4 days	57.3	63% 5 yrs	13.8% 5 yrs	N/A	N/A	46% 5 yrs.	Major WC: 24%:	Overall: 8.6%
3D-CRT: 6.5% VMAT: 41.3% IMRT: 52.2% IGRT: 100%	AI 3 cycles	6-8 weeks	24.4	53% 3 yrs	3 of 41 resected tumors (7%)	N/A	67% 2 yrs	N/A	Major WC: 34%. Overall: °1-°4: 44%	pending
SBRT IMRT VMAT IGRT	20% pre-op	8.6 weeks (median)	20.7	≈ 85% 3 yrs	0% 2 yrs	N/A	≈ 85% 3 yrs	N/A	Major WC: 28% 2°: Dermatitis: 48% Edema: 8% 3° Dermatitis:20%	1°: Fibrosis: 34.7% Edema: 21.7% 2°: Fibrosis: 4.3% Edema: 4.3% Stiffness: 13%
3D-CRT > IMRT/ VMAT	No	4.1 weeks (median)	5.1	100%	2 of 17 followed pts (11.8%)	92% 6 mths	N/A	84% 6 mths	Major WC: 29%	N/A
3D-CRT IMRT	AI 3 cycles	6 weeks (median)	29	95%	N/A	95%	N/A	72%	Major WC: 33%	1°: Fibrosis: 50% Stiffness: 16% Edema: 11% 2°: Fibrosis: 6% Stiffness: 6% Edema: 11%

Author	Year and country	Type of trial and Inclusion criteria	N	Median age (years)	Sex ratio (♀:♂ in %)	Histologic grade	Location	Median tumor diameter	Fraction and dose; target volume	EQD2/BEDα/β of 4 (Gy)
Kosela-Paterczyk et al. [58]	2020 Poland	Phase II single center trial Localized extremity or trunk MLPS, ≥ 5cm	27	43	48 : 52	Myxoid liposarcoma only G1-G2: 66.6% G3: 33.3%	LE only	13 cm	5 x 5 Gy = 25 Gy CTV = GTV + 2cm transv.; +4cm long. PTV = CTV + 0.7-1cm	37.5 Gy/ 56.3 Gy
Kalbasi et al. [47]	2020 USA	Phase II single center trial Localized extremity or trunk STS	50	<50: 28% 50-64: 22% 65-79: 40% >79: 10%	44 : 56	G1: 2 % G2: 38 % G3: 60 %	LE: 68% UE: 18% Trunk: 14%	26% ≤5 cm 50% >5 - ≤10 cm 24% >10 cm:	5 x 6 Gy = 30 Gy CTV = GTV + 1.5cm transv.; + 3cm long. PTV = CTV + 0.5cm	50 Gy/75 Gy

Table 2 (continued)

Author	Year and country	Type of trial and Inclusion criteria	N	Median age (years)	Sex ratio (♀:♂ in %)	Histologic grade	Location	Median tumor diameter	Fraction and dose; target volume	EQD2/BEDα/β of 4 (Gy)
Parsai et al. [59]	2020 USA	Retrosp. Analysis Localized extremity or trunk STS	16	64	44 : 56	G2: 50% G3: 18.8% Unknown: 31.2%	LE: 62.5% UE: 25% Trunk: 12.5%	18.8% ≤5 cm 56.2% >5 - ≤10cm 18.8% >10 cm - ≤15 cm 6.2% >15 cm	n=1: 5 x 5 Gy = 25 Gy n=14: 5 x 6 Gy = 30 Gy n=1 5 x 8 Gy = 40 Gy Target volumes: according to RTOG-0630 [35]	n=1 37.5 Gy/ 56.3 Gy n=14 50 Gy/75 Gy n=1 80 Gy/120 Gy
Pennington et al. [60]	2018 USA	Retrosp. Analysis Localized, non-recurrent STS	116	46	40 : 60	G1: 0.9% G2: 13% G3: 79% Unknown: 7%	LE: 79% UE: 21%	17% ≤5cm 35% >5 - ≤10 cm 47% >10 cm	8 x 3.5 Gy = 28 Gy CTV = GTV + 4-5 cm long. PTV: N/A	35 Gy/52.5 Gy

RT modality	CTX	Time to surgery	Median FU (mths)	OS	LR	LC	LRFS	DFS	Acute toxicity	Late toxicity
3D-CRT > IMRT > VMAT	No	7 weeks (median)	27.1	25 of 27 pts (93%)	0%	N/A	N/A	100% 3 yrs G1-G2 50% 3 yrs G3	Wound dehiscence: 10.3% Wound infection: 17.2% Dermatitis: 1°: 34.4% 2°: 3.4% 3°: 3.4%	13.8 % Edema: 1°: 3.4% 2°: 3.4% Fibrosis *1: 3.4% *2: 3.4%
3D-CRT 20 IMRT 76% IGRT 96% Electron 4%	No	4 weeks (median)	29	84%	2 of 35 pts (5.7%)	N/A	N/A	N/A	Major WC: 32% Most common in LE °2 dermatitis: 8%	1°: Fibrosis: 24% Stiffness: 11% Edema: 4% 2°: Fibrosis: 11% Stiffness: 11% Edema: 4%
IMRT VMAT IGRT	N = 2 pts*	1 day (median)	10.7	87.5%	0%	N/A	N/A	N/A	Major WC: 18.8% Minor WC: 12.5%	≥3°: 0%
3D-CRT	AI	1-2 weeks	5.9 yrs	82% 3 yrs 67% 6 yrs	11% 3 yrs 17% 6 yrs	N/A	N/A	N/A	Toxicity recorded for 17 pts: Acute WC: seromas/hematomas: 6 surgical site infection: 5 delayed wound healing: 1	

Table 2 (continued)

Author	Year and country	Type of trial and Inclusion criteria	N	Median age (years)	Sex ratio (♀:♂ in %)	Histologic grade	Location	Median tumor dia- meter	Fraction and dose; target volume	EQD2/BEDα/β of 4 (Gy)
Kubicek et al. [61]	2018 USA	Phase II single center trial Localized extremity STS	13	N/A, all patients > 18 yrs	N/A	G1-G2: 21.4% G3: 78.5%	LE: 71.4% UE: 14.3% Groin: 14.3%	7.6 cm	Most pts: 5 x 7 Gy = 35 Gy 3 of 13 pts: 5 x 8 Gy = 40 Gy Median isodose line: 81% CTV = GTV + 0.5 cm radial; + 3 cm long. PTV= CTV + 0.5 cm	Most pts: 64.17 Gy/96.3 Gy 3 of 13 pts: 80 Gy/120 Gy
Kılıç et al. [62]	2017 Turkey	Retrosp. Analysis Localized, G2-G3 ≥ 4cm or G1 ≥ 8cm extremity STS	67	47	43 : 57	G2: 7.5% G3: 26.9 % Unknown: 65.6%	N/A	9.6 cm	8 x 3.5 Gy = 28 Gy PTV: N/A	35 Gy/52.5 Gy
Koseła-Paterczyk et al. [63]	2016 Poland	Sub-analysis of (64)	32	50	41 : 59	Myxoid liposarcoma only G1: 15.6 % G2: 12.5 % G3: 46.9 % Unknown: 25%	LE: 97% UE: 3%	10.5 cm	53%: 5 x 5 Gy = 25 Gy 47%: 5 x 4 Gy = 20 Gy CTV = GTV + 2cm transv.; + 4cm long. PTV = CTV + 0.7-1cm	53%: 37.5 Gy/ 56.3 Gy 47%: 26.67 Gy/40 Gy
Koseła-Paterczyk et al. [64]	2014 Poland	Phase II single center trial Locally advanced trunk wall or extremity G2-G3 STS or G1 if > 10cm diameter	272	55	53 : 47	G1: 11.8 % G2: 23.6 % G3: 64.6 %	LE: 70.2% UE: 16.2% Trunk: 13.6%	8.5 cm	5 x 5 Gy = 25 Gy CTV = GTV + 2cm transv.; + 4cm long. PTV = CTV + 0.7-1cm	37.5 Gy/ 56.3 Gy

Table 2 (continued)

RT modality	CTX	Time to surgery	Median FU (months)	OS	LR	LC	LRFS	DFS	Acute toxicity	Late toxicity
SBRT	21.4%; agent N/A	37 days (median)	279 days	N/A	7.7%	93%	N/A	N/A	Major WC: 28.5 %	0%
N/A	50% RT+AI vs. 50% RT alone	2-3 Weeks after pre-op RT	37	3yrs: 74.1% vs. 90.0% p=0.4	14.9%	N/A	3 yrs: 77.1% vs. 76.3% p=0.86	3 yrs: 50.5% vs. 65.7% p=0.33	N/A	N/A
3D-CRT	No	3-7 days	60	68% 5 yrs	9.3%	90%[#] 5 yrs	N/A[#]	N/A	Acute:22 % = 7 patients 3 wound infection 2 wound dehiscence 5 prolonged healing Late: 9% = 3 patients 1 prolonged edema 2 tissue fibrosis No differences in RT regimens	
3D-CRT IMRT for trunk lesions only (13.6%)	22.4% substance N/A	3-7 days	35	72% 3 yrs	19.1%	81% 3yrs**	N/A**	N/A	Overall: 32.4%: Inflammation requiring antibiotic treatment: 11.8% Wound dehiscence: 11.8% Prolonged wound healing: 16.5%	Overall: 14.7% 1°-3° Fibrosis: 3.7% Edema: 9.2%

The trial characteristics, patient characteristics, radiotherapy, chemotherapy, time to surgery as well as outcome parameters and rates for acute and late toxicity are included. 1° (grade 1), 2° (grade 2), 3° (grade 3), 3D-CRT (3D conformal radiotherapy), AI (doxorubicin/ifosfamide), BED (Biologically Effective Dose), cm (centimeter), CTV (clinical target volume), CTX (chemotherapy), DFS (disease-free survival), doxo (doxorubicine), DTIC (dacarbazine), EQD2 (Equivalent Dose in 2 Gy Fractions), FU (follow-up), G (grade), GTV (gross tumor volume), Gy (gray), IGRT (image-guided radiotherapy), IMRT (intensity modulated radiotherapy), LC (local control), LE (lower extremity), long. (longitudinally), (LR (local recurrence), LRFS (local recurrence-free survival), mths (months), N/A (not available), OS (overall survival), pts (patients), PTV (planning target volume) Retrosp. Analysis (retrospective analysis), RT (radiotherapy), SBRT (stereotactic body radiotherapy), STS (soft tissue sarcoma), transv (transversally), UE (upper extremity), USA (United States of America), VMAT (Volumetric Intensity Modulated Arc Therapy), WC (wound complication), yrs (years)

*One patient received gemcitabine/docetaxel 6 weeks post-op; one patient received doxorubicin/temsirolimus 1 week prior to RT

[#] The definition of LRFS included the events local recurrence or death. Notably, the trial applied the same definition, however, the value of 90% for 5-year LRFS is higher than the 5-year OS of 68%, which counters the definition of LRFS. The 5-year 90% value is therefore equivalent to the 5-year local control

**Death was not included as an event for the LRFS. The 81% is therefore equivalent to the 3-year LC rate

Table 3 The table summarizes major published studies on preoperative conventionally fractionated RT

Author	Year & country	Type of trial & inclusion criteria	N	Median age (years)	Sex ratio (♀:♂)	Histological grade	Location	Median tumor diameter	Fraction & dose; target volume	EQD2/α/β of 4 Gy	RT modality	CTX	Time to surgery	Median FU (months)	OS	LR	LC	LRFS	DFS	Acute toxicity	Late toxicity
Lansu et al. [65]	2021 Netherlands	Phase II multicenter trial Localized extremity or trunk MLPS	79	45	44: 56	N/A	LE: 91% UE: 3% Trunk: 6%	9.9 cm	18 × 2 Gy = 36 Gy CTV = GTV + 3 cm long.; + 1.5 cm all other directions PTV = CTV + 1 cm	36 Gy/54 Gy	IMRT	No	≥ 4 weeks	25	95% 3 yrs	N/A	100%	N/A	N/A	Overall WC; 22%	2°: 11% 3°: 3%
Lansu et al. [66]	2019 Netherlands	Retrosp. analysis Localized extremity STS	191	60	♀ n = 88 ♂ n = 103	G1: n = 14 G2: n = 76 G3: n = 79 N/A: n = 22	LE: 92% UE: 8%	N/A	25 × 2 = 50 Gy (85% of pts) CTV = GTV + 4 cm long.; + 1.5 cm all other directions PTV = CTV + 1 cm	50 Gy/75 Gy	EBRT	No	6 weeks (median)	21	70% 5 yrs	5%	93% 5 yrs	N/A	N/A	Overall WC: 31%	N/A
Wang et al. [35]	2015 USA	Phase II multicenter trial Localized extremity STS, < 32 cm	86	61	53: 47	G1: 16.5% G2: 26.6% G3: 48.1%	LE: 78.5% UE: 13.9% Other: 7.6%	10.5 cm	25 × 2 Gy = 50 Gy PTV = CTV + 0.5 cm ≥ 8 cm diameter or G2/G3: CTV = GTV + 3 cm long.; + 1.5 cm radial < 8 cm diameter or G1 CTV = GTV + 2 cm long., 1 cm radial	50 Gy/75 Gy	IG-IMRT 74.7% 3DCRT 25.3%	No	4–8 weeks	3.6 yrs	80.6% 2 yrs	N/A	94% yrs	2 N/A	N/A	Major WC: 36.6%	≥ 2°: 10.5% at 2 yrs
O'Sullivan et al. [67]	2013 Canada	Phase II single center trial Localized lower extremity STS	59	56 (mean)	♀ n = 29 ♂ n = 30	G1: n = 4 G2: n = 26 G3: n = 29	LE only	9.5 cm	25 × 2 Gy = 50 Gy CTV = GTV + 4 cm long. + 1.5 cm radial PTV = CTV + 0.5 cm	50 Gy/75 Gy	IG-IMRT	No	N/A	49	N/A	6.8%	N/A	88.2% 5 yrs	N/A	Major WC: 30.5%	No > 2° toxicity
Hui et al. [68]	2006 Australia	Retrosp. analysis Localized extremity or trunk wall STS	67	52	♀ n = 26 ♂ n = 41	G1: n = 19 G2/G3: n = 46 N/A: n = 2	LE: n = 53 UE: n = 9 Trunk: n = 5	6 cm	28 × 1.8 Gy = 50.4 Gy PTV = GTV + 6 cm long.	48.72 Gy/73.08 Gy	EBRT	n = 3 pts: doxo post op	33 days (median)	4.1 yrs	73% 5 yrs	5%	N/A	93% 5 yrs	N/A	3°: Dermatitis: 6% overall WC: 41%	Overall: n = 5 pts

