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Fachbereich Medizin

Klinik für Allgemein-, Viszeral-, Thorax- und Transplantationschirurgie

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Optimierung der chirurgischen Behandlung und Betreuung von Patienten mit retroperitonealen Weichteilsarkomen durch multidimensionale Therapieansätze

Habilitationsschrift

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Abkürzungsverzeichnis

AJCC ..... American Joint Committee on Cancer
BMI ..... Body Mass Index
CCI ..... Comprehensive Complication Index
CI ..... Konfidenzintervall
CR ..... Compartmental resection, Kompartmentresektion
cRD ..... Kumulative Bestrahlungsdosis
CT……..……Computertomographie
DDLPS ..... Dedifferenziertes Liposarkom
DSS…….....disease specific survival, Krankheits-spezifisches Überleben
EBRT……External beam radiotherapy (Perkutane Strahlentherapie)
EORTC QLQ-C30……European Organisation for Research and Treatment of Cancer - Core 30 Quality of Life Questionnaire
FM…….Fernmetastasen
FMFS……..Fernmetastasen-freies Überleben
FNCLCC……Fédération Nationale des Centres de Lutte Contre le Cancer
FoP-Q-SF ..... Fear of Progression Questionnaire (short form)
Gy……..…Gray
Hb.....Hämoglobin
HLM.....Hierachisch lineare Modelle
HR ..... Hazard ratio
HrQoL..... Health-related quality of life (Gesundheitsbezogene Lebensqualität)
IORT ..... Intraoperative Radiotherapie
IQR ..... Interquartilsabstand
LMS ..... Leiomyosarkom
LPS..... Liposarkom
LR.....Lokalrezidiv
LRFS ..... Lokalrezidiv-freies Überleben
MCH .....mittleres korpuskuläres Hämoglobin
MCV .....mittleres korpuskuläres Volumen
MPNST..... Maligner peripherer Nervenscheidentumor
MRT……..Magnetresonanztomographie
MVR ..... Multiviszerale Resektion
MWB..... Psychisches Wohlbefinden (mental well-being)
NOS..... undifferenzierte, pleomorphe Sarkome, not otherwise specified
OS .....Overall survival, Gesamtüberleben
PC-PTSD.....Primary Care - Posttraumatic stress disorder Screening
PRO-CTCAE... ……..Patient Reported Outcomes - Common Terminology Criteria for Adverse Events
PFS ..... Progressionsfreies Überleben
PRO.....Patient reported Outcome
PTSD..... Posttraumatic stress disorder (Posttraumatische Belastungsstörung)
RCT .....Randomisiert kontrollierte Studie
RPS……..…Retroperitoneale Weichteilsarkome
SFT..... Solitär fibröser Tumor
TARPSWEG..... Transatlantic Australasion Retroperitoneal Saroma Working Group
WDLPS.....Well-differentiated Liposarcoma (Gut-differenziertes Liposarkom)
WEMWBS ..... Warwick-Edinburgh Mental Well-Being Scale

1. Einleitung

1.1 Retroperitoneale Weichteilsarkome

1.1.1 Definition und Epidemiologie

Sarkome stellen eine heterogene Gruppe seltener maligner Neoplasien mesenchymalen Ursprungs dar, die an unterschiedlichen anatomischen Lokalisationen auftreten können. Ihre Seltenheit und ausgeprägte Heterogenität stellen sowohl für die klinische Therapie als auch für die Forschung eine besondere Herausforderung dar. Die Gesamtheit der Sarkome repräsentiert lediglich circa ein Prozent aller neu diagnostizierten Krebserkrankungen im Erwachsenenalter. Etwa 84 % dieser Sarkome entfallen auf Weichteilsarkome, die sich in über 70 verschiedenen Subtypen manifestieren.[1]

In der Fachliteratur werden unter dem Begriff retroperitoneale Weichteilsarkome (RPS) nicht nur rein retroperitoneal lokalisierte Sarkome, sondern auch solche zusammengefasst, die im Beckenraum, im Bereich des Musculus iliopsoas oder als intraperitoneale Rezidive primärer retroperitonealer Sarkome auftreten.[2] RPS machen jedoch nur etwa 15 % der Weichteilsarkome aus, was einer geschätzten Inzidenz von 2,7 Fällen pro 1.000.000 Einwohner in Europa entspricht.[1]

Viszerale Sarkome, wie beispielsweise gastrointestinale Stromatumore, weisen signifikante Unterschiede in ihrer Tumorbiologie, ihren Therapieansätzen und ihrer Prognose auf und werden daher als eigenständige Tumorentität betrachtet und nicht den RPS zugeordnet.[1,2]

1.1.2 Klinik

Aufgrund der retroperitonealen Lage werden RPS in der Regel deutlich später diagnostiziert als Weichteilsarkome der Extremitäten oder des Körperstammes. Bei der Diagnosestellung weisen die Tumoren daher im Median eine Größe von 17 bis 20 cm auf.[3,4] Die Symptomatik ist unspezifisch und manifestiert sich zumeist erst durch Kompression oder Verdrängung benachbarter Strukturen, beispielsweise in Form einer Passagestörung, Beinödemen oder Rücken- und Bauchschmerzen.[3] Häufig erfolgt die Diagnosestellung eines RPS jedoch auch durch einen bereits tastbaren Tumor.[5] Darüber hinaus wird ein Teil der RPS durch Zufallsbefunde in bildgebenden Verfahren in asymptomatischen Stadien diagnostiziert.[6]

Rezidive oder metachrone Fernmetastasen werden im Rahmen einer strukturierten, lebenslangen Nachsorge meist in asymptomatischen Stadien diagnostiziert.[7]

1.1.3 Diagnostik

Die Verdachtsdiagnose eines RPS wird mittels Bildgebung gestellt, wobei das bevorzugte diagnostische Verfahren die kontrastmittelverstärkte Computertomographie (CT) ist. Alternativ kann auch eine Magnetresonanztomographie (MRT) durchgeführt werden, insbesondere bei Kontraindikationen gegen Kontrastmittel oder in Fällen, in denen eine Beteiligung von Muskeln, Knochen oder neuroforaminalen Strukturen im CT nicht eindeutig beurteilbar ist.[5,6,8] Die definitive Diagnosesicherung erfolgt durch eine CT-gestützte Stanzbiopsie.[8,9] In Studien konnten die Bedenken hinsichtlich eines erhöhten Rezidivrisikos durch Tumorzellaussaat entlang des Stichkanals nicht bestätigt werden.[9,10] Aufgrund der potenziellen Heterogenität der Differenzierungsgrade innerhalb eines Tumors wird für eine möglichst repräsentative histopathologische Analyse die Entnahme mehrerer Biopsien empfohlen, idealerweise aus dem Areal mit der höchsten Kontrastmittelaufnahme in der Bildgebung.[8,11] In Ausnahmefällen kann auf eine Stanzbiopsie verzichtet werden, wenn die Bildgebung das pathognomonische Erscheinungsbild eines Liposarkoms zeigt und keine neoadjuvante Therapie geplant ist.[8,9] Wird die Verdachtsdiagnose eines RPS während einer diagnostischen Laparoskopie oder Laparotomie gestellt, ist eine Biopsie kontraindiziert, um eine potenzielle peritoneale Tumorzellaussaat zu vermeiden.[9]

Im Rahmen einer vollständigen Staging-Diagnostik ist zusätzlich eine CT des Thorax erforderlich. In Anbetracht der Seltenheit der Erkrankung wird empfohlen, sowohl die weiterführende Diagnostik als auch die histologische Sicherung bereits in einem spezialisierten Zentrum mit hoher Expertise in der Behandlung von RPS durchzuführen.[9] Eine Fallzahl von 10–20 behandelten Patienten pro Jahr gilt als ausreichender Maßstab für ein solches Zentrum.[9]

1.1.4 Stadieneinteilung

RPS können, analog zu anderen malignen Tumoren, nach dem TNM-System des American Joint Committee on Cancer (AJCC) stadiengerecht klassifiziert werden.[12] In der aktuellen 8. Edition der Klassifikation werden neben der Tumorgröße, dem Vorhandensein regionaler Lymphknotenmetastasen und Fernmetastasen auch der Differenzierungsgrad (Grading) berücksichtigt.[12] Im Gegensatz zu anderen malignen Tumoren ist die TNM-Klassifikation bei RPS jedoch nicht zur Prognoseeinschätzung geeignet.[13] Tumore, die eine Größe von über 15 cm aufweisen, werden bereits als T4 klassifiziert. Bei der Diagnosestellung weisen die meisten RPS eine medianen Tumorgröße von 17 - 20 cm auf, sodass sie initial in diese Kategorie fallen.[3,4] Darüber hinaus treten regionale Lymphknotenmetastasen bei RPS äußerst selten auf, und Fernmetastasen sind bei Diagnosestellung nur in wenigen Fällen vorhanden.[14]

Tab. 1: TNM Klassifikation retroperitonealer Weichteilsarkome.[12]

Stadium	Tumor	Regionäre Lymphknoten	Fernmetastasen	Differenzierungs-grad
IA	T1	N0	M0	G1, GX
IB	T2, T3, T4	N0	M0	G1, GX
II	T1	N0	M0	G2, G3
IIIA	T2	N0	M0	G2, G3
IIIB	T3, T4	N0	M0	G2, G3
	Jedes T	N1	M0	Jedes G
IV	Jedes T	Jedes N	M1	Jedes G
T1: ≤5cm; T2: >5cm – 10cm; T3: >10cm – 15cm; T4: >15cm				
N0: keine regionären Lymphknotenmetastasen; N1: regionäre Lymphknotenmetastasen				
M0: keine Fernmetastasen; M1: Fernmetastasen				
GX: Differenzierungsgrad nicht bestimmbar; G1: Summenscore aus Differenzierung, Mitosen und Nekrosen 2-3; G2: Summenscore 4-5; G3: Summenscore 6-8				