Table 3 (continued)

Author	Year & country	Type of trial & inclusion criteria	N	Median age (years)	Sex ratio (♀:♂)	Histological grade	Location	Median tumor diameter	Fraction & dose; target volume	EQD2/α/β of 4 Gy	RT modality	CTX	Time to surgery	Median FU (months)	OS	LR	LC	LRFS	DFS	Acute toxicity	Late toxicity
Kraybill et al. [69]	2006 USA	Phase II multicenter trial G2–G3 extremity and trunk wall sarcoma, ≥ 8 cm, ≤ 4 lung metastases	64	45.5	44: 56	G2: 20% G3: 80%	Extremity 88% Torso: 12%	15 cm	22 × 2 Gy interdigitated = 44 Gy PTV = GTV + 9 cm long. + ≥ 2 cm radial	44 Gy/66 Gy	EBRT	MAID	80 days after day 1 of CTX	6.1 yrs	75.1% 3 yrs	17.6% 3 yrs	N/A	N/A	56.6%3 yrs	3°: Hematological: 13% Nonhematological: 28% 4°: Overall: 84% 5°: Overall: 5% Late toxicity: N/A
Zagars et al. [70]	2003 USA	Retrosp. Analysis Localized, G1–G3 STS	271 pre op	N/A	N/A	G1: 4% G2: 26% G3: 70%	LE: 59% UE: 14% Other: 27%	8 cm	Median single dose: 2.0 Gy Median total dose: 50 Gy	50 Gy/75 Gy	EBRT	doxo	4–6 weeks	6.4 yrs	N/A	N/A	85% 5 yrs 83% 10 yrs	N/A	N/A	N/A	5%
O'Sullivan et al. [25, 26] and Davis et al. [24]	2002 Canada	Phase III multicenter RCT Localized, extremity STS	94 pre op	< 50: 34% ≥ 50–< 70: 43% ≥ 70: 23%	45: 55	G1: 17% G2–G3: 83%	LE: 80% UE: 20%	≤ 10 cm 65% > 10 cm 35%	Pre op: 25 × 2 Gy = 50 Gy (n = 88 pts) Additional post op boost 8 × 2 Gy = 16 Gy (n = 14 pts) pre op PTV = GTV + 5 cm long. Post op boost: PTV = GTV + 2 cm	Pre op: 50 Gy/75 Gy post op boost: 16 Gy/24 Gy	EBRT	No	3–6 weeks	3.3 yrs	73%	N/A	93% 5 yrs	58% 5 yrs	N/A	Major WC: 35%	≥ 2°: Fibrosis: 31.5% Joint stiffness: 17.8% Edema: 15.1%
Pollack et al. [71]	1998 USA	Retrosp. analysis G2–G3 pleom. sarcoma, liposarcoma, synovial sarcoma	128 pre op	54 (mean)	58: 42	G2: 32.8% G3: 67.2%	LE + UE: 82% Other: 18%	10 cm (mean)	25 × 2 Gy = 50 Gy PTV = GTV + 5–7 cm long. + 2–3 cm radial	50 Gy/75 Gy	3D-CRT	doxo, CP, DTIC, VCR	N/A	97	N/A	N/A	82% 5 yrs	N/A	N/A	Acute WC: 25% (entire (pre op) cohort)	6.2%

The trial characteristics, patient characteristics, radiotherapy, chemotherapy, time to surgery as well as outcome parameters and rates for acute and late toxicity are included. 1° (grade 1), 2° (grade 2), 3° (grade 3), 3D-CRT (3D conformal radiotherapy), BED (Biologically Effective Dose), cm (centimeter), CP (cyclophosphamide) CTV (clinical target volume), CTX (chemotherapy), DFS (disease-free survival), doxo (doxorubicine), DTIC (dacarbazine), EBRT (external beam radiotherapy), EQD2 (Equivalent Dose in 2 Gy Fractions), FU (follow-up), G (grade), GTV (gross tumor volume), Gy (gray), IMRT (intensity modulated radiotherapy), IG-IMRT (Image-guided intensity-modulated radiotherapy), LC (local control), LE (lower extremity), long. (longitudinally), LR (local recurrence), LRFS (local recurrence-free survival), MLPS (myxoid liposarcoma), mths (months), N/A (not available), OS (overall survival), pts (patients), pre op (preoperative), post op (postoperative), PTV (planning target volume), RCT (randomized controlled trial), Retrosp. analysis (retrospective analysis), RT (radiotherapy), STS (soft tissue sarcoma), transv (transversally), UE (upper extremity), USA (United States of America), VCR (vincristine), VMAT (Volumetric Intensity Modulated Arc Therapy), WC (wound complication), yrs (years)

associated with a WC rate of 35%, while 17% of participants showed postoperative WCs (Table 3) [26].

In a 2021 published, non-controlled, interventional trial by Koseła-Paterczyk et al., 311 patients treated with a short preoperative course of 5×5 Gy showed lower WC rates of 28% compared to the SR-2 trial [53]. The average tumor size was even larger while the histological grade, tumor location, and median age of participants were comparable. Treatment planning was also similar in both trials: In the trial by Koseła-Paterczyk et al. the clinical target volume (CTV) was 2 cm transversally and 4 cm longitudinally. The planning target volume (PTV) was 1 cm in all directions (Table 2). In the SR-2 trial, preoperative RT treatment consisted of 25×2 Gy to a volume of 5 cm proximal and distal to the tissue at risk displayed on computed tomography (CT). A minor subgroup of patients with positive surgical margins after preoperative RT received a sequential boost (16–20 Gy in 2 Gy fractions) defined as lesion volume plus 2 cm in all directions.

Possible explanations for the difference in WC rates between both trials may be: (i) Increased precision by image-guided radiotherapy (IGRT) conducted via daily cone-beam CTs in the trial by Koseła-Paterczyk et al.; (ii) the use of contrast enhanced magnetic resonance imaging (MRI) fused with CT for planning, although the exact proportion of patients where MRI was applied is not given; (iii) a possible difference in the tumor depth as another risk factor for WC, also not given in the trial by Koseła-Paterczyk et al.; (iv) a difference in patients comorbidities (e.g. increased body mass index (BMI), smoking, diabetes) adversely affecting wound complication rates [82–85].

One essential limitation of the 2021 trial of Koseła-Paterczyk et al. is the absence of intensity modulated radiotherapy (IMRT) technique. It would have been interesting to observe whether adding IMRT techniques to the hypofractionated 5×5 Gy regimen would have reduced toxicity rates even more. In 2014, Koseła-Paterczyk et al. had applied HFRT to a comparable group of 272 patients (mostly G3 sarcomas located in the lower extremity), but without IMRT or IGRT. Herein, major WC rates were higher and similar to the rates in the SR-2 trial (32.4% vs. 35% in the SR-2), while late toxicities were less common, suggesting IMRT and IGRT as important influence parameters [64].

For normofractionated RT, more data exists suggesting a clear benefit of image-guided and intensity modulated radiotherapy (IG-IMRT) techniques. The group of O'Sullivan et al. published another trial showing beneficial toxicity rates by using IG-IMRT and standard target volume delineations [67]. Although the rate of WCs was numerically lower, yet not statistically significant, the need for tissue transfer was significantly reduced [67]. Supporting this approach, Wang et al. investigated the impact of normofractionated IGRT on toxicity rates in preoperative normofractionated RT for STS applying the same definitions for late toxicity and acute WCs as in the SR-2 trial [24, 26]. By adding IGRT, the late toxicity rate again dropped substantially to 10.5% in the RTOG-0630 trial [35].

Interestingly, two interventional trials evaluating stereotactic body radiotherapy (SBRT) used even higher doses of 5×8 and 5×7 Gy and revealed acute WC rates similar to conventional HFRT yet lower than in the normofractionated SR-2 trial (28% and 28.5% respectively) [55, 61]. Notable other adverse events were vascular occlusions described in a small proportion of patients after 5×8 Gy SBRT requiring disarticulation surgery ($n = 3$) and one case of amputation [55]. The amount of literature describing damage to tumor vasculature under intense hypofractionation has been growing recently [86, 87]. This effect has first been described in in vitro experiments after single fractions ≥ 10 Gy which may explain the described adverse effects [88]. Nevertheless, the SBRT data on STS are limited by the small number of participants (25 in the trial of Leite et al. vs. 13 in the trial of Kubicek et al.) and the short median follow-up of 9.3 months in the latter trial, which therefore could detect no late toxicities [55, 61]. Nevertheless, it is undoubted that advances in RT planning and techniques such as IGRT and IMRT have improved precision and reduced toxicity rates for STS patients. An upcoming Russian trial is currently recruiting patients for a 3-step sequence of preoperative stereotactic RT (5×5 Gy), surgery, and postoperative normofractionated RT (25×2 Gy). The primary endpoint is the complication rate after each step of the protocol [89](NCT04330456).

To further elucidate the effect of preoperative HFRT and chemotherapy on R0 limb-sparing surgery and toxicity rates for marginally resectable STS, a phase II trial with 46 patients from the Warsaw sarcoma center by Spałek et al. was published in 2021. R0 resection was achieved in 72% of patients while acute WCs were observed in 34% of patients comparable to the 35% in the SR-2 trial. Data on late toxicity rates are still pending [26, 54]. However, in this trial the median tumor diameter of 17.4 cm was remarkably larger compared to most other trials with perioperative HFRT for STS and to the SR-2 trial (< 10 cm in 65% in the preoperative RT group). Supporting this association, the multivariable analysis in the SR-2 trial also revealed a significant correlation between baseline tumor size and WCs [26]. Thus, having almost equal WC rates in hypofractionated and normofractionated RT despite a substantial difference in size attenuates the argument of increased WCs in HFRT for STS.

Only one trial has shown slightly higher rates of acute WCs using HFRT (37.9% vs. 35% in SR-2) [63]. However, in this trial, the sample size was relatively small (n = 34) because only myxoid liposarcomas (MLPS) were included. Moreover, most patients were irradiated with conventional 3D conformal radiotherapy (3D-CRT) and a short time gap of 3–7 days between RT and surgery [63]. Besides, MLPS are known for their favorable prognosis and radiosensitivity [90, 91]. So, even if further trials on this rare malignant tumor would bring forth more evidence of increased toxicity with HFRT, one could still discuss a de-escalation concept due to their high radiosensitivity. The Dutch multicenter DOREMY trial has applied reduced preoperative normofractionated RT (18×2 Gy instead of 25×2 Gy standard dose) for MLPS patients in an attempt to deescalate radiation dose. The authors achieved remarkably low acute WCs of 17% when compared to the preoperative RT group in the SR-2 trial. However, while the definition of major WC as a clinical diagnosis is equal, the DOREMY trial defined acute WCs by 30 days after surgery while the SR-2 trial applied 120 days [92] (NCT02106312).

A lot of knowledge on risk factors for major WCs stems from large surgical and RT data analyses. As such, it is an interesting finding throughout all treatment modalities and trials investigated in this review that the vast majority of WCs are located in the lower extremities, accounting for substantial postoperative morbidity (Table 2). This observation has been confirmed in different multicenter data analyses [84, 85]. In addition, the authors also found influenceable risk factors like increased BMI and smoking to be associated with postoperative WCs [84, 85]. In line with this, further trials confirmed the above-mentioned risk factors and added diabetes, tumor size > 10 cm, vascular tumor infiltration, and proximity to the skin < 3 mm as further predictors of major WCs [82, 83]. These findings may alter the preoperative management (nutrition, smoking cessation, diabetes training, surgical technique) to optimize post-surgical outcomes in STS patients [82, 83].

Furthermore, while acute WCs constitute serious adverse events, they are usually curable by local treatment. In contrast, long-term analysis of the patients in the Canadian SR-2 trials has revealed significantly lower functional scores in patients suffering from late and irreversible toxicities such as fibrosis, joint stiffness, and edema [24]. This observation may explain the increasing trend towards preferring pre- over postoperative RT in the treatment of STS [22, 23].