Die histologische Subtypisierung findet jedoch keine Berücksichtigung in der TNM-Klassifikation. Die Histologie stellt jedoch einen zentralen Faktor dar, da sich die verschiedenen Subtypen von RPS im Krankheitsverlauf erheblich unterscheiden und dementsprechend unterschiedliche Therapiemaßnahmen erfordern.[4,15]

1.1.5 Histologie

Aufgrund ihrer geringen Inzidenz wurden RPS mit unterschiedlichen histologischen Subtypen in Forschung und Klinik lange Zeit als homogene Entität betrachtet. Neuere Erkenntnisse zeigen jedoch deutlich, dass sich die verschiedenen Subtypen erheblich in ihrer Tumorbiologie unterscheiden, was eine differenzierte Herangehensweise in Diagnostik, Therapie und Prognose unabdingbar macht.[4,16] In diesem Zusammenhang sind insbesondere Lipo- und Leiomyosarkome zu nennen, die im Retroperitoneum vorherrschend sind.

1.1.5.1 Liposarkome

Liposarkome (LPS) stellen mit einem Anteil von ca. 65 % den am häufigsten im Retroperitoneum vorkommenden Subtyp dar.[4,17] Sie werden in gut differenzierte (WDLPS) und dedifferenzierte Liposarkome (DDLPS) unterteilt. Etwa 40 % der LPS entfallen auf gut differenzierte und 60 % auf dedifferenzierte Formen, während myxoide oder pleomorphe Subtypen eine untergeordnete Rolle spielen.[4,17] Die Prognose variiert in Abhängigkeit von der Differenzierung erheblich. WDLPS entwickeln nur selten Fernmetastasen, weisen jedoch ein anhaltend hohes Risiko für Lokalrezidive auf. Das Lokalrezidiv-freie Überleben betrug nach fünf Jahren 53 % und nach zehn Jahren lediglich 21 %, während das Fernmetastasen-freie Überleben nach fünf und zehn Jahren konstant über 90 % lag.[3] Innerhalb der DDLPS unterscheiden sich die Prognosen erheblich je nach Grading nach der Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC). Tumoren des Grads G2 zeigen ein hohes Lokalrezidivrisiko von 44 % nach 5 Jahren, entwickeln jedoch nur selten Fernmetastasen

(10 % nach 5 Jahren).[16] G3-DDLPS weisen hingegen sowohl ein hohes Lokalrezidivrisiko von 33 % als auch eine deutlich höhere Fernmetastasierungsrate von 44 % nach 5 Jahren auf. [16] Es ist zudem relevant, dass das Risiko für Fernmetastasen nach etwa 5 Jahren sistiert, während das Lokalrezidivrisiko weiterhin bestehen bleibt.[3,16] Die Differenzierung des Tumors steht in direktem Zusammenhang mit dem Gesamtüberleben. So liegt das 5-Jahresüberleben bei WDLPS bei 87 %, bei G2-DDLPS bei 54 % und bei G3-DDLPS lediglich bei 41 %.[16]

1.1.5.2 Leiomyosarkome

Leiomyosarkome (LMS) stellen mit einem Anteil von ca. 20 % die zweithäufigste Tumorentität unter den RPS dar.[4,17] Sie haben ihren Ursprung häufig in den venösen Gefäßen des Retroperitoneums (V. renalis, V. cava inferior, V. testicularis/ovarica) und sind bezüglich Therapie und Prognose von uterinen Leiomyosarkomen sowie solchen der Extremitäten zu unterscheiden.[2,15] Das häufigste Wachstumsmuster ist extravasal, wobei in einem Drittel der Fälle Leiomyosarkome sowohl intra- als auch extravasal wachsen.[18]Des Weiteren treten retroperitoneale LMS ähnlich wie LPS, im perirenalen oder posterior pararenalen Raum auf.[19] LMS bilden nur selten Lokalrezidive aus (6 % nach 5 Jahren), zeigen jedoch ein hohes Fernmetastasierungsrisiko (56 % nach 5 Jahren), was sich in einem 5-Jahres-Gesamtüberleben von 58 % widerspiegelt.[16]

1.1.5.3 Seltenere retroperitoneale Weichteilsarkome

Darüber hinaus existieren weitere, deutlich seltenere histologische Subtypen, wie maligne periphere Nervenscheidentumore (MPNST) (6 %), solitär fibröse Tumoren (SFT) (3 %) und andere noch seltenere Tumorentitäten, wie beispielsweise pleomorphe/undifferenzierte Sarkome (NOS) oder Desmoidfibromatosen.[4,16] MPNST entstehen aus peripheren Neurofibromen und zeigen eine moderate Lokalrezidiv- und niedrige Fermetastasierungsrate.[4,16] SFT werden auch als semimaligne Tumore bezeichnet, da sie kaum Lokalrezidive ausbilden. In seltenen Fällen können sie Fernmetastasen entwickeln, insgesamt ist jedoch die Prognose gut, mit einem 5-Jahres-Überleben von über 80 %.[4,16]

1.1.6 Therapie

1.1.6.1 Chirurgische Therapie

1.1.6.1.1 Chirurgische Therapie in der primären Erkrankungssituation

Die vollständige chirurgische Tumorresektion stellt den einzigen kurativen Therapieansatz für RPS dar, wobei zunehmend empfohlen wird, das chirurgische Vorgehen in Abhängigkeit von der Tumorentität und dem Grading zu modifizieren.[9,15] Insbesondere retroperitoneale WDLPS und G2-DDLPS neigen zu Lokalrezidiven mit geringem Metastasierungsrisiko und sind mit bloßem Auge sowie im intraoperativen Schnellschnitt nicht von normalem retroperitonealem Fettgewebe zu unterscheiden. Daher wird die Kompartmentresektion (CR) als erweitertes

chirurgisches Vorgehen empfohlen.[9,15] Ursprünglich wurde die CR als systematische Resektion makroskopisch unbeteiligter Nachbarorgane um den Tumor herum definiert, um freie Resektionsränder zu gewährleisten. Die CR umfasst in der Regel die En-bloc-Resektion des Hemikolons, der Niere und des Psoas-Muskels auf der jeweiligen Seite sowie, falls erforderlich, die Resektion weiterer Nachbarorgane.[20] Eine CR wird auch bei retroperitonealem G3-DDLPS als angemessen angesehen, da insbesondere marginale G1-Anteile des Tumors intraoperativ nicht vom umgebenden Fettgewebe unterscheidbar sind und neben Fernmetastasen auch Lokalrezidive in signifikantem Ausmaß auftreten, wenngleich die metastatische Ausbreitung eher das onkologische Outcome bestimmt.[4] In einer italienischen Kohorte von 288 konsekutiven retroperitonealen Sarkomen konnte die 5-Jahres-Lokalrezidivrate durch die Einführung der Kompartmentresektion gegenüber der einfachen Tumorexzision signifikant von 61 % auf 36 % gesenkt werden.[21] In einer chinesischen Serie von 61 retroperitonealen LPS wurde in 61 % der Fälle eine Infiltration benachbarter Organe und in 77 % der Fälle eine Infiltration des umgebenden Fettgewebes nachgewiesen.[22] Entsprechend scheinen LPS-Patienten am deutlichsten von der retroperitonealen Kompartmentresektion zu profitieren, weswegen für LPS die vollständige Entfernung des retroperitonealen Fettgewebes auf der betroffenen Seite empfohlen wird.[15,21,23]

Demgegenüber sind die Tumorränder beim LMS, aber auch beim SFT und MPNST in der Regel deutlich vom umgebenden Gewebe abgrenzbar. In der Folge wird die Resektion der anhaftenden Strukturen unter Schonung des übrigen Kompartiments als geeignete chirurgische Therapie diskutiert.[9,15] Aufgrund des häufig vaskulären Ursprungs von LMS kann in diesen Fällen eine Gefäßresektion und/oder Rekonstruktion notwendig sein. Im Gegensatz zu LPS ist hier ein intraoperativer Schnellschnitt zwingend erforderlich, um die Tumorfreiheit der vaskulären Absetzungsränder zu überprüfen.[2,15]

In der Abwägung zwischen onkologischem Nutzen und chirurgischem Risiko wird das aggressive chirurgische Vorgehen jedoch auch kritisch diskutiert.[24,25] Die bislang umfassendste retrospektive Studie zu dieser Thematik zeigt jedoch eine durchaus vertretbare perioperative Morbidität und Mortalität der CR auf.[26] In einer internationalen Kollektivstudie mit insgesamt 1007 Resektionen primärer RPS lag die 30-Tagesmortalität bei 1,8 %, die Komplikationsrate (Clavien-Dindo $\geq$ 3) bei 16,4 % und die Reoperationsrate bei 11 %.[26] Die Nachblutung oder Hämatombildung (2,9 %) sowie die Anastomoseninsuffizienz oder Ausbildung einer enterischen Fistel (2,6 %) stellten die häufigsten Komplikationen dar.[26] Ein akutes Nierenversagen trat hingegen auch nach einseitiger Nephrektomie selten auf (0,7 %).[26] Andere Studien zeigen übereinstimmend, dass die einseitige Nephrektomie das Risiko eines transienten Nierenversagens erhöht, sehr selten jedoch zu chronischem Nierenversagen oder Dialysepflichtigkeit führt.[27,28] Mit einem signifikant erhöhten Risiko für perioperative

Komplikationen waren im Falle rechtsseitiger RPS die simultane Pankreatikoduodenektomie sowie im Falle linksseitiger Tumoren die Kombination aus Nephrektomie links, Hemikolektomie, Pankreaslinksresektion und Splenektomie verbunden. Ausgedehnte Gefäßresektionen waren ebenfalls mit einer erhöhten Morbidität assoziiert. [26] Die postoperative Morbidität der retroperitonealen und multiviszeralen CR ist jedoch mit der bei anderen anspruchsvollen chirurgisch-onkologischen Eingriffen vergleichbar.[29] Die Komplexität des chirurgischen Eingriffs sowie des postoperativen Verlaufs legen die Notwendigkeit einer Behandlung in einem Zentrum mit entsprechender Expertise nahe. In diesen Zentren werden höhere Raten makroskopisch kompletter Resektionen erreicht, während die Morbiditäts- und Mortalitätsraten niedriger und das rezidivfreie Überleben länger sind. [9,30,31]

1.1.6.1.2 Chirurgische Therapie in der Rezidivsituation

Eine der substanziellen Herausforderungen in der RPS-Therapie stellt die hohe Rezidivrate dar, die trotz aggressiver chirurgischer Ansätze und makroskopisch vollständiger Resektion besteht.[21,23] Die Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG), eine internationale Arbeitsgruppe, die sich auf die Erforschung von RPS spezialisiert hat, identifizierte ein langes Intervall bis zum ersten Tumorrezidiv und die Rezidivresektion als günstige prognostische Faktoren in Bezug auf das Gesamtüberleben.[32] Die Resektion hepatischer und pulmonaler Metastasen kann bei gutem Allgemeinzustand der Patienten, dem Fehlen weiterer Metastasen und einer Kontrolle des Primärtumors erfolgen, da sich unter diesen Bedingungen ein Vorteil für das krankheitsfreie und Gesamtüberleben nach Metastasenresektion zeigte.[32–35]

1.1.6.2 Stellenwert der Strahlentherapie

Mehrere retrospektive Studien haben positive Effekte der externen Strahlentherapie (EBRT) auf die LR-Rate oder das Gesamtüberleben nahegelegt.[3,36,37] In diesen Studien wurde eine neoadjuvante Herangehensweise empfohlen, da insbesondere strahlensensibler Dünndarm nach Resektion in das Tumorbett fällt und aufgrund der geringen Strahlentoleranz eine effektive postoperative Bestrahlung deutlich erschwert wird.[38] Allerdings konnte die einzige randomisierte Studie (STRASS EORTC 62092), die eine präoperative EBRT mit anschließender Tumorresektion mit alleiniger Chirurgie bei der Behandlung von RPS verglich, keine vorteilhaften Effekte der präoperativen Strahlentherapie auf die Lokalrezidiv-Rate nachweisen, mit Ausnahme in der Subgruppe der retroperitonealen LPS.[39] Die Ergebnisse dieser Subgruppen-Analyse wurden in einer umfangreichen multizentrischen Kohortenstudie (STREXIT) bestätigt, die zusätzlich zur STRASS-Kohorte auch die Patienten umfasste, die an STRASS nicht teilnehmen konnten.[40] Der allgemeine Konsens favorisiert daher anhand der aktuellen Evidenzlage bei G1- und G2-LPS eine neoadjuvante Radiatio, während bei allen anderen Entitäten auf diese verzichtet wird.[9,41]

1.1.6.3 Stellenwert der Chemotherapie

In der aktuellen wissenschaftlichen Diskussion zur Behandlung primär resektabler RPS nimmt die Chemotherapie derzeit eine untergeordnete Rolle ein und ist aktuell weder neoadjuvant noch adjuvant Bestandteil der Standardtherapie.[9] In der aktuellen STRASS-2-Studie (NCT04031677) wird der Nutzen einer neoadjuvanten Chemotherapie mit anschließender Operation mit der alleinigen Resektion bei G3-LPS und LMS, die zur Ausbildung von Fernmetastasen neigen, verglichen. Die Ergebnisse dieser Studie könnten zu einer Neubewertung des Stellenwerts der neoadjuvanten Chemotherapie in der Behandlung primärer RPS führen.

In makroskopisch unvollständig resezierten, metastasierten oder inoperablen Krankheitsstadien wird eine Chemotherapie standardmäßig durchgeführt. In diesen Fällen stellt Doxorubicin in Kombination mit Ifosfamid die bevorzugte therapeutische Option dar.[35] In Abhängigkeit des Ansprechens und der Histologie werden aber auch alternative Therapeutika eingesetzt.[42]

1.1.7 Prognose

Die Prognose von Patienten mit RPS wird maßgeblich von der Tumorhistologie und -biologie beeinflusst. Die aktuelle Studienlage zeigt ein 5-Jahres-Überleben von etwa 67 % für alle RPS-Patienten und ein durchschnittliches 10-Jahres-Gesamtüberleben von 46 %.[4] Allerdings weisen die Ergebnisse eine signifikante Variabilität in Abhängigkeit von dem histologischen Subtyp und der Differenzierung auf (s. Tabelle 2).

Tab. 2: Rezidivverhalten und Prognose der häufigsten Entitäten retroperitonealer Weichteilsarkome. Datenquelle: Gronchi et al. 2015 [16]

	Anteil (%)		Lokalrezidiv-Inzidenz (%)	Fernmetastasen-Inzidenz (%)	Gesamtüberleben (%)
			Nach 5 Jahren	Nach 5 Jahren	Nach 5 Jahren
WDLPS	26	-	19	0	87
DDLPS	37	G2	44	10	54
		G3	33	44	41
LMS	19	-	6	56	58
MPNST	6	-	20	13	67
SFT	3	-	5	17	85
WDLPS = gut differenziertes Liposarkom, DDLPS = dedifferenziertes Liposarkom, LMS = Leiomyosarkom, MPNST = maligner peripherer Nervenscheidentumor, SFT = solitär fibröser Tumor					

Des Weiteren verschlechtert sich die Prognose signifikant, wenn eine Resektion des Primärtumors, eines Lokalrezidivs und/oder Fernmetastasen nicht mehr möglich ist. In dieser

Palliativsituation beträgt das mediane Gesamtüberleben etwa 16 Monate, wobei auch hier der histologische Subtyp und die Tumordifferenzierung eine entscheidende Rolle spielen.[3] Das Gesamtüberleben von Patienten mit WDLPS ist im Vergleich zu Patienten mit DDLPS doppelt so lang. DDLPS weisen im palliativen Stadium hingegen eine prognostisch ähnliche Situation auf wie pleomorphe/undifferenzierte Sarkome.[3]

Zu den iatrogen beeinflussbaren prognostischen Faktoren gehören die Qualität der chirurgischen Therapie im Sinne einer makroskopisch vollständigen En-bloc Resektion des Tumors sowie die Behandlung an einem spezialisierten Zentrum.[9,23]

Für die prognostische Einschätzung von RPS-Patienten existieren sowohl für Primärtumore als auch für Lokalrezidive validierte Nomogramme (SARCULATOR), die eine individuelle Prognoseabschätzung ermöglichen.[43–45]

1.2 Fragestellung und Ziele

Die Erforschung von RPS gestaltet sich im Vergleich zu anderen Tumorentitäten als erschwert, was auf die Seltenheit und Heterogenität der Erkrankung zurückzuführen ist. In den vergangenen zwei Jahrzehnten wurden lediglich drei randomisiert kontrollierte Studien publiziert, die sich explizit mit der Therapie von RPS - ohne die Berücksichtigung von Weichteilsarkomen der Extremitäten oder des Körperstammes - befassen.[39,46,47] Kohortenstudien und retrospektive Auswertungen sind daher von entscheidender Bedeutung für den Fortschritt in der Behandlung von RPS und bilden aktuell das Fundament von Leitlinien und internationalen Therapieempfehlungen.[8,9,41,48]

Die größten Herausforderungen in der Therapie von Patienten mit RPS sind die hohen Rezidivraten sowie der Umgang mit Rezidiven. Zudem sind die Langzeitfolgen wiederholter, ausgedehnter Operationen bislang nur unzureichend erforscht. Ziel dieser Arbeit war es daher, wichtige Komponenten multidimensionaler Therapieansätze hinsichtlich ihres Potentials zur Optimierung chirurgischer Behandlungsergebnisse bei RPS-Patienten zu untersuchen.

Erstens sollten die Effekte von intraoperativer Strahlentherapie und hohen kumulativen Strahlendosen auf das Lokalrezidiv-freie Überleben nach chirurgischer Resektion untersucht werden (siehe 3.1 und 4.1).

Zweitens sollte die Bedeutung einer chirurgischen Kompartmentresektion in Abhängigkeit von Tumorhistologie und Tumorbiologie auf onkologische Ergebnisse bestimmt werden (siehe 3.2 und 4.2).

Drittens sollte der Einfluss von mehrfachen Rezidivresektionen auf das Gesamtüberleben analysiert werden (siehe 3.3 und 4.3).