Apart from one trial, no other trials analyzed in our systematic review have found higher rates of early or late toxicity with HFRT for STS [63]. Quite the contrary, most trials have shown reduced risks of toxicity with advanced RT techniques. However, no large randomized phase III controlled trial has yet compared HFRT to normofractionated RT with a particular focus on toxicity rates and morbidity. One of the few controlled trials investigating this very topic is currently enrolling patients at the University of Wisconsin Hospital and Clinics (Madison, Wisconsin, United States, section 4.3 Upcoming data) [93].

Oncological outcomes

The outcome benefits of HFRT for STS are promising. Well-established independent risk factors for LR and mortality comprise positive surgical margins, histological grade, tumor depth, and previous LR for subsequent recurrences and mortality. Additionally, specific histological subtypes (e.g., malignant peripheral nerve sheath tumor or myxofibrosarcomas) are associated with disadvantageous clinical outcomes [11, 12, 15, 16].

Overall, LC as a quality criterion for HFRT shows good to excellent results, ranging between 80–100% between 3 to 5 years in the largest studies analyzed herein (Table 2). The most comprehensive trial comprising 311 representative patients with locally advanced sarcomas treated with a short course of 5×5 Gy has achieved acceptable rates of 5-year LR of 13.8% when compared to previous literature [14, 53, 94]. About 83% of tumors were resected with clear margins, a protective factor for LR as described in previously published analyses [95]. The additional preoperative chemotherapy with doxorubicin and ifosfamide or dacarbazine administered to one third of patients did not significantly alter survival or LR, although the trial was not powered for this factor [53]. On multivariable analysis, specific histological subtypes such as malignant peripheral nerve sheath tumors or leiomyosarcomas have confirmed the previous literature on their increased malignancy and resistance to treatment (5-year LC of approximately 65–70%) [11, 96].

Again, the addition of IG-IMRT to HFRT has substantial benefits and improves LC rates. Kalbasi et al. have applied 5×6 Gy IMRT in 76% of patients and IGRT in almost all 50 patients enrolled in 2020 [47]. With a minimum follow-up of two years, only 5.7% of patients with LR were observed [47]. Limitations in comparability are the pending long-term follow-up data [47]. The improvement by IMRT is supported by data on normofractionated postoperative RT, where IMRT has shown significant benefits on LC compared to conventional external beam RT [97, 98]. Altogether, the presented data on preoperative HFRT has shown similar LC rates when compared to preoperative normofractionated RT for STS [70, 71].

An interesting secondary finding in the study by Kalbasi et al. is the significant increase in both patient accrual and distance traveled by patients, when they were enrolled into 5×6 Gy RT compared to standard

25 × 2 Gy in the 2-year period preceding study initiation [47]. This approves the logistical and convenience argument by many other studies on patient preferences and therapy adherence to shorter RT courses, which particularly holds true for elderly patients [44, 46, 99].

MLPS repeatedly stand out by their remarkably high radiosensitivity, which sustains also in HFRT regimens. In 27 patients with large MLPS (median size: 13 cm), treated with preoperative 5 × 5 Gy and a median follow-up of 27 months, none of the patients had a LR. OS was 93% because of two patients who died after metastatic spread [58]. In another trial, published four years earlier, the same authors from the Warsaw sarcoma center have used 5 × 5 or 5 × 4 Gy for MLPS patients and have shown similarly favorable LC rates of 90% after five years. The 5-year OS was 68%. All deaths were related to distant recurrences, again proving the excellent radiosensitivity and local controllability by HFRT [63]. This radiosensitivity is confirmed in multiple previous studies and large database analyses on normofractionated RT and may be exploited to further deescalate local therapy regimens [90, 91, 100].

We can therefore conclude that the present data strongly suggests modern HFRT regimens and techniques to be comparable to normofractionated RT in LC rates of STS. However, the present results are, at best, derived from phase II trials. So far, no randomized phase III trial comparing normofractionated RT to HFRT for STS has been conducted. Both the study population and the specific tumor entities are highly heterogeneous, and most of the trials are non-controlled trials or retrospective data analyses (Table 2) [101]. The included articles demonstrated moderate to serious overall risk of bias and therefore hamper comparability (Additional file 2: Risk of bias assessment according to ROBINS-I, Table 1). Moreover, the available trials differ in RT, surgical techniques, concomitant chemotherapy regimens, and the therapy modalities' order. Research on STS as "orphan diseases" is impeded by low prevalence and lower funding compared to other cancer entities [102]. Thus, the present data is generating strong hypotheses and future results are eagerly awaited.

Upcoming data

More than 15 trials on HFRT + / − chemotherapy in STS are currently ongoing (Table 4). Due to the low prevalence, most trials have long recruiting phases. Among the first trials to compare conventionally fractionated vs. HFRT for STS has recently begun accruing patients at the University of Wisconsin, USA [93] (NCT05109494). Another randomized interventional trial focuses on acute postoperative WCs in localized head and neck, trunk and extremity STS after 14 × 3 Gy preoperative RT (study arm B) compared to standard preoperative RT (25 × 2 Gy) [103]. The study began recruiting in June 2021 at two Dutch university medical centers in Leiden and Groningen and is expected to reach primary completion by April 2025 [103] (NCT04425967).

Many studies are testing different preoperative, HFRT regimens to shorten therapy time and improve patient convenience. For instance, 15 × 2.85 Gy is applied to investigate major WCs (as defined by O'Sullivan et al.) for an estimated number of 120 STS patients at the Mayo Clinic, Rochester, USA [26]. Secondary outcome measures include oncological outcomes and for the first time, patient reported outcomes with regard to changes in the quality of life. Estimated primary completion is November 2025 [104] (NCT04562480). The same regimen also investigating major WC rates in localized, resectable STS and comparing them to historical controls is conducted at the M.D. Anderson Cancer Center and expected to reach completion by August 2023 [105] (NCT03819985). Similarly, the McGill University in Montreal, Canada, is accruing patients to apply a short, preoperative, HFRT regimen of 5 × 7 Gy within one week (PRESTO trial). The primary outcome is radiation-associated toxicity. For the secondary outcomes, the authors apply established questionnaires and functional scoring systems (Toronto Extremity Salvage Score [TESS], Musculoskeletal Tumor Society Score MSTS) to evaluate patients' daily performance activity and quality of life. The study commenced in June 2020 and is estimated to reach primary completion by January 2025 [106] (NCT04617327).

Other groups apply evolving technology to improve outcomes for STS patients under HFRT: Another phase II trial at the University of Wisconsin will be accruing around 48 patients to test advanced highly conformal HFRT with 2-year LC rates as primary endpoint; the estimated primary completion date is July 2023 [107] (NCT03972930). Moreover, two phase II randomized German trials are investigating the feasibility of modern, neoadjuvant, hypofractionated particle therapy (C12 carbon ions vs. protons) with 3 Gy to 39 Gy for STS of the extremities and retroperitoneal STS. Both are currently accruing patients at the University of Heidelberg [108, 109] (NCT04946357 and NCT04219202).

Summary

STS are rare, heterogenous malignancies and therefore challenging in both research and multidisciplinary treatment. Preoperative, five to six weeks RT regimens currently represent the mainstay of management at high-volume sarcoma centers in high-grade STS (G2-G3). Shortening RT courses can improve therapy convenience, raise cost-effectiveness, and provide more treatment opportunities for a wider range of patients. The suggested risk of higher

Table 4 The table summarizes currently ongoing and recruiting trials on preoperative hypofractionated radiotherapy for soft tissue sarcoma

NCT number/phase	Title	RTX fraction × dose	Outcome measures	Dates	Center
NCT05109494/Phase II	Hypofractionated vs Conventional Fractionated RT in Soft Tissue Sarcomas	25 × 2 Gy = 50 Gy vs 5 × 5.5 Gy = 27.5 Gy	1°: Pathological necrosis 2°: Surgical margins, WC, late toxicity, PFS, LR	Start: December 2021 Study completion: November 2026	University of Wisconsin Hospital and Clinics, Madison, Wisconsin, United States
NCT04425967/Phase II	Short Course Of Preoperative Radiotherapy in Head and Neck-, Trunk- and Extremity Soft Tissue Sarcomas	25 × 2 Gy = 50 Gy vs 14 × 3 = 42 Gy	1°: Acute toxicity (30 days post op) 2°: LC, late toxicity (2 years)	Start: June 2021 Study completion: April 2034	Universitair Medisch Centrum Groningen, Groningen, Netherlands Leids Universitair Medisch Centrum, Leiden, Netherlands Radboudumc, Nijmegen, Netherlands
NCT04562480/Phase II	Hypofractionated Radiation Therapy Before Surgery for the Treatment of Localized, Resectable Soft Tissue Sarcoma of the Extremity and Superficial Trunk	15 × 2.85 Gy = 42.75 Gy	1°: Major WC (within 120 days) 2°: LR, DFS, OS, late toxicity, pattern of relapse, QoL changes	Start: November 2020 Study completion: November 2026	Mayo Clinic in Rochester, Rochester, Minnesota, United States
NCT03819985/Phase II	Shorter Course, Hypofractionated Pre-Surgery Radiation Therapy in Treating Patients With Localized, Resectable Soft Tissue Sarcoma of the Extremity of Superficial Trunk	15 × 2.85 Gy = 42.75 Gy vs 25 × 2 Gy = 50 Gy (historical control)	1°: Non-inferiority design for time till major WC (within 120 days) 2°: LRFS, DFS, Time to relapse, Disease specific survival time, pattern of local relapse, acute toxicity other than WC, late toxicity, functional outcomes, QoL	Start: December 2018 Study completion: August 2023	MD Anderson Cancer Center, Houston, Texas, United States
NCT04617327/Phase I/II	Pre-operative RadiothErapy for Soft Tissue SarcOmas (PRESTO)	5 × 7 Gy = 35 Gy every other day (3 fractions per week)	1°: Acute toxicity (within 1 month) according to CTCAE V.5 2°: Performance measure by Physicians Muscle Tumor Rating Scale	Start: June 2020 Study completion: December 2027	McGill University Health Centre-Cedars Cancer Centre, Montréal, Quebec, Canada
NCT03972930/Phase II	Hypofractionated Radiotherapy for Soft Tissue Sarcomas	Highly conformal RT in 3–8 fractions maximum prescribed dose, total of 60 Gy in ≤ 8 weeks	1°: LC (2-year) 2°: LC (5-year), CR-rate, PFS, OS, acute toxicity, late toxicity	Start: June 2019 Study completion: July 2026	University of Wisconsin, Madison, Wisconsin, United States
NCT04946357/Phase II	Neoadjuvant Irradiation of Extremity Soft Tissue Sarcoma With Ions (EXTREM ION)	Proton: 13 × 3 Gy = 39 Gy (RBE) vs Carbon ion: 13 × 3 Gy = 39 Gy (RBE)	1°: Absence of wound healing disorders (till 120 days after surgery) 2°: LC, LPFS, DFS, OS	Start: June 2021 Study completion: July 2023	University Hospital Heidelberg, Heidelberg, Germany
NCT02634710/Phase II	Hypofractionated Pre-operative Radiation Therapy for Soft Tissue Sarcomas of the Extremity and Chest-wall	5 × 7 Gy = 35 Gy every other day	1°: LC (2 year) 2°: Serious adverse events (CTCAE V.4.0), Musculoskeletal Tumor Rating Scale Score, QoL, DFS, OS, radiological changes (T2 MRI), pathological changes	Start: February 2016 Study completion: December 2025	Froedtert Hospital, Milwaukee, Wisconsin, United States

The National Clinical Trial number, the study phase, study title, radiotherapy fractionation and dose, the primary and secondary outcomes, the dates and the participating centers are included. 1° (primary), 2° (secondary), CR (complete remission), CTCAE (Common Terminology Criteria of Adverse Events), DFS (disease-free survival), doxo (doxorubicine), LC (local control, LPFS (local progression-free survival), LR (local recurrence), LRFS (local recurrence-free survival), MRI (Magnetic resonance imaging), NCT (National Clinical Trial), OS (overall survival), QoL (quality of life), RBE (relative biological effectiveness), WC (wound complication)

rates of adverse effects and worse oncological outcomes cannot be confirmed by the available data and studies. Toxicity rates are mostly equal or less than in representative trials for normofractionated RT. Preoperative RT is preferred over postoperative RT due to lower rates of irreversible late toxicity. Preoperative HFRT achieves comparable LC rates with shorter duration of therapy. However, all data are derived from retrospective data analyses and phase II trials. The interpretation must therefore be made with caution. Multiple trials on HFRT are underway and the results in this evolving field are awaited with great interest.

Abbreviations

3D-CRT: 3D conformal radiotherapy; AI: Doxorubicin/ifosfamide; BMI: Body mass index; CT: Computed tomography; CTV: Clinical target volume; CTX: Chemotherapy; DFS: Disease-free survival; GTV: Gross tumor volume; HFRT: Hypofractionated radiotherapy; IGRT: Image-guided radiotherapy; IG-IMRT: Image-guided intensity modulated radiotherapy; IMRT: Intensity modulated radiotherapy; LC: Local control; LR: Local recurrence; LRFS: Local recurrence-free survival; MLPS: Myxoid liposarcomas; MRI: Magnetic resonance imaging; MSTS: Musculoskeletal Tumor Society Score; OS: Overall survival; PFS: Progression-free survival; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PTV: Planning target volume; ROBINS-I: Risk of Bias In Non-randomized Studies of Interventions tool; RT: Radiotherapy; SBRT: Stereotactic body radiotherapy; STS: Soft tissue sarcoma; TESS: Toronto Extremity Salvage Score; USA: United States of America; VMAT: Volumetric Intensity Modulated Arc Therapy; WC: Wound complication.