Viertens sollte der Ernährungsstatus und die Prävalenz präoperativer Anämien über den Krankheitsverlauf analysiert und der Einfluss auf onkologische Ergebnisse untersucht werden (siehe 3.4 und 4.4).

Fünftens sollte die Lebensqualität nach (mehrfacher) RPS-Resektion erfasst und mögliche Einflussfaktoren sowie mögliche therapeutische Ansätze identifiziert werden (siehe 3.5 und 4.5).

2. Methodik

2.1 Sarkomdatenbank

Alle in dieser Arbeit vorgestellten Studien basieren auf der Sarkomdatenbank der Chirurgischen Klinik des Universitätsklinikums Heidelberg. Die Datenbank beinhaltet Angaben zu demografischen Daten, Diagnose, Tumorlokalistation, klinischem Staging, neoadjuvanter und adjuvanter Therapie, Zeitpunkt und Art der Operation, Art und Management der perioperativen Komplikationen, Histopathologie, pathologisches Staging, Ernährungszustand, Nachsorge, Zeitpunkt und Art der Therapie von Rezidiven, Überlebensdaten und Todesursachen. Diese Datenbank wurde ab 2016 von mir geführt und beinhaltet aktuell 1064 Patienten (Stand 06/2024), die von Oktober 2001 bis Juni 2024 in der chirurgischen Universitätsklinik Heidelberg aufgrund eines Weichteilsarkoms operiert wurden. Die Datenbank wurde alle zwei Wochen aktualisiert. Eine Nachsorge der noch lebenden Patienten erfolgte mindestens jährlich.

Für alle Studien dieser Arbeit wurden aufgrund der divergierenden Tumorbiologie Patienten mit gastrointestinalen Stromatumoren, embryonalen, pädiatrischen oder gynäkologischen Weichgewebsarkomen sowie Weichgewebssarkomen der Extremitäten und des Körperstammes ausgeschlossen.

2.2 Statistik

Die statistische Auswertung der Daten erfolgte mit SPSS Version 22.0.0.0 bis zuletzt 29.0.2.0 (SPSS Inc., Chicago, Illinois, USA). Die Grafiken wurden mit Prism für Mac (Version 7.0.0 bis zuletzt 9.0.0) erstellt. Die Überlebenszeiten wurden mittels Kaplan-Meier-Methode geschätzt und als Median mit 95 % Konfidenzintervall (CI) berichtet. Die statistische Signifikanz wurde mit dem log-rank Test geprüft. Zur Identifizierung unabhängiger Prognosefaktoren wurden multivariable COX-Regressionen durchgeführt. Hinsichtlich der Anzahl an Events wurden backward stepwise und forward stepwise Regressionen gerechnet.[49] Das Gesamtüberleben (overall survival, OS) wurde als Zeitraum zwischen dem Datum der Operation und dem Todesdatum definiert. Das Krankheits-spezifische Überleben (disease specific survival, DSS) wurde als Zeitraum zwischen dem Datum der Operation und dem Todesdatum definiert, wenn die Todesursache RPS bedingt war. Bei Versterben aus einem anderen Grund, wurde das Todesdatum zensiert. Bei lebenden Patienten wurde das Follow-up zum Datum der letzten Krankheitsbewertung zensiert. Ein Lokalrezidiv (LR) wurde als Tumorrezidiv im Retroperitoneum oder Abdomen definiert, wobei Lebermetastasen ausgeschlossen wurden.

Lebermetastasen und alle anderen Metastasen wurden als Fernmetastasen (FM) definiert. Das LR-freie und FM-freie Überleben (LRFS und FMFS) wurden als Zeitraum zwischen dem Datum der Operation und dem Datum des LR bzw. der FM oder dem letzten Follow-up definiert. Patienten mit makroskopisch unvollständiger Tumorresektion (R2) wurden für Analysen des LR-freien Überlebens ausgeschlossen.

Für die deskriptive Statistik wurden nicht parametrische Tests durchgeführt: Qualitative Merkmale wurde mittels $\chi 2$- oder Kruskal-Wallis-Test und quantitative Merkmale mittels Mann-Whitney-U-Test verglichen. Alle Tests wurden zweiseitig durchgeführt und ein p-Wert $\leq 0{,}05$ galt als statistisch signifikant.

Darüber hinausgehende spezifische statistische Berechnungen für einzelne Fragestellungen werden in den entsprechenden Abschnitten der jeweiligen Studie beschrieben.

3. Ergebnisse der eigenen Arbeiten

3.1 Bedeutung der intraoperativen Strahlentherapie und hoher kumulativer Strahlendosen bei retroperitonealen Weichteilsarkomen

Trotz aggressiver chirurgischer Ansätze sind hohe Lokalrezidivraten, eine Herausforderung in der Therapie von RPS-Patienten. Zu den Faktoren, die die LR-Rate beeinflussen, gehören die Tumorentität, das Tumorgrading und die chirurgischen Resektionsränder, wobei letztere, neben der Behandlung an einem Zentrum, den einzigen iatrogen beeinflussbaren Ansatzpunkt darstellen.[3,17] Aufgrund der anatomischen Begebenheiten im Retroperitoneum mit engem Lagebezug zur Wirbelsäule und den großen Gefäßen können häufig keine weiten Sicherheitsabstände erreicht werden. Daher besteht die Notwendigkeit zusätzlicher Therapieoptionen. Bei Weichteilsarkomen der Extremitäten beeinflusst eine adjuvante EBRT mit Dosen über 60 Gy positiv die LR-Rate.[50] Aufgrund der großen Resektionsflächen und der begrenzten Strahlentoleranz der angrenzenden Organe können solche Dosierungen jedoch selten bei RPS erreicht werden. In diesem Zusammenhang wurde der Zusatznutzen einer intraoperativen Strahlentherapie (IORT) diskutiert. Die IORT ermöglicht die Verabreichung eines zusätzlichen Strahlenboost von 10-15 Gy an Stellen mit Verdacht auf mikroskopisch positive Resektionsränder. In Kombination mit einer neoadjuvanten Bestrahlung, die üblicherweise 45–54 Gy umfasst und vor der Veröffentlichung der STRASS-Studie (STRASS EORTC 62092) ein integraler Bestandteil der RPS-Therapie war,[39] können kumulative Bestrahlungsdosen (cRD) von über 60 Gy erreicht werden. Diesbezüglich gibt es jedoch noch keine hinreichende Evidenz. Die hierzu bestehenden Studien umfassen nur kleine Patientenkollektive - häufig ohne eine adäquate Vergleichsgruppe mit uneinheitlichen Ergebnissen: Einige Autoren beschreiben einen Vorteil hinsichtlich der LR-Rate,[51–53] während andere keinen Zusatznutzen einer IORT nachweisen konnten.[54,55]

Das Ziel dieser retrospektiven Analyse war es daher, den Einfluss der IORT auf die LR-Rate und das Gesamtüberleben zu untersuchen und ihre Bedeutung in der multimodalen Therapie für RPS zu klären.

Hierfür wurden alle Patienten analysiert, die zwischen Oktober 2001 und Dezember 2016 in der Chirurgischen Klinik des Universitätsklinikums Heidelberg aufgrund eines Primärtumors, Lokalrezidivs und/oder Fernmetastasen eines RPS operiert wurden (Ethikvotum S-649/2012). Als Endpunkte wurden das LR-freie sowie das Gesamtüberleben beurteilt. Zusätzlich wurde ein Propensity-Score Matching durchgeführt, um die Effekte der IORT und cRD unabhängig

von Patienten- und tumorspezifischen Störfaktoren zu analysieren. Uni- und multivariable Analysen wurden wie oben beschrieben durchgeführt. Hierbei wurden alle möglichen Prädiktoren mit einem $p \leq 0{,}2$ aus der univariaten Analyse in die multivariable COX-Regressionsanalyse eingeschlossen. Zusätzlich erfolgten Subgruppen-Analyse für Patienten mit Primärtumoren sowie mit LPS.

Es wurden 272 Patienten mit RPS identifiziert, von denen 119 (43,7 %) eine IORT erhielten, während eine kumulative Strahlendosis (cRD) ≥60 Gy nur bei 63 (23,2 %) erreicht wurde. Nach einem medianen Follow-up von 33,6 Monaten (IQR: 11,6–69,3) und 48,3 Monaten (IQR: 21,4–84,5) bei noch lebenden Patienten betrug das mediane Gesamtüberleben 78,1 Monate (95 % CI: 47,2–109,1) und das LR-freie Überleben 44,3 Monate (95 % CI: 28,7–59,9). Die Tumorpräsentation (Primärtumor vs. Rezidiv) ($p < 0{,}001$), der Resektionsstatus ($p = 0{,}014$) und die Tumorhistologie ($p = 0{,}002$) wurden als unabhängige prognostische Faktoren für das LR-freie Überleben identifiziert. Die Applikation einer IORT ($p = 0{,}613$) war nicht signifikant mit einer Verbesserung des LR-freien Überlebens assoziiert (s. Abb. 1).