Supplementary Information

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Additional file 1. The PRISMA 2020 checklist.

Additional file 2. Risk of bias assessment according to ROBINSI.

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Competing interests

The authors declare no conflict of interest.

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2.6 Impact of a specialized palliative care intervention in patients with advanced soft tissue sarcoma - a single-centre retrospective analysis.

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Weichgewebssarkome machen weniger als 1% aller Malignome beim Erwachsenen aus [2]. Bei circa 50% der Erkrankten kommt es im Verlauf zu einer Metastasierung mit dann sehr limitierter Prognose. In dieser Situation stehen die Symptomkontrolle sowie die Verbesserung der Lebensqualität im Vordergrund. Bisher stehen nur wenige Daten zur Symptomlast und palliativen Interventionen bei Patient:innen mit Weichgewebssarkomen zur Verfügung. In Publikation 2.6 wird der Einfluss von palliativmedizinischen Interventionen auf die Symptomlast und die Lebensqualität bei dieser Population untersucht.

Insgesamt konnten 53 Fälle von 34 Patient:innen mit fortgeschrittenem Weichgewebssarkom, welche zwischen 2012 und 2018 auf der Palliativstation des Campus Virchow Klinikums der Charité behandelt worden sind, retrospektiv ausgewertet werden. Die individuelle Symptomlast wurde mittels eines standardisierten Basisassessments jeweils bei der stationären Aufnahme und bei der Entlassung erfasst. Hierfür wurden zusätzlich zu den jeweiligen anamnestischen Angaben der *Eastern Cooperative Oncology Group performance status* (ECOG), die Numerische Schmerzskala (*Numeric pain scale*, NRS), das Distress Thermometer und das Minimale Dokumentationssystem (MIDOS) analysiert. Sowohl die NRS als auch das Distress Thermometer umfassen eine Skala von 0-10 (kein Schmerz bis maximal vorstellbarer Schmerz bzw. keine bis maximale psychosoziale Belastung). Bei dem MIDOS handelt es sich um ein palliativmedizinisches Werkzeug in welchem die Symptomlast (u.a. Schwindel, Übelkeit und Obstipation) auf einer Skala von 0-3 (keine Symptome bis stärkste Symptome) abgefragt wird.

Die mediane Erkrankungsdauer vor Aufnahme auf die Palliativstation betrug 24 Monate. Bei 85% der Patient:innen lag bereits eine metastasierte Situation vor. Die häufigsten Gründe für die stationäre Aufnahme waren Schmerzen, Schwächegefühl und Fatigue. Durch die palliativmedizinische Intervention konnte eine signifikante

Reduktion von Schmerzen und anderen Symptomen erzielt sowie das Stresslevel gesenkt werden. Der mittels der NRS angegebene Akutschmerz wurde von 3 auf 1 von maximal 10 gebessert ($p<0.001$), Schmerz innerhalb der letzten 24h von 5 auf 2 ($p<0.001$), der mediane Score im MIDOS von 18 auf 13 ($p < 0.001$) und das mediane Stresslevel im Distress Thermometer von 7,5 auf 5 ($p =0.027$).

Die Analyse zeigt, dass eine spezialisierte palliativmedizinische Intervention bei Patient:innen mit fortgeschrittenem STS zu einer signifikanten Abnahme der Symptomlast führt. Diese sollte darum bei Vorliegen eines hohen Risikos für einen schweren symptomatischen Erkrankungsverlauf auch frühzeitig in die Behandlung integriert werden.

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Impact of a specialised palliative care intervention in patients with advanced soft tissue sarcoma – a single-centre retrospective analysis

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Abstract

Background: Soft tissue sarcomas (STS) account for less than 1% of all malignancies. Approximately 50% of the patients develop metastases with limited survival in the course of their disease. For those patients, palliative treatment aiming at symptom relief and improvement of quality of life is most important. However, data on symptom burden and palliative intervention are limited in STS patients.

Aim: Our study evaluates the effectiveness of a palliative care intervention on symptom relief and quality of life in STS patients.

Design/setting: We retrospectively analysed 53 inpatient visits of 34 patients with advanced STS, admitted to our palliative care unit between 2012 and 2018.
Symptom burden was measured with a standardised base assessment questionnaire at admission and discharge.

Results: Median disease duration before admission was 24 months, 85% of patients had metastases. The predominant indication for admission was pain, weakness and fatigue. Palliative care intervention led to a significant reduction of pain: median NRS for acute pain was reduced from 3 to 1 ($p < 0.001$), pain within the last 24 h from 5 to 2 ($p < 0.001$) and of the median MIDOS symptom score: 18 to 13 ($p < 0.001$). Also, the median stress level, according to the distress thermometer, was reduced significantly: 7.5 to 5 ($p = 0.027$).

Conclusions: Our data underline that specialised palliative care intervention leads to significant symptom relief in patients with advanced STS. Further efforts should aim for an early integration of palliative care in these patients focusing primarily on the identification of subjects at high risk for severe symptomatic disease.

Keywords: Palliative care, Soft tissue sarcoma, MIDOS symptom score, Symptom burden, Early palliative care intervention, Pain, Inpatient palliative care

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Key statements

What is already known about the topic?

- In a variety of advanced cancer diseases integration of palliative care has a significant impact on patient outcome, quality of care, length of hospital stay and hospital costs and leads to a less aggressive therapeutic approach during end-of-life care as well as to more contentment in patients and their relatives
- The early integration of palliative care leads to an overall survival (OS) benefit
- Only limited data are available on the specific challenges of palliative care interventions in the context of soft tissue sarcoma (STS) and there are no published data concerning an early integration of palliative care in patients with sarcoma

What this paper adds

- This is the first report in STS patients analysing hospital-based palliative care intervention, which does not focus on end-of-life care, but on palliative care intervention throughout the entire course of the disease
- The interventions resulted in a significant reduction of pain, an improvement of symptom burden and a decreased stress level

Implications for practice, theory or policy

- Our analysis demonstrates that specialised palliative care intervention leads to a significant symptom relief throughout the entire course of the disease
- Further exploration of the effects of early integration of palliative care on symptom relief, quality of life and the possible improvement of overall survival in STS patients is warranted

Background

Soft tissue sarcomas (STS) are rare and account for less than 1% of malignancies [1, 2]. Originating from mesenchymal tissue, they represent a heterogeneous group with more than 100 different histopathologically defined tumours.

Comprising all disease stages, the 5-year overall survival is 50 to 60%. Nevertheless, metastases occur in up to 50% of cases resulting in a poor outcome with overall 5-year survival of ~ 15%, only [3]. For patients with advanced disease, chemotherapy is the standard of care to prolong survival and improve the quality of life. In this setting, the median overall survival (OS) is 12.8 to 14.3 months, progression-free survival (PFS) is 4.6 to 7.4 months for doxorubicin monotherapy and doxorubicin combination therapy, respectively [4]. These data demonstrate a high unmet need for modern, effective therapies for this group of patients and highlight the importance of adequate palliative care strategies. Published data on the symptom prevalence and severity in advanced STS remain limited. Nevertheless, they sufficiently describe the high symptom burden and demonstrate the need for specialised diagnostics and optimised care [5–7]. Additionally, since OS remains reduced, the importance of palliative care needs to be increasingly spotlighted.

The WHO defines palliative care as follows: "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual " [8]. Palliative care is also defined as „applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life " [8], and a relevant number of analyses have addressed the benefit of early integration of palliative care into cancer care [9]. According to Jack et al., cancer patients in general benefit from a hospital-based palliative care intervention regarding symptom relief, with the largest effects on pain and anorexia [10]. Data about palliative care intervention in the context of STS are sparse, and most authors concentrate on the description of symptom burden rather than assessing the symptom relief achieved through palliative care intervention. For example, Kawashima et al. reported that 93 and 78% of STS patients suffer from pain and nausea, respectively, and that a total of 98% of STS patients requires opioids within the last 2 weeks of life [11].

Our study aimed to assess the patterns of symptoms in STS patients ($n_p = 34$) who have been treated in a hospital-based palliative setting ($n_i = 53$ interventions), and we further intended to measure the benefit and effectiveness of a hospital-based palliative care intervention regarding symptom relief and quality of life in these patients.

In the context of STS, an optimal assessment for quality of life is not yet defined. During the last years, several tools, e.g. standardised questionnaires, electronic patient self-reporting and assessment by medical professionals, have been evaluated. For example, Gough et al. used questionnaires as well as semi-structured interviews in a mixed methods longitudinal study in patients with advanced STS [12]. In the analysis published by Schuler et al., patient-reported outcomes (PROs) were utilised to evaluate overall quality of life (QoL) in patients undergoing a palliative chemotherapy [13]. Hentschel et al. performed multiple standardised assessments for QoL in patients receiving systemic therapy and the value of additional expert-consented supportive treatment recommendations [14].

To our knowledge, there are only sparse data analysing hospital-based palliative care in STS patients primarily

focusing on early interventions throughout the entire course of the disease, instead of end-of-life care.

Methods

We conducted a retrospective analysis of patients with symptomatic advanced STS who were admitted to our palliative care unit at the Charité between 2012 and 2018. The analysis was performed after patients' consent and according to the local ethical guidelines. Prerequisite for inclusion in the analysis was the availability of data both for admission and discharge.

This analysis included $n_i = 53$ interventions of $n_p = 34$ STS patients who presented with different STS subtypes (leiomyosarcoma as the most frequent subtype). Additionally, we gathered information on disease duration and prior therapies. Please see Table 1 for detailed patients' characteristics.

The palliative care unit at Charité Virchow-Klinikum belongs to the oncologic department and consists of an inpatient ward with ten single bed rooms. The patients are treated by a multidisciplinary team, including specialised palliative care physicians, palliative care nurses, physiotherapists, psychologists, dietists, musical therapists and social service. Patients are either admitted from home or transferred from other departments within the Charité/ external clinics. Patients known to our oncologic department, which was the case for all sarcoma patients, can be admitted/transferred without prior assessment of our palliative consulting service. For all other patients, the palliative consulting service supervises the indication for an admission to the palliative care unit. If no admission is realised, the team simply counsels and evaluates the needs of patients with palliative malignancies/ chronic diseases. The aim for all patients is an early integration of our palliative consulting service to accompany these patients throughout the course of their disease. For patients admitted to our ward, an individualised therapeutic plan based on the patient's symptom burden is set up after the primary assessment, thoroughly documented and individually adjusted daily according to the standards of specialised inpatient palliative care intervention defined by the German Association for Palliative Medicine [15]. The therapeutic interdisciplinary interventional approach is a combination of pharmacological pain and symptom relief, conversational psychotherapy, music therapy, physiotherapy and support of family care takers by social service. This specialised inpatient palliative care intervention was offered to all of the sarcoma patients.

Symptom burden was measured with a standardised palliative base assessment questionnaire on admission and at discharge. It consisted of an evaluation of the Eastern Cooperative Oncology Group performance status (ECOG), ranking from 0 to 5, which was first published by Oken et al. in 1982 [16], pain (numeric rating scale, NRS), a German version of the National Comprehensive Cancer Network (NCCN) distress thermometer (a self-reported tool for cancer patients to screen for symptoms of distress using a scale from 0 to 10) [17], MIDOS (minimal documentation system, the German version of the Edmonton Symptom Assessment Scale) and personal situational challenges. MIDOS corresponds to a self-assessment of patients in palliative care indicating e.g. the

Table 1 Patients' characteristics

Characteristic	Total ($n = 34$)
Gender n (%)	
male	19 (54)
female	15 (46)
Age at admission (years)	
mean (range)	59 (21–80)
Tumour subtypes n (%)	
Leiomyosarcoma	6 (17)
Angiosarcoma	4 (12)
Liposarcoma	3 (9)
MPNST	3 (9)
Pleomorphic sarcoma	3 (9)
Synovial sarcoma	3 (9)
Others	12 (35)
Tumour stage at diagnosis n (%)	
curative	14 (41)
locally adcanced	7 (21)
metastasized	13 (38)
Tumour stage on admission n (%)	
locally advanced	5 (15)
metastasized	29 (85)
Disease duration until admission (months)	
mean (range)	24 (1–125)
Patients with initial surgery n (%)	
yes	25 (74)
no	9 (26)
Patients with previous treatment lines n (%)	
0	2 (6)
≥ 1	32 (94)
Patients with previous radiation n (%)	
yes	25 (74)
no	9 (26)
Palliative care interventions n (%)	
1	22 (67)
2	4 (12)
3 or more	7 (21)

n number, *MPNST* malignant peripheral nerve sheath tumor

intensity of drowsiness, nausea, constipation, dyspnea, weakness, fatigue, anxiety, lymphedema and well-being on different scales. MIDOS ranges from 0 to 3, MIDOS 0 representing the absence of the symptom, MIDOS 3 indicating a severe manifestation. It was developed to facilitate and to standardise the evaluation of symptom clusters of cancer patients. Validation of the MIDOS was first published in 2000 by Radbruch et al. [18]. The MIDOS symptom score summarises the symptom burden and consists of a summation of each MIDOS score for all symptoms (no symptom = 0 points/MIDOS 0, severe symptom = 3 points/MIDOS 3; maximum 48 for 16 symptoms in total).

Additional information on pain medication was collected from patient records.

Data analysis was performed using IBM SPSS Statistics 25 (IBM Corp., Armonk, N.Y., USA) and Microsoft Excel 14.4.7. The following nonparametric tests were used: Wilcoxon signed ranks test for metric parameters as well as McNemar test for dichotomic parameters. All p values were two-sided, and $p < 0.05$ was considered statistically significant. Concerning the duration of hospitalisation, generalized estimating equation (GEE) was combined with paired t tests and Sidak correction.

Results

Patient cohort and interventions

In our retrospective analysis 53 palliative care interventions in 34 STS patients were analysed. Thirty-three percent of the patients ($n_p = 11$) received more than one palliative care intervention (21%, $n_p = 7$ more than three). In our cohort, the median disease duration before admission to the palliative care unit was 24 months (range 1–125 months).

85% of patients ($n_p = 29$) had metastases at admission, 15% had locally advanced disease ($n_p = 5$). In contrast, only 59% of patients ($n_p = 20$) were in a palliative treatment situation at the time of diagnosis (metastasised or locally advanced). The majority of patients (94%, $n_p = 32$) had already received one or more regimen of chemotherapy, and 74% of patients ($n_p = 25$) had received radiation before their first intervention. The same number of patients (74%) had received surgery. The median patients' age was 59 years (y) (range 21-80y). Please see Table 1 for detailed patients' characteristics.

The majority of admissions was from home (70%, $n_i = 37$). The mean duration of hospitalisation was 15 days (d) (range 2-36d). Analysing the different subgroups (one, two and three or more interventions) there was a significant difference concerning the duration of hospitalisation between the first (mean 17d) and the second intervention (mean 11d, $p = 0.007$) as well as between the second and the third intervention (mean 18d, $p = 0.047$). Patients who died on the ward had comparable durations of inpatient interventions (13d, range 2–32).

Since parts of the palliative base assessment questionnaires were filled out by the patients themselves, on admission only 47% ($n_i = 25$) were filled out completely (excluding BMI), 45% ($n_i = 24$) were incomplete, and 8% ($n_i = 4$) were not filled out. These numbers decreased further at discharge: nearly the same number of questionnaires were filled out completely (45%, $n_i = 18$), but only 30% ($n_i = 12$) were filled out partly, and 25% ($n_i = 10$) were not filled out at all. Comparing the numbers on admission, patients who died on the ward only completed the form in 15% ($n_i = 2$) of cases (77% ($n_i = 10$) incomplete, 8% ($n_i = 1$) not filled out). The most frequent missing feature was the distress thermometer. Therefore, for subsequent analysis, only a reduced number of interventions was included, respectively: pain $n_i = 53$, ECOG $n_i = 34$, MIDOS $n_i = 28$, BMI $n_i = 5$, distress $n_i = 13$.

Palliative care intervention

The predominant indication for admission to the palliative care unit was pain ($n_i = 23$, 67% of patients), followed by weakness ($n_i = 15$, 28%) and symptomatic tumor progression ($n_i = 15$, 28%).

Pain management

Regarding pain medication, 68% ($n_i = 36$) of patients were already treated with opioid medication before admission, the majority of them at a high WHO cancer pain ladder level (9% ($n_i = 5$) WHO level II, 59% ($n_i = 31$) WHO level III). 23% ($n_i = 12$) of patients were admitted without any pain medication. Palliative care intervention led to a significant reduction of pain: median NRS for acute pain was reduced from 3 to 1 ($p < 0.001$), while the pain experienced within the last 24 h before admission and at discharge was reduced from 5 to 2 ($p < 0.001$, see Fig. 1). 32% ($n_i = 17$) of patients received an intensification of medication according to the WHO cancer pain ladder. In contrast, patients who already received potent opioids (WHO III) stood to benefit from an opioid rotation (35%, $n_i = 11/31$) and/or a change in the route of administration (39%, $n_i = 12$), e.g. transdermal to intravenous. Notably, in 28% ($n_i = 15$) pain medication was not changed (see Table 2). Patients who died throughout hospitalisation had higher pain levels on admission (median NRS acute pain: 4, median 24 h: 6). Due to the clinical deterioration throughout the hospital stay in these patients, no reliable data could be documented on the development of individual pain perception.

Performance status

Interestingly, the median ECOG did not change throughout the palliative care intervention (median of 3 on admission and at discharge).

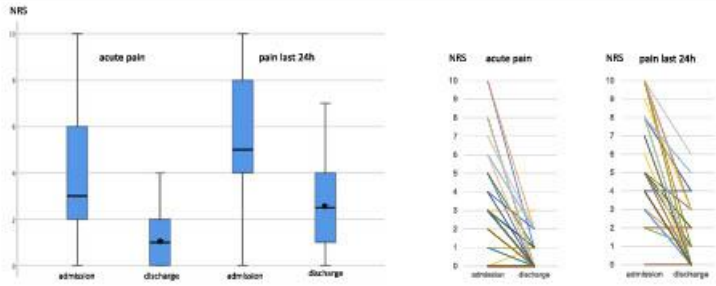

Fig. 1 Pain relief. **a** Boxplot for the assessment of pain relief achieved by inpatient palliative treatment; NRS = numeric rating scale, *$p < 0.001$. **b** Individual pain relief

Stress level

The median psychosocial stress level, according to the distress thermometer, was significantly reduced from 7.5 to 5 ($p = 0.027$) (see Fig. 2).

Symptom burden

Median MIDOS symptom score was reduced from 18 to 13 throughout the specialised palliative care intervention ($p < 0.001$, see Fig. 3). Regarding the predominant severe symptoms (MIDOS 3) weakness and fatigue, patients benefited from the palliative care intervention. In particular, this consisted of specific spatial conditions, e.g. single-bed-room, shared kitchen, terrace, and the multiprofessional team approach at the palliative care unit. The available supportive programs included psychooncologic counselling (as support for the whole family) as well as depending on the respective symptom music therapy (e.g. for pain, distress), physiotherapy (e.g. for lymphedema, fatigue) in addition to optimisation of general care and medication (antiemetics, laxatives).

While 57% ($n_i = 16$) reported weakness on admission, the rate dropped to 29% ($n_i = 8$) at discharge ($p = 0.008$). In concordance, fatigue dropped from 43% ($n_i = 12$) on admission to 18% ($n_i = 5$) at discharge ($p = 0.004$). Other symptoms such as dyspnea, nausea and constipation were only present in less than 20% (dyspnea: 18%, nausea: 7%, constipation: 7%). For details on different symptoms please refer to Table 3.

Table 2 Drug usage for pain relief

	Total ($n = 53$)	%
Medication on admission		
WHO 0	12	23
WHO I	5	9
WHO II	5	9
WHO III	31	59
Medication at discharge		
No change	15	28
Step up	17	32
Opioid rotation	11	21
Change in administration	14	26
reduction	4	8
WHO III on admission		
opioid rotation at discharge	11 of 31	35
Change in administration at discharge	12 of 31	39

n number

Nutritional status

The BMI on admission and at discharge was documented for only 9% of visits ($n_i = 5$). Except for one patient, there was a tendency towards an improvement of anorexia in the remaining $n_i = 4$ patients. This was achieved by enteral and/or partly parenteral high caloric nutrition as well as appetite-enhancing drugs.

Patient discharge management

After completing the specialised palliative care intervention, the majority of our STS patients (58%, $n_i = 31$) could be discharged home, 11% of patients ($n_i = 6$) were transferred to a hospice and 6% ($n_i = 3$) to other institutions such as geriatric clinics for further physiotherapeutic treatment. Twenty-five percent ($n_i = 13$) of our patients died at the palliative care unit due to their advanced disease. For 32% ($n_i = 10$) of the discharged patients, a continuation of antineoplastic therapy (e.g. chemotherapy or radiation) was planned, and 42% ($n_i = 13$) of the discharged patients were provided with additional supportive care by a specialised palliative home care team.

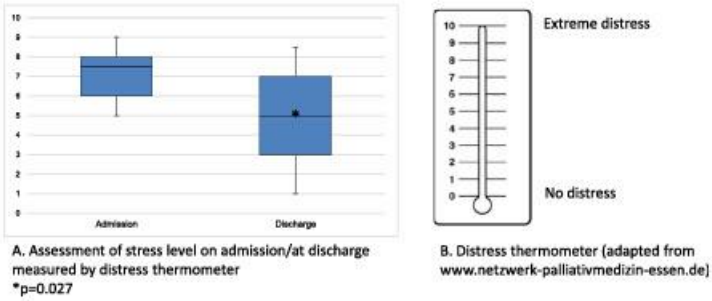

Fig. 2 Stress level. **a** Assessment of stress level on admission/discharge measured by distress thermometer; *$p = 0.027$. **b** Distress thermometer (adapted from www.netzwerk-palliativmedizin-essen.de)

Discussion

Main findings/results of the study

This study of 34 STS patients admitted for specialised palliative care intervention clearly demonstrates the effectiveness of these interventions documented by a standardised palliative base assessment. In detail, our patients experienced a significant reduction of pain, an improvement of symptom burden measured by the MIDOS symptom score and a decreased stress level. Therefore, our analysis demonstrates that specialised palliative care intervention leads to significant symptom relief and is useful for patients with advanced STS.

The importance and effectiveness of palliative care interventions have been shown for multiple oncologic diseases and are increasingly accepted [19–21]. Notably, the early integration of palliative care leads to an OS benefit which was first shown by Temel et al. in advanced lung cancer [22, 23]. In a variety of advanced cancer diseases integration of palliative care has a significant impact on patient outcome, quality of care, length of hospital stay and hospital costs [20]. Additionally, the involvement of a specialised palliative care team reduces acute care hospital treatments [24] and leads to a less aggressive therapeutic approach during end-of-life care as well as to higher levels of satisfaction among patients and their relatives [23]. Consequently, the early inclusion of palliative care within the first 8 weeks after the diagnosis of advanced cancer disease is now part of national and international clinical practice guidelines [25, 26].

Palliative care in an outpatient setting focusses on coping and support, symptom control, decision-making and future planning [27]. In general, reasons for admittance to an inpatient palliative care unit are symptom management, support for distressed families, or care for the imminently dying patient [20]. There are little data directly comparing community- and hospital-based palliative

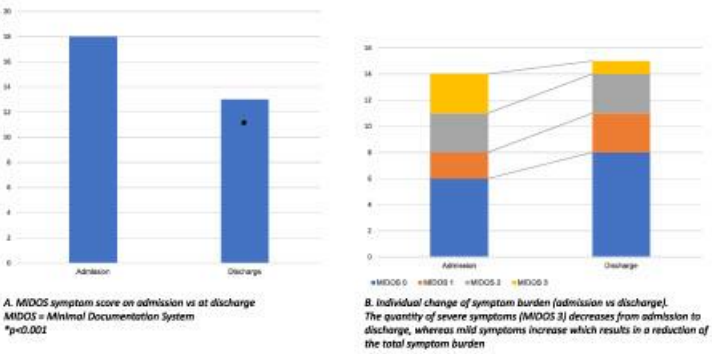

Fig. 3 *MIDOS symptom burden.* **a** *MIDOS symptom score on admission vs. at discharge; MIDOS = Minimal documentation system, *$p < 0.001$.* **b** *Individual change of symptom burden (admission vs. discharge). The quantity of severe symptoms (MIDOS 3) decreases from admission to discharge, whereas mild symptoms increase which results in a reduction of the total symptom burden*

Table 3 only including symptoms classified as severe (= MIDOS 3) by patients

	n = 28	
Symptom	**Admission**	**Discharge**
Weakness	16 (57%)	8 (29%)
Fatigue	12 (43%)	5 (18%)
Dyspnea	5 (18%)	1 (4%)
Insomnia	5 (18%)	1 (4%)
Fear	5 (18%)	2 (7%)
Loss of appetite	5 (18%)	3 (11%)
Family distress	5 (18%)	2 (7%)
Need for assistance in ADL	4 (14%)	6 (21%)
Lymphedema	4 (14%)	0 (0%)
Supply problems	3 (11%)	2 (7%)
Wound lesions	3 (11%)	0 (0%)
Nausea	2 (7%)	0 (0%)
Constipation	2 (7%)	2 (7%)
Depression	2 (7%)	0 (0%)

n number, *ADL* activities of daily living

care. Generally, patients requiring a hospital stay often have a higher symptom burden, or a faster disease progression limiting the necessary transitions in their homes. In the inpatient setting, a decrease of symptom burden can often be enabled faster. For instance, an optimisation of the opioid medication requires frequent clinical feedback, which cannot always be realised in the outpatient setting.

So far, only limited data are available on the specific challenges of palliative care interventions in the context of STS. Similarities can be found comparing our patients to other well-defined cohorts with different oncologic diseases receiving specialised palliative care intervention, especially when being integrated early into the therapeutic schedule [9, 23, 24, 28]. Patients with advanced STS are known to require multidisciplinary approaches due to the aggressiveness of the heterogeneous diseases and the high occurrence of a severe symptom burden [6]. Additionally, treatment of advanced and metastasised STS often includes repeated surgical interventions, which may be associated with complications and/or mutilating procedures. Furthermore, the majority of therapeutic approaches in advanced or metastatic STS comprises of chemotherapy and/or radiotherapy, possibly resulting in diverse side effects. STS often occurs at a younger age, leading to explicitly challenging therapeutic demands. Especially in younger patients, maintenance and/or recovery of abilities regarding activities of daily living (ADL) is very important. Pain, weakness and fatigue have been the predominant indications for admission in our cohort. Nevertheless, the median NRS for acute pain at admission was not very high (median 3). In our experience, patients with chronic pain often underestimate their actual pain level referring to the NRS. Accordingly, the mental burden of pain may not directly correlate with the respective pain level. Presumably, the majority of patients would retrospectively estimate their acute pain level on admission higher than they did in the situation of admission itself. Thus, the documented pain level within the previous 24 h was significantly higher in most cases (median 5).