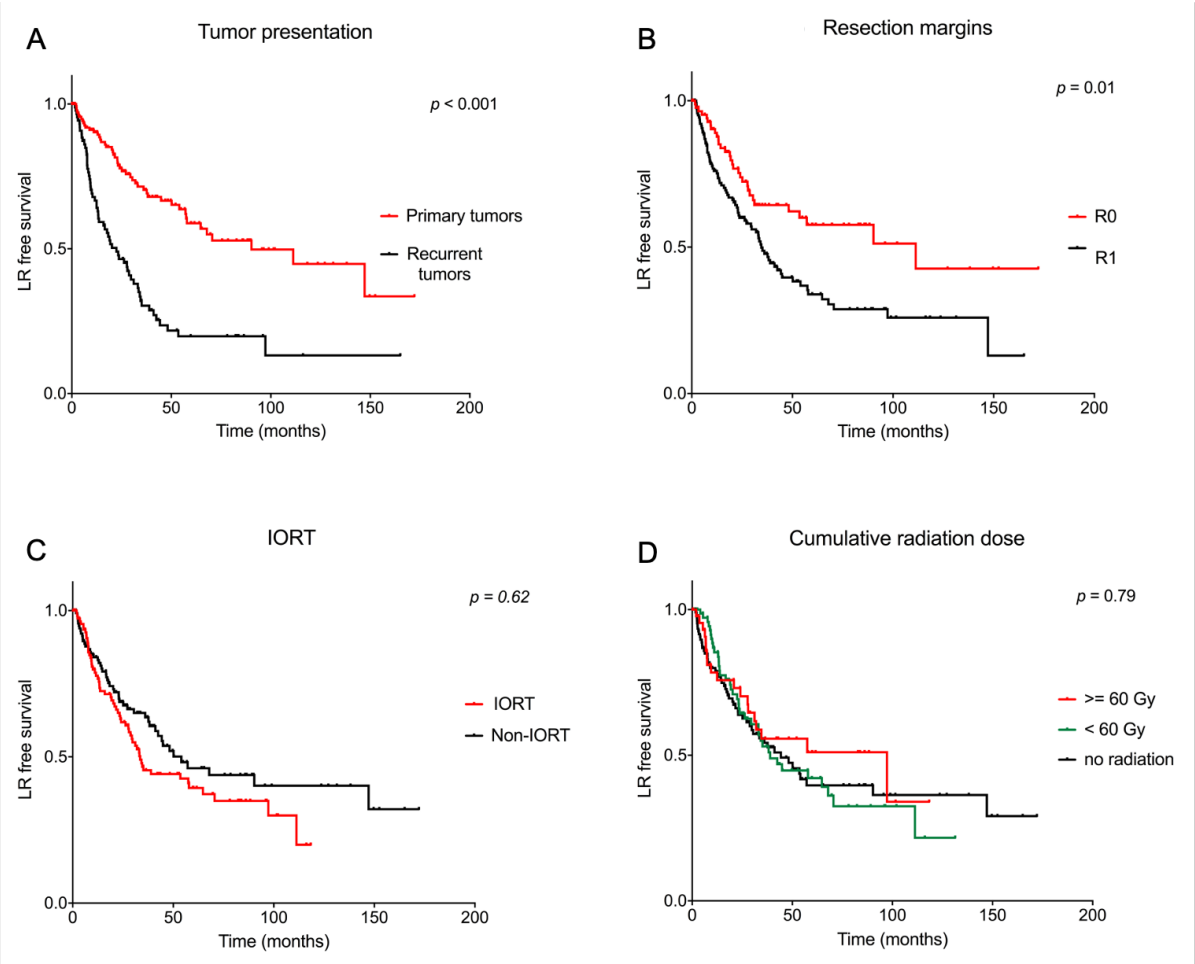

Abb. 1: Kaplan-Meier-Kurven mit Ergebnissen des log-rank Test für LR-freies Überleben in Abhängigkeit von A) Tumorpräsentation, B) Resektionsrändern, C) Applikation einer IORT und D) kumulativen Strahlendosis für die gesamte Kohorte.

In einer Propensity-Score-Matched-Analyse (52 IORT- vs. 52 Non-IORT-Patienten) blieb der Resektionsstatus ein signifikanter prognostischer Faktor (p = 0,001), jedoch zeigte die IORT keinen Effekt auf das LR-freie Überleben (p = 0,176). Eine cRD ≥ 60 Gy zeigte eine Tendenz zu einem besseren LR-freien Überleben, erreichte jedoch keine statistische Signifikanz (p = 0,074) (s. Abb. 2 A-B). In einer zweiten Propensity-Score-Matched-Analyse (40 Patienten mit cRD ≥ 60 Gy vs. 40 mit cRD 10–59 Gy) zeigte weder die cRD ≥ 60 Gy (p = 0,930) noch die IORT (p = 0,320) einen Effekt auf das LR-freie Überleben (s. 2. Xy C-D).

Auch in der Subgruppe der LPS, die am meisten von einer Strahlentherapie zu profitieren scheinen,[39,40] konnte kein Zusatznutzen einer IORT oder cRD ≥ 60 Gy auf das LR-freie Überleben nachgewiesen werden. Bezüglich des Gesamtüberlebens waren eine makroskopisch unvollständige Tumorresektion (p = 0,010), ein höheres Tumorgrading (p = 0,038) und ein höheres Patientenalter (p = 0,038) signifikant mit einem schlechteren Gesamtüberleben assoziiert, während die IORT (p = 0,210) und eine Strahlentherapie (p = 0,490) keinen Einfluss hatten.

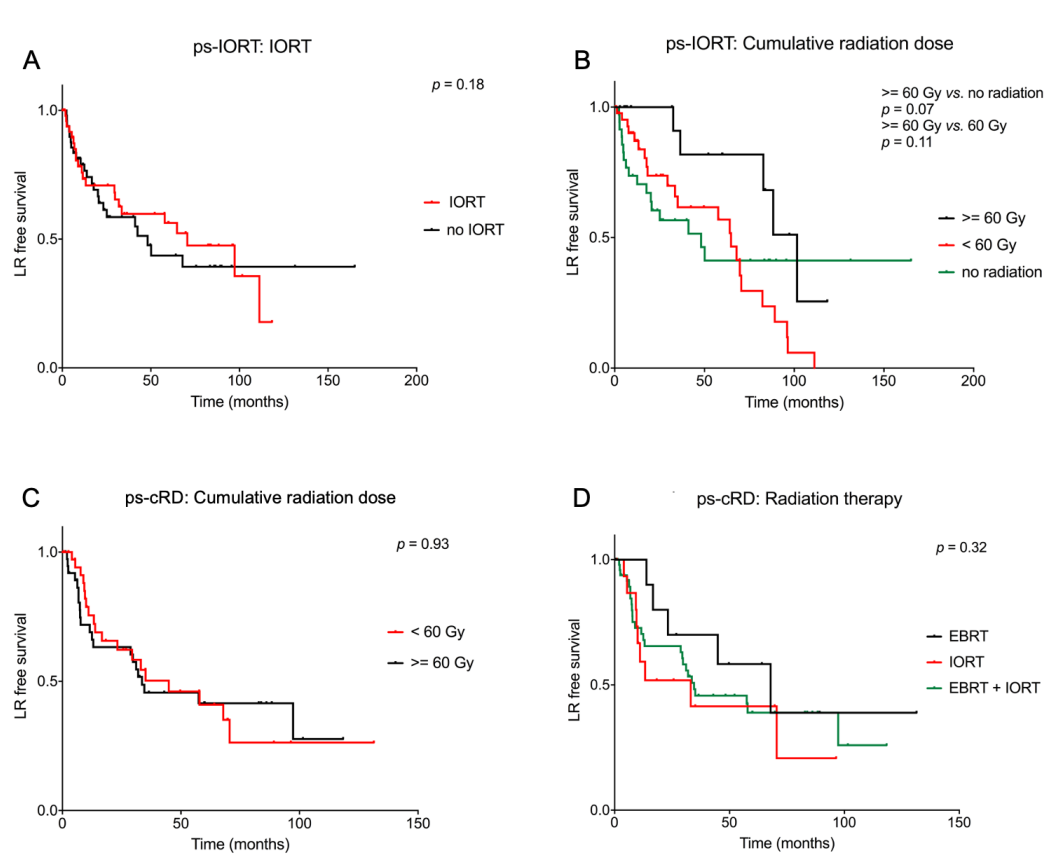

Abb. 2: Kaplan-Meier-Kurven mit Ergebnissen des log-rank Test für LR-freies Überleben nach dem Propensity-Score-Matching nach IORT (A&B) und kumulativer Strahlendosis (C&D) in Abhängigkeit von A) IORT Applikation, B & C) kumulativer Bestrahlungsdosis in der jeweiligen Propensity-Score gematchten Gruppe und D) Applikationsart der Strahlentherapie.

3.2 Bedeutung der Kompartmentresektion bei retroperitonealen Weichteilsarkomen

Wie unter 1.1.5. dargelegt, sind hohe Rezidivraten für die Mehrzahl der RPS kennzeichnend. Sie manifestieren sich jedoch in spezifischen klinischen Phänotypen und einem charakteristischen Rezidivverhalten, das für die tumorbedingte Mortalität verantwortlich ist.[3,4] Dementsprechend wird in den aktuellen Guidelines auch ein Histologie-basierter chirurgischer Ansatz favorisiert (siehe auch 1.1.6).[9,15] Die aktuellen Empfehlungen diesbezüglich stützen sich jedoch auf wenige retrospektiven Studien, in denen die Rolle der Kompartmentresektion (CR) als unabhängiger prognostischer Faktor für das onkologische Outcome in Abhängigkeit von der Tumorhistologie nicht systematisch untersucht wurde.[21,23,56] Vor diesem Hintergrund ist es das primäre Ziel unserer Studie, die Auswirkungen der CR in Abhängigkeit von Tumorhistologie und Tumorbiologie zu untersuchen. Dieser Ansatz sollte zu einem besseren Verständnis der Rolle der CR bei der RPS-Behandlung und somit möglicherweise zu einer Verfeinerung der chirurgischen Strategien führen, um bessere Patientenergebnisse zu erzielen.