Our data compare well to Gough et al. on patients with advanced STS, who have documented pain, fatigue and sleep disturbances as the most frequent symptoms [6]. To our knowledge, there are no published data concerning an early integration of palliative care in patients with sarcoma. Even though we aim to integrate palliative care early in the course of disease of our patients, some patients were admitted late (median disease duration until first admission 24 months, maximum 125 months), had aggressive disease or unfortunately died throughout the repeated palliative care interventions. These circumstances can partially explain why 25% of patients died before they were discharged. Another reason for this high percentage might be a less aggressive anti-tumour therapeutic approach in those patients.

Published literature covering an end-of-life setting describes symptoms like dyspnea and fever more predominantly than in our study. Our analysis also does not entirely compare to other early palliative care interventions, which are most often realised in an outpatient and/or community-based setting [9, 27, 29].

Strength and weaknesses/limitations of the study

Our study is limited by the sample size of 34 patients and the known restrictions of single-centre evaluation. Furthermore, for many of theinterventions data was incomplete. This was in part due to theself-assessment of some outcomes by the patients, a high symptom burden and a sometimes occuring communication barrier. Information about e.g. the pain level, which is simple to assess with the NRS, was available for all interventions. In contrast, information about more complex questions such as MIDOS and the distress thermometer was less often complete. Additionally, there were obviously no follow-up data about the deceased patients at discharge. To evaluate the benefit of the intervention for these patients, follow-up assessments could have been done earlier during the stay.

Besides the cohort size of our study, the heterogeneity of sarcomas as well as the retrospective character of our analysis make universal conclusions difficult, and in accordance our data should be validated prospectively and in a larger patient cohort.

However, even though the optimal assessment for QoL in patients with STS is not yet defined, and despite our small patient population, we could show clinically relevant effects and we still consider our data as profoundly useful as published information on these patients remains sparse. Our study emphasises the importance of palliative care intervention in advanced oncologic disease, specifically in STS patients, and even gives further evidence to support the earlier integration of palliative care intervention in STS patients. Therefore, we recommend an early integration of palliative care measurement in the first 8 weeks, according to ASCO clinical practice guidelines [25].

Some of our patients showed pain relief optimised without any change in medication. Besides the amelioration achieved by causal treatment of the pain source, other essential factors are influencing the pain level. For instance, an intensified individual support structure including psychooncologic counselling, music therapy and a reduction of psychosocial stress level, in general, may also influence the pain intensity in the individual patient.

BMI was only evaluable in a tiny subset of patients (n_i = 5,9%). In general, the administration of parenteral nutrition might be considered in patients with a survival of more than some weeks, only [26]. Despite the small sample size, in n_i = 4 (8%) patients, we found a discrete gain of body weight by optimisation of antiemetic treatment and/or appetite increase as well as the provision of high caloric nutrition if indicated.

What this study adds

To our knowledge, this is the first report in STS patients analysing hospital-based palliative care intervention, which does not focus on end-of-life care, but on palliative care intervention throughout the entire course of the disease.

Conclusion

Our data show the impact of specialised palliative care interventions with a multiprofessional approach on symptom relief and quality of life in patients with advanced STS. Further exploration of the effects of early integration of palliative care on symptom relief, quality of life and the possible improvement of overall survival in STS patients is warranted. Analyses in larger cohorts are warranted to answer these questions.

For this purpose, patients with suspected STS should be transferred to a specialised centre led by an interdisciplinary team to complete histologic workup and initiate causal therapy. This could simultaneously enable an early standardised screening for physical and psychosocial symptoms. With repeated assessments during the course of their disease, subgroups with special need for intensified support could be identified.

Abbreviations

ADL: activities of daily living; ASCO: American Society of Clinical Oncology; BMI: body mass index; d: days; ECOG: Eastern Cooperative Oncology Group; e.g.: exempli gratia, for example; GEE: generalised estimating equation; h: hours; MIDOS: Minimal Documentation System; MPNST: Malignant peripheral nerve sheath tumor; N_i: number of interventions; n_{pi}: number of patients; NCCN: National Comprehensive Cancer Center; NRS: numeric rating scale; OS: overall survival; PFS: progression free survival; QoL: quality of life; PROs: patient reported outcomes; STS: soft tissue sarcoma; WHO: World Health Organisation

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Authors' contributions

F.B. and J.K.S. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: F.B., J.K.S. and A.F. Acquisition, analysis or interpretation of data: F.B., J.K.S. and A.F. Drafting of the manuscript: F.B. J.K.S, L.B. and A.F. Critical revision of the manuscript for important intellectual content: J.K.S, F.B., A.D., M.S., S.M., G.K, D.K., A.B., P.T., J.A., U.P., L.B. and A.F. Statistical analysis: F.B., J.K.S. and A.F. Administrative, technical or material support: F.B., J.K.S., L.B., and A.F. All authors have read and approved the manuscript.

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Availability of data and materials

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Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
Patients were included with institutional review board approval and written patient informed consent in accordance with the local ethical guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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3 Diskussion

Sarkome treten im Erwachsenenalter sehr selten auf und sind gleichzeitig sehr heterogen in ihrem biologischen Verhalten. Umso mehr ist das Erzielen eines besseren Krankheitsverständnisses von elementarer klinischer Bedeutung. Die Durchführung großer prospektiver randomisierter klinischer Studien ist aus den o.g. Gründen aber zwangsläufig erschwert. Somit bleiben systematische retrospektive Auswertungen eine wichtige Grundlage für die Erkenntnisgenerierung.

3.1 Prognostische Faktoren im Kontext der Weichgewebssarkome (Originalarbeiten 2.1 und 2.2)

Um effektivere und innovative Behandlungsoptionen zu entwickeln, ist die Identifikation prognostischer und prädiktiver Marker notwendig. Hierfür kommen sowohl Patient:innen- als auch Tumor-spezifische Charakteristika infrage.

Diese individuellen prognostischen und prädiktiven Faktoren können angesichts der oftmals fehlenden eindeutigen therapeutischen Standards einen maßgeblichen Einfluss auf die jeweilige Therapieempfehlung haben.

Bisher haben sich sowohl für die Abschätzung des Risikos als auch des Therapieerfolgs bei Sarkomerkrankungen lediglich allgemeine Erkrankungs-assoziierte Parameter etabliert. Hierzu zählen neben der Tumorgröße (<5cm vs. ≥5 cm) die Lokalisation (Extremität vs. Stamm, tief/subfaszial vs. oberflächlich/epifaszial), der histopathologische Subtyp, das Grading (G1 vs. G2/3) und der Resektionsstatus (R0 vs. R1 vs. R2) [1].

Darüber hinaus beeinflusst auch die pathologische Beurteilung der residuellen vitalen Tumorzellen, d.h. des Regressionsgrades nach erfolgter neoadjuvanter Behandlung, maßgeblich die weitere bzw. postoperative Therapiestrategie [74]. Möglicherweise wird diese zukünftig noch durch andere Kriterien wie z.B. dem Vorliegen einer Sklerohyalinose ergänzt oder sogar ersetzt werden können [75].

Molekulargenetische Untersuchungen sind abgesehen von der Analyse pathognomonischer genetischer Veränderungen wie u.a. der EWSR1-FLI1-Fusion bei Ewingsarkomen oder der MDM2-Amplifikation bei hoch- und dedifferenzierten Liposarkomen nicht Bestandteil der klinischen Routine [1].

Eine gewisse prognostische Aussagekraft konnte bisher lediglich für die Unterscheidung zwischen Sarkomen mit komplexem Karyotyp und Translokations-assoziierten Sarkomen, die Tumormutationslast (TMB) sowie Alterationen des *Cyclin Dependent Kinase Inhibitor 2A* (CDKN2A) gezeigt werden [69].

Bezüglich prädiktiver Marker ist die Datenlage für Sarkomerkrankungen spärlich. Selbst die für die Prädiktion der Wirkung einer Immuntherapie bei diversen Tumorentitäten etablierten Marker wie z.B. PD1/PD-L1 oder der Mikrosatellitenstatus sind hier wenig verlässlich [76]. Dagegen erscheint die Bestimmung Tumor-infiltrierender Lymphozyten (TILs), der TMB und insbesondere der Nachweis von tertiären lymphoiden Strukturen (*tertiary lymphoid structures*, TLS) bei bestimmten Subentitäten wie Angiosarkomen oder undifferenzierten pleomorphen Sarkomen vielversprechend [76]. So sind TLS u.a. auch Bestandteil der Unterteilung in bestimmte Phänotypen (*immune-low* vs. *immune-high* sowie *highly vascularized*) [77], [78].

Darüber hinaus deuten Proteomanalysen darauf hin, dass durch Kombination mit Komplementinhibitoren bei *immune-low* Sarkomen die Effektivität der Immuntherapie gesteigert werden könnte [79]

Angesichts der ausgeprägten Heterogenität und der Notwendigkeit eines besseren Erkrankungsverständnisses erscheint die weitere molekulargenetische Charakterisierung wie sie z.B. im Rahmen umfassender Hochdurchsatz-Analysen im akademischen Kontext möglich ist umso wichtiger. Neben dem MASTER-Programm des Deutschen Krebsforschungszentrums (DKFZ), des Nationalen Centrums für Tumorerkrankungen (NCT) sowie des Deutschen Konsortiums für Translationale Krebsforschung (DKTK) ist die französische MULTISARC-Studie (NCT03784014) ein weiteres Beispiel für den Versuch einer unmittelbaren Translation der Ergebnisse umfassender molekulargenetischer Analysen in eine zielgerichtete bzw. personalisierte Therapie [42], [80].

Neben der Identifizierung zusätzlicher Targets führt die erweiterte Diagnostik in circa 10% der Fälle zu einer Modifizierung der ursprünglichen Diagnose, welche unter Umständen auch Einfluss auf die weitere Therapieentscheidung haben kann [81].

Insgesamt weist jedoch lediglich ein Drittel der Sarkome therapeutisch adressierbare genetische Alterationen auf, weshalb für die Integration der in vielerlei Hinsicht aufwändigen Diagnostik in die klinische Routineversorgung sicherlich eine Selektion geeigneter Fälle notwendig ist [81]. Eine essentielle Grundlage hierfür ist die individuelle Befundkonstellation der konventionellen pathologischen Diagnostik (Morphologie, Immunhistochemie, Zytogenetik). Darüber hinaus sollten weitere Kriterien wie beispielsweise die höhere Prävalenz möglicher therapeutischer Zielstrukturen bei Nachweis von EWSR1-Fusionen mit seltenen Fusionspartnern

berücksichtigt werden [43]. Klare Empfehlungen liegen jedoch bis dato nur für die Analyse von NTRK-Fusionen vor [82].

Wie bei anderen soliden Tumorerkrankungen wird auch bei Sarkomen zunehmend die Rolle der sogenannten *Liquid Biopsies* für die Diagnostik und die Verlaufsbeurteilung untersucht. Hierzu gehören Zytokine, extrazelluläre Vesikel, micro RNA, zirkulierende Tumorzellen und zellfreie Tumor-DNA [69]. Am aussichtsreichsten erscheint die Bestimmung von zirkulierender zellfreier Tumor-DNA, welche bereits zur Früherkennung von Rezidiven beitragen kann [83], [84]. Bisher hat sich keiner der genannten Biomarker aus dem peripheren Blut für die klinische Routine bewährt, so dass die Bestimmung noch auf Studien bzw. akademische Fragestellungen beschränkt bleibt.

Zu den Patient:innen-assoziierten Charakteristika zählt unter anderem das Alter, welches im Mittel bei Erstdiagnose bei beiden Geschlechtern bei circa 69 Jahren liegt [2]. Dennoch sind Patient:innen >65 Jahre in Studien oft nicht erfasst bzw. unterrepräsentiert [85].

Dies gilt insbesondere auch für die Familie der Ewingtumore, einer bei älteren Patient:innen eher selten auftretenden Sarkomsubentität, deren Altersgipfel im 2. Lebensjahrzehnt liegt [2]. So orientiert sich das therapeutische Vorgehen bei dieser Erkrankung auch bei erwachsenen Patient:innen an pädiatrischen Protokollen. Neben dem Stadium, der Tumorgröße und der -lokalisation ist u.a. auch das Alter >15 Jahre ein wichtiger prognostischer Faktor. Umso relevanter ist die Frage, welches das adäquate therapeutische Vorgehen bei erwachsenen Patient:innen ist. In Abhängigkeit vom biologischen Alter und von Komorbiditäten lassen sich die intensiven pädiatrischen Protokolle in der klinischen Praxis nicht immer vollständig umsetzen. Unter dieser Annahme und mit der Frage nach den daraus resultierenden therapeutischen Ergebnissen erfolgte die in Publikation 2.1 dargestellte systematische monozentrische Analyse von Patient:innen mit EFT in den Altersgruppen ≤25 vs. 26–40 vs. ≥41 Jahre.

Hier ließen sich signifikante Unterschiede in Bezug auf das mediane PFS in Abhängigkeit des Tumorstadiums und von Komorbiditäten identifizieren. Aufgrund der kleinen Fallzahl und signifikanter Unterschiede zwischen den Altersgruppen bezogen auf Komorbiditäten, den Tumorursprung und die Anzahl der Therapiezyklen lässt sich der Einfluss des höheren Lebensalters (≥26 Jahre) allein jedoch nicht eindeutig davon abgrenzen. Entgegen unserer Erwartungen fand sich kein signifikanter Unterschied bezüglich der Therapieintensität und der Notwendigkeit von Dosismodifikationen in

den verschiedenen Altersgruppen. Dies ist möglicherweise der Grund für die vergleichbaren Überlebensraten von jüngeren und älteren Patient:innen in der untersuchten Kohorte und legt die entscheidende prognostische Bedeutung einer intensiven Therapie auch bei älteren Patient:innen in einem entsprechenden biologischen Alter bzw. Allgemeinzustand nahe.

Im Allgemeinen wird jedoch bei älteren Patient:innen häufig eine weniger intensive Therapie als bei jüngeren Patient:innen gewählt [85]. Dies bezieht sich auf sämtliche Modalitäten (chirurgische, medikamentöse und Strahlentherapie) und wirkt sich ungünstig auf die meist ohnehin schlechtere Prognose älterer Patient:innen aus [85]. Wie auch aus der Publikation 2.1 ersichtlich kann durch die Durchführung der intensiveren Standardtherapien eine mit jüngeren Patient:innen vergleichbare Erkrankungskontrolle und somit Prognose erreicht werden [85].

Bezüglich der Auswahl von trotz eines höheren Lebensalters für eine intensive Therapie geeigneter Patient:innen stehen verschiedene geriatrische Assessments zur Verfügung, welche teilweise auch schon in Studienprotokolle integriert werden: *Comprehensive Geratric Assessment* (CGA), *Activities of Daily Living* (ADL), *Instrumental Activities of Daily Living* (IADL) oder das *Mini Nutrition Assessment* (MNA). Auch ist eine Einschätzung der zu erwartenden Therapie-assoziierten Toxizität mittels spezifischer Werkzeuge möglich: *Chemotherapy risk assessment scale for high age patients* (CRASH), *Cancer and Aging Research Group* (CARG) [85].

Für Sarkomerkrankungen werden solche standardisierten Assessments bisher nur in einer sehr geringen Anzahl von Studien erprobt. Ein Beispiel hierfür ist die Phase III TOLERANCE Studie (NCT04780464) der *European Organisation for Research and Treatment of Cancer* (EORTC), in welche Patient:innen ≥65 Jahre mit fortgeschrittenem STS eingeschlossen werden konnten. Primärer Endpunkt ist der Vergleich der physischen Funktion und der Rollenfunktion unter der Therapie mit Doxorubicin bzw. Cyclophosphamid. Die Studie musste jedoch kürzlich aufgrund zu schlechter Rekrutierung vorzeitig beendet werden.

Die Durchführung immer intensiverer Therapieregime führt nicht nur bei Patient:innen im höheren Lebensalter zu einem größeren Risiko stärkerer Nebenwirkungen. So zeigten sich in der LMS-04 Studie, in welcher im Sinne einer Therapieintensivierung Doxorubicin und Trabectedin kombiniert worden sind, im Vergleich mit der Doxorubicin-Monotherapie deutliche Unterschiede bezogen auf höhergradige (Grad 3-4) hämatologische Toxizitäten: febrile Neutropenie 28 vs. 9%, Anämie 31 vs. 5% und

Thrombozytopenie 47 vs. 0% [30]. Neben langanhaltenden ausgeprägten Zytopenien bzw. den in deren Folge möglicherweise auftretenden lebensbedrohlichen Infektionen können auch andere Therapie-assoziierte Toxizitäten unter Umständen dazu führen, dass eine intensivmedizinische Betreuung notwendig wird.

In einer bereits im Jahre 2018 veröffentlichten Konsensuserklärung der deutschen und österreichischen Fachgesellschaften für Intensivmedizin bzw. Hämatologie und Onkologie wird angesichts der infolge verbesserter intensivmedizinischer und hämato-onkologischer Therapien oft vergleichbaren Prognose von Tumorpatient:innen und kritisch Kranken eine Gleichbehandlung empfohlen [86]. Nichtsdestotrotz bleibt die Indikationsstellung einer intensivmedizinischen Auf- oder Übernahme bei onkologischen Patient:innen oft schwierig und gibt Anlass für kontroverse interdisziplinäre Diskussionen.

Bezüglich klinischer Entscheidungshilfen mittels prognostischer Faktoren bei Sarkompatient:innen fand sich zum Zeitpunkt der in Publikation 2.2 dargestellten Analyse lediglich eine weitere veröffentlichte Auswertung [87]. Wie in der von Gupta et al. beschriebenen Kohorte war das Überleben der von uns untersuchten Population vergleichbar mit derjenigen von Patient:innen mit anderen soliden Tumorerkrankungen. Entscheidend für die Prognose waren weniger die jeweiligen spezifischen Tumorcharakteristika sondern in erster Linie allgemeine Faktoren wie die Höhe der Sepsis- und Performance Scores (SOFA, SAPS II) bzw. der sich darin jeweils widerspiegelnde Grad der Organ(dys)funktion.

Somit sollten bei der Entscheidung für oder wider eine intensivmedizinische Behandlung auch bei Patient:innen mit Sarkomerkrankungen allgemeine Charakteristika bzw. Sepsis- und Performance-Scores neben der malignen Grunderkrankung zu Rate gezogen werden.

3.2 Therapieoptimierung

Im Fokus der Therapieoptimierung steht unter anderem die Kombination etablierter Behandlungsschemata mit neuen zielgerichteten Substanzen. Hierfür hat sich in den bisherigen Untersuchungen wiederholt die Wichtigkeit der Therapiestratifizierung nach Sarkom-Subgruppen gezeigt. Angesichts der limitierten Verfügbarkeit großer randomisierter Studien für Sarkomerkrankungen stellen retrospektive Auswertungen eine wichtige Grundlage für die Verbesserung der Therapiekonzepte dar.

3.2.1 Medikamentöse Therapie (Originalarbeit 2.3)

Wie bei anderen Tumorerkrankungen werden zunehmend auch zielgerichtete Substanzen in die Therapiestrategien integriert. Ein Beispiel hierfür ist die Hemmung von PDGFRα, welches insbesondere bei Sarkomen mit komplexem Karyotyp exprimiert wird [88]. Der korrespondierende Antikörper Olaratumab hatte in der ersten Auswertung von Phase Ib/II Daten in Kombination mit Doxorubicin zunächst eine sehr vielversprechende Wirkung mit Verbesserung des Progressionsfreien Überlebens sowie des Gesamtüberlebens gezeigt [70]. Darüber hinaus war im Vergleich mit der Doxorubicin-Monotherapie auch eine bessere lokale Kontrollrate erzielt worden. In der anschließenden Phase III Studie konnten diese Ergebnisse dann jedoch nicht reproduziert werden [71]. Dieses Beispiel verdeutlicht die Wichtigkeit größerer randomisierter Studien für eine valide Beurteilung der Wirksamkeit neuer Substanzen bzw. Therapiestrategien.

Als mögliche Ursache für die diskrepanten Ergebnisse wurde die Heterogenität der in die Phase Ib/II bzw. III eingeschlossenen Patient:innenpopulation bezogen auf die histologischen Sarkom-Subentitäten sowie die Erkrankungssituation (lokal fortgeschritten vs. metastasiert) diskutiert [71]. Wie in Publikation 2.3 dargestellt, ließ sich in der Kohorte von an der Charité zwischen 2016 und 2019 mit Doxorubicin und Olaratumab behandelten Patient:innen keine Subgruppe identifizieren, welche von der Hinzunahme des Antikörpers besonders profitiert hat. Es zeigte sich aber eine besonders gute lokale Kontrolle bei Durchführung einer ergänzenden regionalen Tiefenhyperthermie, was deren Einsatz in der neoadjuvanten Situation vielversprechend erscheinen lässt.

Neben Pazopanib, einem ab der Zweitlinie für diverse Weichgewebssarkom-Subentitäten zugelassenen Multityrosinkinaseinhibitor, zeigen auch andere zielgerichtete Substanzen vielversprechende Ergebnisse: Ein neueres Beispiel hierfür ist der Einsatz von MDM2-Inhibitoren bei Subentitäten mit Vorliegen der entsprechenden Genamplifikation. Diese ist pathognomonisch für hoch- und dedifferenzierte Liposarkome, kommt aber zum Beispiel auch bei Intimasarkomen häufig vor [1], [89], [90]. Es sind bereits Substanzen mehrerer Hersteller verfügbar, aktuell werden diese jedoch noch ausschließlich im Rahmen klinischer Studien eingesetzt [52], [91].

Gleiches gilt für CDK4/6 Inhibitoren, auch hier stehen insbesondere fortgeschrittene dedifferenzierte Liposarkome aufgrund der Expression von CDK4 im Mittelpunkt des Interesses. Die Höhe der CDK4-Expression scheint zudem eine prädiktive Aussagekraft

zu besitzen, Palbociclib zeigte hier eine gute Wirksamkeit [56], [92]. Darüber hinaus sind auch andere CDK4-hemmende Substanzen mit vielversprechenden Ergebnissen bei dedifferenzierten Liposarkomen erprobt worden [93]. Weitere Untersuchungen dieser Zielstruktur erscheinen somit aussichtsreich.

Auch immuntherapeutische Strategien sind teilweise erfolgreich eingesetzt worden. Neben der Immuncheckpointblockade, welche insbesondere bei Angiosarkomen und ASPS gute Ergebnisse erzielt, werden auch zielgerichtete Immuntherapien getestet [64], [66], [94], [95]. Die hier adressierten Tumor/Testis Antigene sind u.a. NY-ESO1 und PRAME, welche in circa 10% der Weichgewebssarkome exprimiert sind [96]–[98]. Neben T-Zell-Konstrukten gegen NY-ESO1, welches insbesondere bei myxoid rundzelligen Liposarkomen attraktiv erscheint, da diese ein hohes Expressionslevel des NY-ESO1 Antigens aufweisen, werden Tumorvakzinen in mehreren Studien erprobt [61], [99].

Die Prognose bzw. Therapiestrategie hängt auch davon ab, ob ein Translokations-assoziiertes Sarkom (u.a. myxoide Liposarkome, Synovialsarkome, mesenchymale Chondrosarkome, alveoläre Weichgewebssarkome) oder eine Entität mit höherer Mutationslast (engl. *Tumor mutational burden*, TMB) vorliegt. Translokations-assoziierte Sarkome zeigen beispielsweise anders als Sarkome mit komplexem Karyotyp eine mit Anthrazyklinen vergleichbare Ansprache auf Trabectedin [100].

Zu den Entitäten mit hoher TMB gehören u.a. undifferenzierte pleomorphe Sarkome, Liposarkome und Angiosarkome [81]. In der Regel haben diese bei Einsatz konventioneller Chemotherapien eine schlechtere Prognose [81], [101]. Durch Integration von Immuntherapien in die jeweiligen Therapiekonzepte könnte dies möglicherweise geändert werden [81].

3.2.2 Lokale Therapie (Originalarbeiten 2.4 und 2.5)

Ein wichtiger Bestandteil der multimodalen Therapie von Sarkomen ist die perioperative Strahlentherapie. In diesem Kontext werden unterschiedliche Fraktionierungen und Behandlungszeitpunkte (normo- vs. hyperfraktioniert, gleichzeitige vs. sequentielle Radiochemotherapie, neo- vs. adjuvant) untersucht. Hierdurch soll die Therapieeffektivität gesteigert und gleichzeitig das Risiko des Auftretens von Toxizitäten so niedrig wie möglich gehalten werden.

Am besten untersucht wurde die Frage der perioperativen Strahlentherapie bisher bei retroperitonealen Sarkomen, u.a. im Rahmen der randomisierten Phase III EORTC-62092 (STRASS)- Studie und der Daten der italienischen Sarkomgruppe [102], [103].

Hier wurde bei Patient:innen mit Liposarkomen das abdominale rezidivfreie Überleben (*abdominal recurrence-free survival*, ARFS) mit bzw. ohne neoadjuvante Radiatio verglichen. In der Kohorte mit neoadjuvanter Strahlentherapie konnte ein Vorteil bezogen auf das ARFS für bestimmte Subgruppen nachgewiesen werden [104].

Durch die Kombination der Radiatio mit einer Chemotherapie kann nicht nur das lokale Ansprechen weiter gesteigert, sondern auch das Risiko einer Fernmetastasierung reduziert werden [105]–[107]. Ein direkter Vergleich der verschiedenen neoadjuvanten Modalitäten steht bisher nicht zur Verfügung, so dass sich das klinische Vorgehen aktuell an retrospektiven Auswertungen wie u.a. Publikation 2.4 orientiert.

In der untersuchten Kohorte von Patient:innen mit lokalisierten hochgradigen Weichgewebssarkomen konnte eine verbesserte lokale Kontrolle nachgewiesen sowie eine Reduktion des Risikos für Fernmetastasen gezeigt werden. Gleichzeitig wurde unter der Kombination der neoadjuvanten Bestrahlung mit einer medikamentösen Therapie aber auch eine gesteigerte Therapie-assoziierte Toxizität beobachtet.

In Abhängigkeit der jeweiligen Strahlendosis bzw. Fraktionierung sowie der eingesetzten medikamentösen Therapie können bei mehr als 50% der Patient:innen Grad 3-4 hämatologische Toxizitäten auftreten [108]. Somit ist die kombinierte perioperative Radiochemotherapie trotz ihrer Effektivität sicherlich nicht für alle Patient:innen die optimale Behandlung.