Hierfür haben wir alle LPS und LMS Patienten, die zwischen 01/2002 und 12/2019 in der Chirurgischen Klinik des Universitätsklinikums Heidelberg an einem Primärtumor operiert wurden, in die Studie eingeschlossen (Ethikvotum S-649/2012). Die Patienten wurden anhand klinisch-pathologischer Parameter und klinischer Ergebnisse analysiert, wobei der Schwerpunkt auf der Durchführung der CR lag. Als Endpunkte wurden das Krankheits-spezifische Überleben (DSS) sowie das Lokalrezidiv-freie Überleben (LRFS) und das Fernmetastasen-freie Überleben (FMFS) festgelegt.

Insgesamt wurden 165 Patienten identifiziert. Die Kohorte umfasst 119 (72,1 %) LPS-Fälle [29 (24,4 %) G3-DD-LPS, 51 (42,9 %) G2-DD-LPS, 26 (21,9 %) WD-LPS, 13 (10,9 %) ohne Angabe eines Gradings nach neoadjuvanter Therapie] und 46 (27,9 %) LMS-Fälle. Unter LPS-Patienten waren diejenigen, bei denen eine CR durchgeführt wurde, signifikant älter zum Zeitpunkt der Diagnose (p = 0,039), die Anzahl an resezierten Organen war höher (p < 0,001) und häufiger erfolgte eine makroskopisch komplette Tumorresektion (R0/R1) als bei Patienten ohne CR (p = 0,019). In der Gruppe der LMS-Patienten gab es weniger G2-Tumoren und mehr Patienten mit einem nicht bestimmbaren Tumorgrading (p = 0,045), was wahrscheinlich auf eine höhere Rate an präoperativer Bestrahlung im Vergleich zu Patienten ohne CR zurückzuführen ist. Auch hier wurden bei Patienten mit CR im Median mehr Organe reseziert als bei Patienten ohne CR (p < 0,001).

Sowohl in LPS als auch in LMS Patienten war die CR mit einer längeren Operationszeit verbunden (LPS: $p = 0{,}006$; LMS: $p = 0{,}001$). Bei LPS Patienten war die CR ebenfalls mit einer erhöhten postoperativen Morbidität ($p = 0{,}021$) und einem verlängertem stationären Aufenthalt ($p = 0{,}013$) bei gleichbleibender Mortalität assoziiert (alle $p > 0{,}05$).

In der multivariablen COX Regressionsanalyse für LPS war die Durchführung einer CR signifikant mit einem besseren DSS assoziiert, unabhängig vom Alter der Patienten, dem Resektionsstatus und dem präoperativen Grading (CR vs. keine CR: HR = 0,46; 95 % CI: 0,21-1,00; $p = 0{,}049$) (Abb. 3). Für LMS Patienten konnte kein statistisch signifikanter Vorteil für die Durchführung einer CR gezeigt werden (alle $p > 0{,}05$) (Abb 3).

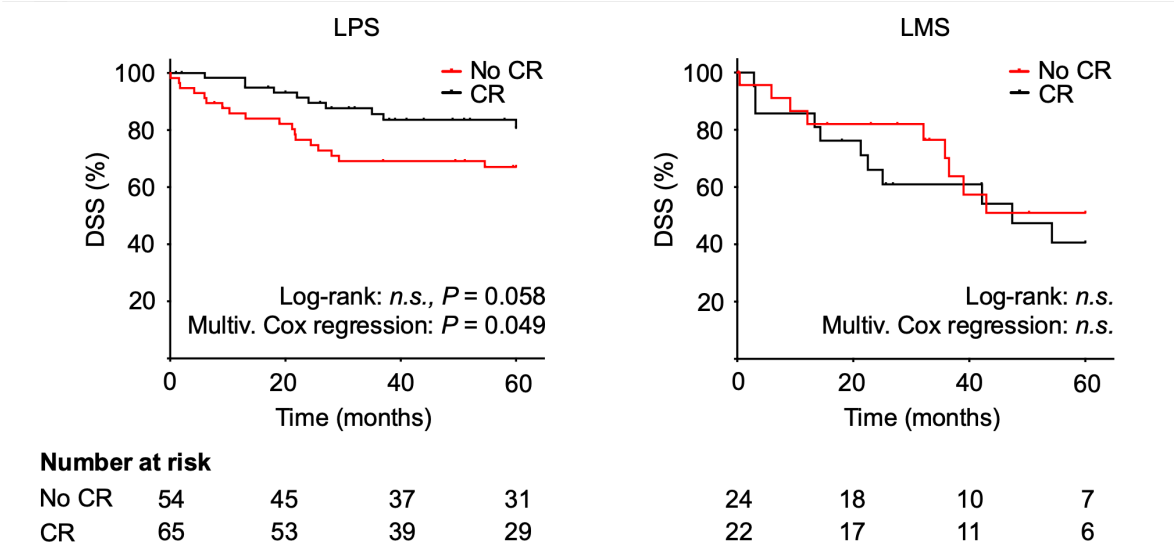

Abb. 3: Kaplan-Meier-Kurven dargestellt mit Ergebnissen des log-rank Test und der multivariablen COX-Regression für das Krankheitsspezifische Überleben (DSS) für die Kohorte der Liposarkome (LPS) und Leiomyosarkome (LMS). n.s. = nicht signifikant

Sowohl für LPS als auch für LMS Patienten war die Durchführung einer CR nicht mit einem verbesserten LRFS assoziiert (alle $p > 0{,}05$). Erwähnenswert ist jedoch, dass bei Vorliegen eines LPS das mediane Intervall bis zum Auftreten eines Lokalrezidivs bei den mit CR behandelten Patienten signifikant länger war als bei den ohne CR behandelten Patienten (CR: 25 Monate; IQR 15,0 - 54,0 Monate; keine CR: 15,5 Monate; IQR 8,8 - 25,3 Monate; $p = 0{,}023$).

Die Durchführung einer CR war in keiner der untersuchten Gruppen mit einem verbesserten FMFS assoziiert (alle $p > 0{,}05$).

Aufgrund der unterschiedlichen LPS-Rezidivmuster in Abhängigkeit vom Tumorgrading wurden Subgruppenanalysen für G2- und G3-LPS durchgeführt. In der Analyse von DSS, LRFS und FMFS für primäre G2- und G3-LPS war die Durchführung einer CR nur bei G3-

Tumoren ein unabhängiger prognostischer Faktor für ein verbessertes DSS (CR vs. keine CR: HR = 0,19; 95 % CI: 0,04 - 0,93; *p* = 0,040) und FMFS (CR vs. keine CR: HR = 0,19; 95 % CI: 0,04-0,93; *p* = 0,041), aber nicht für das LRFS (Abb. 4).