Für die alleinige neoadjuvante Bestrahlung ist der aktuelle Standard eine auf 25 Fraktionen aufgeteilte Gesamtdosis von 50 Gy mit somit einer Therapiedauer von insgesamt fünf Wochen. Gerade für ältere und/oder komorbide Patient:innen stellt die mehrwöchige tägliche Strahlentherapie eine große Belastung dar. Dies kann im Extremfall auch dazu führen dass die Behandlung vorzeitig abgebrochen oder gar nicht erst begonnen wird [109], [110].

Zur Verkürzung der Therapiedauer und einer dadurch möglicherweise verbesserten Therapieadhärenz kann u.a. eine hypofraktionierte Durchführung dienen [111]. Darüber hinaus scheint sich durch die Applikation der Gesamtstrahlendosis in kürzerer Zeit sogar eine bessere lokale Kontrolle als mittels normofraktionierter Applikation erzielen zu lassen [112].

Die Häufigkeit postoperativer akuter Wundkomplikationen unter der hypofraktionierten Therapie ist im Vergleich mit konventionell fraktionierten historischen Kontrollen teilweise sogar geringfügig niedriger [20].

Bisher ist jedoch keine randomisierte prospektive Untersuchung zu normo- vs. hypofraktionierter Radiotherapie verfügbar, auch unterscheiden sich die jeweiligen Fraktionierungen in den bisher erprobten Protokollen teilweise deutlich voneinander wie die in Publikation 2.5 zusammengefasste Analyse zeigt.

Angesichts der mit einer normofraktionierten Bestrahlung vergleichbaren Verträglichkeit kann auch die hypofraktionierte Radiatio in ausgewählten Fällen mit einer medikamentösen Therapie kombiniert werden. Eine der wenigen aktuelleren Studien hierzu hat retrospektiv die Wirkung einer kombinierten hypofraktionierten Radiatio mit Trabectedin bei high risk lokalisierten bzw. metastasierten STS untersucht. Im Median wurden 5 Zyklen mit einer medianen Dosis von 30 Gy verabreicht [113]. Darüber hinaus werden auch Kombinationen mit Immuntherapie erprobt (NCT03602833) [114].

3.2.3 Palliative/Supportive Therapie (Originalarbeit 2.6)

Für die Beurteilung einer Therapie hat neben einer guten Erkrankungskontrolle auch deren Auswirkungen auf die Lebensqualität (*Health-related quality of life*, HRQoL) eine immer größere Bedeutung. Diese spielt nicht nur eine wichtige Rolle für das Wohlbefinden des:der Patient:in, sondern kann sich auch auf die Therapieadhärenz auswirken. Darüber hinaus etabliert die HRQoL sich auch bei Sarkomerkrankungen immer mehr als unabhängiger prognostischer Faktor [115]–[117].

Die Notwendigkeit einer intensiven, multimodalen Therapie von Sarkomerkrankungen geht mit vielfältigen Toxizitäten bzw. Einschränkungen einher. Insbesondere bei jungen Patient:innen ist aber der Erhalt der Selbstständigkeit und der Funktionen bzw. der Aktivitäten des alltäglichen Lebens besonders bedeutsam. Dies bestätigte zum Beispiel die Untersuchung von Sarkom-Überlebenden im Rahmen der SURVSARC Studie, in welcher bei jungen und mittelalten Patient:innen im Zusammenhang mit medikamentöser Tumortherapie die höchste Symptomlast und die schlechteste HRQoL beobachtet wurde [118].

Für die Evaluation der Symptomlast und des Unterstützungsbedarfs stehen u.a. die in Publikation 2.6 beschriebenen standardisierten Messinstrumente NRS, MIDOS und das Distress Thermometer zur Verfügung. Diese können aber jeweils nur einen Teil der verschiedenen Dimensionen der HRQoL abbilden, deren Erfassung in der Regel wesentlich komplexer ist als beispielsweise die Angabe der Schmerzintensität auf der NRS.

Dies macht die individuelle Dokumentation zu einer Herausforderung. Auch in der o.g. Untersuchung waren die Angaben teilweise sehr lückenhaft, da diese durch den:die Patient:in selbst oder ggf. durch eine Pflegekraft notiert werden müssen.
Insbesondere in Situationen mit akut oder im Verlauf zusehends erhöhter Symptomlast kann das eine Überforderung bedeuten[116], [119].
Durch sogenannte *patient-reported outcomes* (PROs), deren Erfassung auch mittels Internet-basierter Anwendungen bzw. elektronischer Geräte wie Smartphones oder Tablets möglich ist, soll eine bessere Akzeptanz und regelmäßigere Dokumentation durch die Patient:innen selbst erreicht werden [120]. Auch können durch ihre Nutzung Sprach- oder andere Kommunikationsbarrieren bei komplexeren Fragen reduziert werden [121]. Die wichtige Bedeutung der PROs spiegelt sich in ihrer Berücksichtigung bei der Bewertung neuer Arzneimittel durch die FDA bzw. die Aufnahme in die Graduierung von Toxizitäten im Rahmen klinischer Studien anhand der *Common Terminology Criteria for Adverse Events* (CTCAE) wider [121].
Die Aufrechterhaltung oder ggf. auch Wiederherstellung der Lebensqualität rückt immer mehr in den Fokus der therapeutischen Bemühungen. Die Messung der QoL und die Integration supportivmedizinischer Konzepte sollte angesichts der signifikanten Auswirkungen sowohl auf die Lebensqualität als auch auf die Prognose nicht nur in fortgeschrittenen Stadien frühzeitig begleitend zur Behandlung der Tumorerkrankung selbst erfolgen [115]. Eine Möglichkeit hierzu bietet u.a. die Erfassung der PROs im Rahmen klinischer Studienprotokolle, wie es beispielsweise in der *Prospective Study to Evaluate Patient Reported Outcomes (PRO) During Rechallenge With Trabectedin in Sarcoma Patient* (PROTraSarc) Studie realisiert wurde (NCT06050434). Auf diese Weise kann die Bedeutung der Lebensqualität für die klinische Entscheidungsfindung und auch Prognose verdeutlicht werden, welche dann optimalerweise auch in der klinischen Routineversorgung außerhalb von Studien zusehends eine höhere Priorität erhält.

4 Zusammenfassung

In dieser Arbeit werden verschiedene Dimensionen der Therapieoptimierung von Sarkomerkrankungen dargestellt. Beginnend bei der Identifizierung prognostischer bzw. prädiktiver Marker zur präziseren Patient:innenselektion werden Beispiele für verschiedene Ansätze des medizinisch-technischen Fortschritts der Therapie gegeben. Abschließend geht es um die Begleitung der Behandlung, sowohl nach Ausschöpfen der therapeutischen Optionen als auch zur Unterstützung der kurativ intendierten Tumortherapie.

Als Grundlage für die Entwicklung zielführender Studienkonzepte, welche eine weitere Therapieoptimierung herbeiführen können, ist eine Verbesserung des Krankheitsverständnisses notwendig. In Anbetracht der Seltenheit und Heterogenität der Sarkomerkrankungen sind retrospektive Auswertungen und Reviews bzw. Metaanalysen hierfür ein wichtiger Ausgangspunkt. Insbesondere ist auch die differenzierte Betrachtung von Subgruppen anhand histopathologischer bzw. molekulargenetischer Kriterien und ggf. auch der anatomischen Lokalisation notwendig [71], [69].

Eine wichtige Voraussetzung für die Sammlung einer aussagekräftigen Menge klinischer Informationen ist der Aufbau von Daten- und Biobanken, welcher sich nur durch sowohl interdisziplinäre als auch zentrenübergreifende Kooperation realisieren lässt. Das *German Interdisciplinary Sarcoma Registry* (GISAR) stellt einen Versuch der Deutschen Sarkomgruppe (*German interdisciplinary sarcoma group*, GISG) dar, hierfür eine Infrastruktur zu etablieren (NCT041228729). Aus dieser ist auch ein erstes molekulares Subprojekt (*Molecular analyses of advanced or metastatic sarcoma patients via comprehensive genomic profiling*, MORNING) hervorgegangen, welches bereits vollständig rekrutiert hat.

Durch den Einsatz molekulargenetischer Analytik und die Entwicklung spezifischer Panels wird die Diagnosestellung immer präziser. Die molekulargenetischen Erkenntnisse tragen durch Ergänzung der Zytomorphologie zu einer Erleichterung der Entitätszuordnung bei, da diese häufig definierende Aberrationen aufweisen [81]. Darüber hinaus gewinnen Methylierungsanalysen zunehmend an Bedeutung [122], [123].

Aus der Panel-Diagnostik lassen sich teilweise auch prognostische und prädiktive Rückschlüsse ziehen und ggf. zusätzliche zielgerichtete oder immuntherapeutische Optionen identifizieren [69], [81]. Ein im klinischen Alltag bereits etabliertes Beispiel

für die prädiktive Bedeutung somatischer Aberrationen ist der Nachweis von cKIT bzw. PDGFRα-Mutationen bei GIST [124].

Die Behandlungseffektivität der bereits etablierten therapeutischen Strategien kann beispielsweise durch Intensivierung der medikamentösen Therapie, Kombination mit lokalen Behandlungsverfahren oder individualisierter Fraktionierung der Strahlentherapie gesteigert werden.

Neben der genauen Kenntnis des jeweiligen Subentitäts-spezifischen bzw. Erkrankungs-assoziierten Risikos ist auch eine optimale Patient:innenselektion entscheidend. Insbesondere bei Weichgewebssarkomen, welche am häufigsten im höheren Lebensalter (>65 Jahre) auftreten, besitzt die Abwägung der Behandlungs-assoziierten Toxizitäten in Bezug auf den zu erreichenden therapeutischen Benefit eine herausragende Bedeutung [2]. Eine Hilfestellung bieten standardisierte Assessments.

Die Verbesserung der Verträglichkeit wird u.a. ein effektives Nebenwirkungs-management, ggf. auch unter intensivmedizinischen Bedingungen, und die Adressierung von Komorbiditäten erreicht. Hierbei kann die Integration von PROs die Interaktion des:der Patient:in mit dem medizinischen Personal und damit auch die HRQoL maßgeblich verbessern [121].

Zunehmend werden auch im Kontext der Sarkomtherapie immuntherapeutische und zielgerichtete Strategien erprobt, welche im Vergleich mit der konventionellen zytostatischen Therapie ein deutlich günstigeres Nebenwirkungsprofil besitzen und bei ausgewählten Entitäten sehr vielversprechend sind. Beispielsweise zeigt die Immuncheckpointblockade insbesondere bei Angiosarkomen und ASPS eine herausragende Effektivität [64], [95]. Modifizierte T-Zellen mit tumorspezifischen T-Zellrezeptoren (*T cell receptor-engineered T cells*, TCR-T) stellen einen weiteren auch bei Weichgewebssarkomen zum Einsatz kommenden Ansatz dar. Zielantigene sind hier z.B. MAGE und NY-ESO1, welche insbesondere von Synovialsarkomen und myxoid/rundzelligen Sarkomen exprimiert werden [125], [126].

Die aktuell vielversprechendsten zielgerichteten Therapien sind bei ausgewählten Sarkomsubentitäten bzw. hoch- und dedifferenzierten Liposarkomen die Hemmung von MDM2 und CDK4/6. MDM2 scheint zu erhöhten p53-Konzentrationen und dem Erhalt der Funktionalität des Tumorsuppressorgens zu führen[89]. Dies macht es aufgrund der Prävalenz von p53 Mutationen in diversen Tumorarten zu einer attraktiven Zielstruktur [127]. Für die Hemmung von MDM2 sind Moleküle unterschiedlicher Hersteller verfügbar, welche bei hoch- und dedifferenzierten Sarkomen im Rahmen von Phase

II/III Studien unter anderem auch in Kombination mit Immuncheckpointblockade erprobt werden [91], [128].

Ein weiterer vielversprechender Ansatzpunkt insbesondere bei Liposarkomen ist die Hemmung von CDK4/6. Hier werden Palbociclib und Abemaciclib eingesetzt, das Ansprechen scheint abhängig von der CDK4 Expression zu sein[56], [93].

Für Desmoidtumore stehen Gammasekretase-Inhibitoren im Rahmen von Phase III Studien seit kurzem auch in Deutschland zur Verfügung (NCT03785964) [129].

Auch die Kombination von zielgerichteten Strategien bzw. Tyrosinkinaseinhibitoren und Immuntherapie erzielt vielversprechende Ergebnisse [130], [131]. So konnte mit dieser selbst bei intensiv vorbehandelten Angiosarkomen in 59% der Fälle ein Ansprechen und ein medianes PFS von knapp 10 Monaten erreicht werden [130].

Zusätzlich zu der Steigerung der Therapieeffektivität durch Entwicklung bzw. Einsatz neuer Substanzen lässt auch eine Verbesserung der Prognose unter den etablierten Behandlungsregimen beobachten: Im Jahre 2014 lag das mediane OS unter der Monotherapie mit Doxorubicin bei knapp 13 Monaten, während es 2019 bereits bei über 20 Monaten lag [27], [71]. Auch wenn die Studienpopulationen nicht direkt miteinander verglichen werden können, ist hier zumindest ein positiver Trend zu vermuten.

Zusammenfassend sollte durch die Optimierung der diagnostischen und therapeutischen Effektivität im Kontext der Sarkomerkrankungen zukünftig neben der Verlängerung des PFS auch eine Verbesserung des OS realisierbar werden.

5 Literaturangaben

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité
Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,
- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité - Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Hamburg, 18.12.2023
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