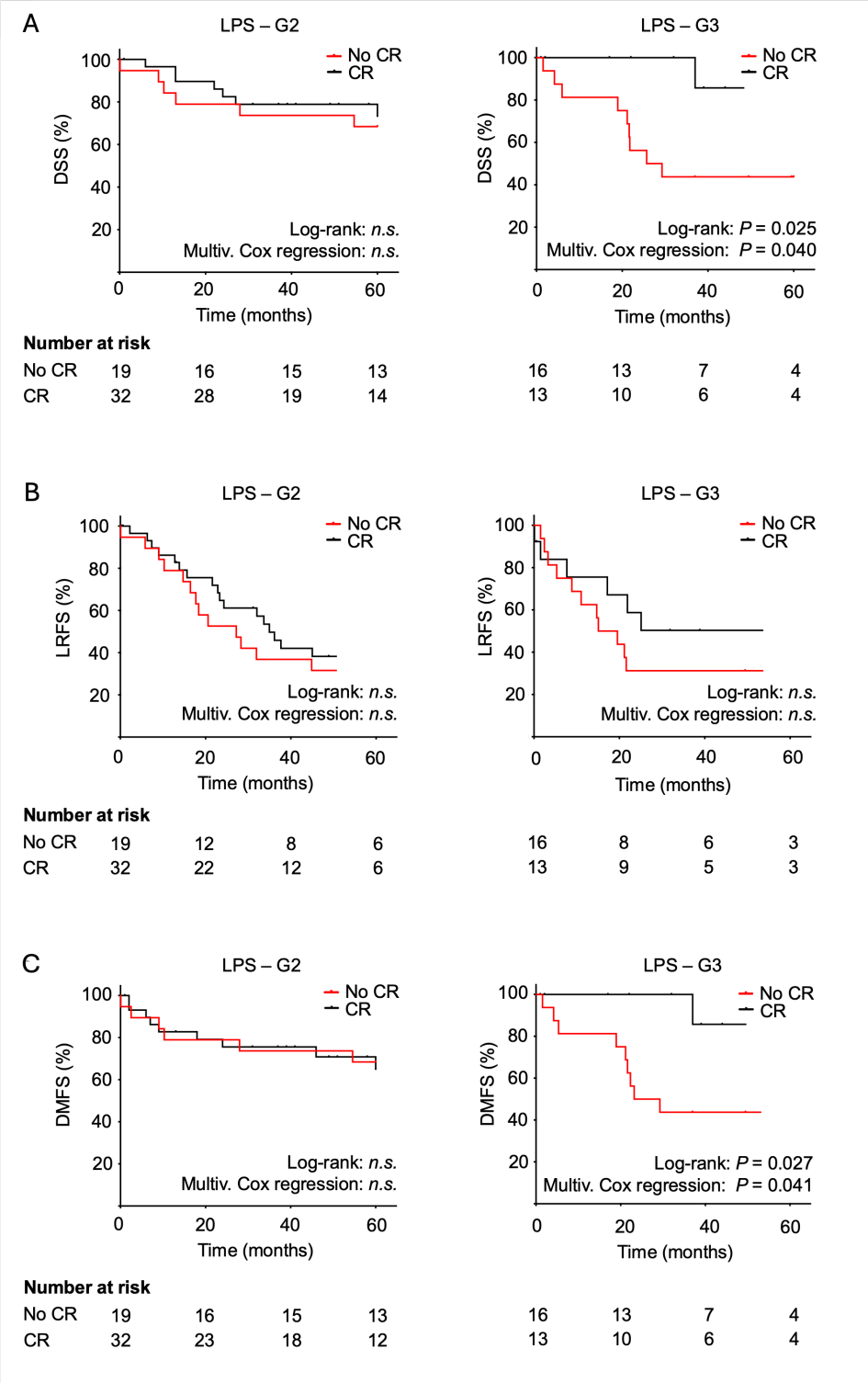

Abb. 4: Kaplan-Meier-Kurven dargestellt mit Ergebnissen des log-rank Test und der multivariablen COX-Regression für die Subgruppe der G2- (links) und G3-Liposarkome (rechts). für das A) Krankheits-spezifische Überleben (DFS), das B) Lokalrezidiv-frei Überleben (LRFS) und C) das Fernmetastasen-frei Überleben (DMFS). n.s. = nicht signifikant

3.3 Ergebnisse nach Resektion mehrfach rezidivierender retroperitonealer Weichteilsarkome

Basierend auf einer retrospektiven Auswertung einer großen Kohorte der TARPSWG wird die Resektion von RPS-Rezidiven empfohlen.[41] In der vorliegenden Studie wurde ein langer Zeitraum bis zum ersten Wiederauftreten des Tumors sowie die Resektion als günstige prognostische Faktoren in Bezug auf das Gesamtüberleben identifiziert.[32] Allerdings wurde in dieser Kohorte eine Inzidenz von 58 % für die Entwicklung eines weiteren Rezidivs innerhalb von fünf Jahren nach der Resektion des initialen Lokalrezidivs (LR) und von 16 % für Fernmetastasen (FM) beobachtet.[32] Die Evidenzlage bezüglich prognostischer Faktoren für Rezidive, die über das initiale Rezidiv hinausgehen, ist begrenzt, da nur wenige retrospektive Studien mit kleinen Patientenkollektiven vorliegen.[57–59] Ziel der vorliegenden Studie war es daher, prognostische Faktoren im Hinblick auf das Gesamtüberleben bei mehrfach rezidivierenden RPS zu identifizieren.

Hierfür wurden alle Patienten analysiert, die zwischen Oktober 2001 und Dezember 2017 in der Chirurgischen Klinik des Universitätsklinikums Heidelberg aufgrund eines Primärtumors, Lokalrezidivs und/oder Fernmetastasen eines RPS operiert wurden (Ethikvotum S-649/2012). Es wurde wie im Methodenteil beschrieben, univariate und multivariable COX-Regressionen für das Gesamtüberleben sowie LR- und FM-freies Überleben durchgeführt. Es wurden alle möglichen Prädiktoren mit einem $p \leq 0{,}2$ aus der univariaten Analyse in die multivariable COX Regression eingeschlossen. Zusätzlich erfolgten Subgruppen-Analyse für Patienten mit Primärtumoren, erstem, zweiten und drittem Rezidiv sowie getrennt für LPS und LMS, da diese beiden Entitäten unterschiedliche Rezidivmuster aufweisen.[4] Zusätzlich wurde für LPS im Falle eines resezierten Rezidivs die monatliche Wachstumsrate bestimmt. Diese war definiert als Tumorgröße bei Resektion des Rezidivs geteilt durch den Zeitabstand zur letzten Tumorresektion. Da diese Variable jedoch nicht für alle LPS Patienten verfügbar war, wurde sie nicht in der multivariablen Analyse berücksichtigt. Aufgrund der geringen Anzahl an LMS-Patienten mit nur wenigen LR, wurde bei dieser Patientengruppe das progressionsfreie Überleben (PFS) als Outcome-Parameter für die Analyse von Krankheitsrückfällen verwendet.

Es wurden insgesamt 332 Patienten identifiziert, von denen 201 Patienten mit Primärtumoren, 101 Patienten mit ersten, 66 Patienten mit zweitem und 43 Patienten mit drittem LR sowie 75 Patienten mit FM analysiert wurden. Insgesamt entwickelten 144 (43 %) Patienten ein LR und 75 (23 %) FM. Multiple Rezidive traten bei 82 (25 %) Patienten auf.

Verglichen mit Patienten, die nach Resektion des Primärtumors kein Rezidiv erlitten, war das mediane Überleben bei Patienten mit Entwicklung eines LR und/oder FM reduziert. In der

multivariablen COX-Regression wurden das initiale Tumorgrading (p = 0,004), das Alter der Patienten bei der primären Operation (p < 0,001) sowie die Durchführung einer MVR (p = 0,004) als unabhängige prognostische Faktoren für das Gesamtüberleben in der Subgruppe der Primärtumore identifiziert. Für Patienten mit erstem, zweitem und drittem Rezidiv war eine makroskopisch unvollständige Tumorresektion (R2) mit einem reduzierten Gesamtüberleben in der multivariablen COX-Regression assoziiert (Abb. 5 A-C).

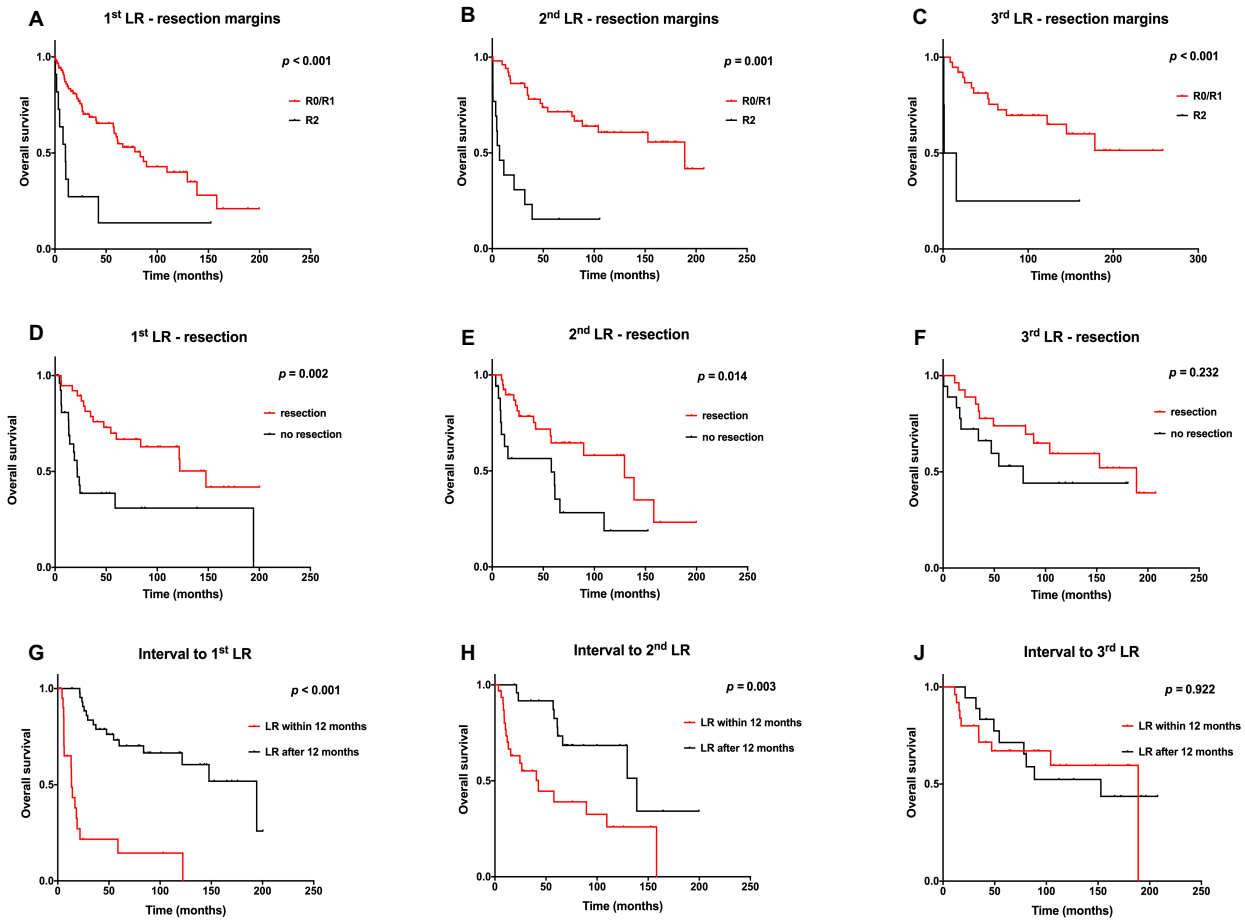

Abb. 5: Kaplan-Meier-Kurven für das Gesamtüberleben dargestellt mit Ergebnissen des log-rank Test in Abhängigkeit von A-C) den Resektionsrändern, D-F) der Resektion eines Lokalrezidivs und G-J) dem Intervall bis zum Auftreten des Lokalrezidivs für die gesamte Kohorte, unterteilt nach ersten, zweiten und dritten Rezidiven.

In der Subgruppe der Patienten, die ein LR entwickelten, ging die LR-Resektion mit einem verbessertem Gesamtüberleben nicht nur nach Resektion des ersten, sondern auch nach Resektion des zweiten Rezidivs einher (Abb. 5 D-F). Trat das LR innerhalb der ersten zwölf Monate nach der vorausgegangenen Operation auf, war dies mit einem schlechteren Gesamtüberleben assoziiert, verglichen mit einer späteren Entwicklung eines Lokalrezidivs (Abb. 5 G-J). Gleichermaßen war das Auftreten von FM mehr als 12 Monate nach der initialen Tumorresektion ein unabhängiger prognostischer Faktor für ein verbessertes

Gesamtüberleben. Diese Ergebnisse aus der Gesamtkohorte ließen sich für Liposarkome reproduzieren (Abb. 6 A-I).

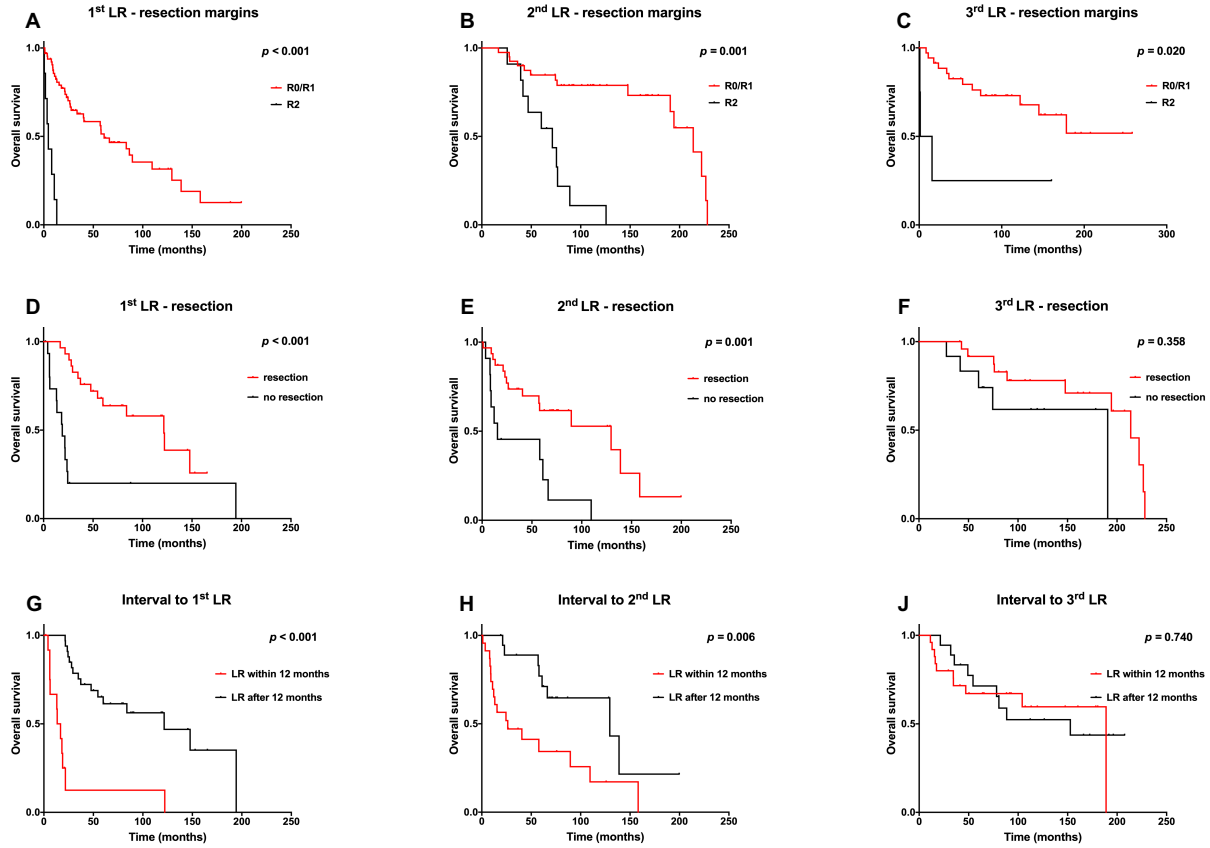

Abb. 6: Kaplan-Meier-Kurven für das Gesamtüberleben dargestellt mit Ergebnissen des log-rank Test in Abhängigkeit von A-C) den Resektionsrändern, D-F) der Resektion eines Lokalrezidivs und G-J) dem Interval bis zum Auftreten des Lokalrezidivs für die Subgruppe der Liposarkome unterteilt nach ersten, zweiten und dritten Rezidiven.

Für LMS Patienten zeigte die multivariable COX-Regressionen keine unabhängigen prognostischen Faktoren für das Gesamtüberleben. In der Subgruppe der LMS Patienten mit LR oder FM, war die Resektion des Rezidivs (p = 0,048) sowie das Auftreten später als 12 Monate nach der primären Operation (p = 0,027) mit einem verbesserten Gesamtüberleben assoziiert.

3.4 Erfassung und zeitliche Variation des Ernährungsstatus und präoperativer Anämien bei retroperitonealen Weichteilsarkomen

Infolge des etablierten aggressiven chirurgischen Vorgehens bei an RPS erkrankten Patienten sind Eingriffe, die unter anderem eine Teilresektion der Organe des Verdauungstraktes bedingen, keine Seltenheit.[9,26] Die Auswirkungen dieser Operationen auf den Ernährungszustand wurden bisher noch nicht untersucht. Nur wenige Studien mit begrenzten Patientenzahlen haben den Einfluss des präoperativen Ernährungszustandes auf das postoperative Ergebnis bei RPS analysiert und dabei hohe Mangelernährungsraten (40-50 %) festgestellt.[60,61] Veränderungen des Ernährungszustands aufgrund von Tumorrezidiven und wiederholten Operationen sind jedoch noch unerforscht. Ziel dieser Studie war es daher, den präoperativen Ernährungszustand sowie die Prävalenz von präoperativen Anämien von RPS-Patienten zu beurteilen und Veränderungen im Krankheitsverlauf zu untersuchen, um mögliche Strategien für die Prähabilitation zu identifizieren.

Hierfür wurden alle Patienten analysiert, die zwischen Oktober 2001 und Dezember 2019 in der Chirurgischen Klinik des Universitätsklinikums Heidelberg aufgrund eines Primärtumors, Lokalrezidivs und/oder Fernmetastasen eines RPS operiert wurden (Ethikvotum S-649/2012). Zur Beurteilung des präoperativen Ernährungszustandes wurden der präoperative Body Mass Index (BMI), das präoperative Albumin als Surrogatparameter für den Proteinstatus und das Hämoglobin (Hb) sowie das mittlere korpuskuläre Volumen (MCV) und das mittlere korpuskuläre Hämoglobin (MCH) bestimmt. Bei multiplen Tumorresektionen in unserer Abteilung wurden die oben genannten Parameter innerhalb von zwei Tagen vor jeder Operation bestimmt. Es wurde wie im Methodenteil beschrieben, univariate Kaplan-Meier Analysen und multivariable COX-Regressionen für das Gesamtüberleben durchgeführt. Es wurden alle möglichen Prädiktoren mit einem $p \leq 0{,}1$ aus der univariaten Analyse in die multivariable COX eingeschlossen. Bezüglich der Ernährungsparameter wurden nur Albumin und Hämoglobin für die multivariablen Analysen berücksichtigt, um Verzerrungen durch zu viele fehlende BMI-Werte zu vermeiden. Die Analysen erfolgten getrennt für Patienten mit Primärtumoren, erstem, zweitem und drittem Rezidiv. Um Veränderungen der Ernährungsparameter über den Krankheitsverlauf zu beurteilen wurden zusätzlich hierarchische lineare Modelle berechnet. Multivariable lineare Regressionsmodelle wurden verwendet, um Zusammenhänge zwischen Ernährungsparametern und der postoperativen Komplikationslast sowie der Krankenhausverweildauer zu testen.

Es wurden 370 Patienten analysiert, darunter 219 mit Primärtumoren und 151 mit Rezidiven. BMI-Werte lagen lediglich für 69 % der Patienten vor, wobei die Mehrheit übergewichtig war

(37 %). Mit zunehmender Anzahl der Resektionen nahm der Anteil normal- und untergewichtiger Patienten zu. Serumalbuminwerte lagen meist im Referenzbereich, während Anämien bei 41 % der Patienten auftraten, davon 19 % als mittelschwere oder schwere Formen, oft mikrozytär und/oder hypochrom, was auf einen Eisenmangel hinweisen kann.

BMI und Serumalbumin blieben bei wiederholten Resektionen stabil ($p > 0,05$), während Hämoglobinwerte signifikant mit der Anzahl der Resektionen abnahmen ($p = 0,022$) (s. Abb.7). Niedrige präoperative Hb-Werte waren mit einer erhöhten 30-Tage-Mortalität assoziiert (9,4 % vs. 0,8 %; $p = 0,004$), jedoch nicht mit dem Auftreten postoperativer Komplikationen oder längeren stationären Aufenthalten.

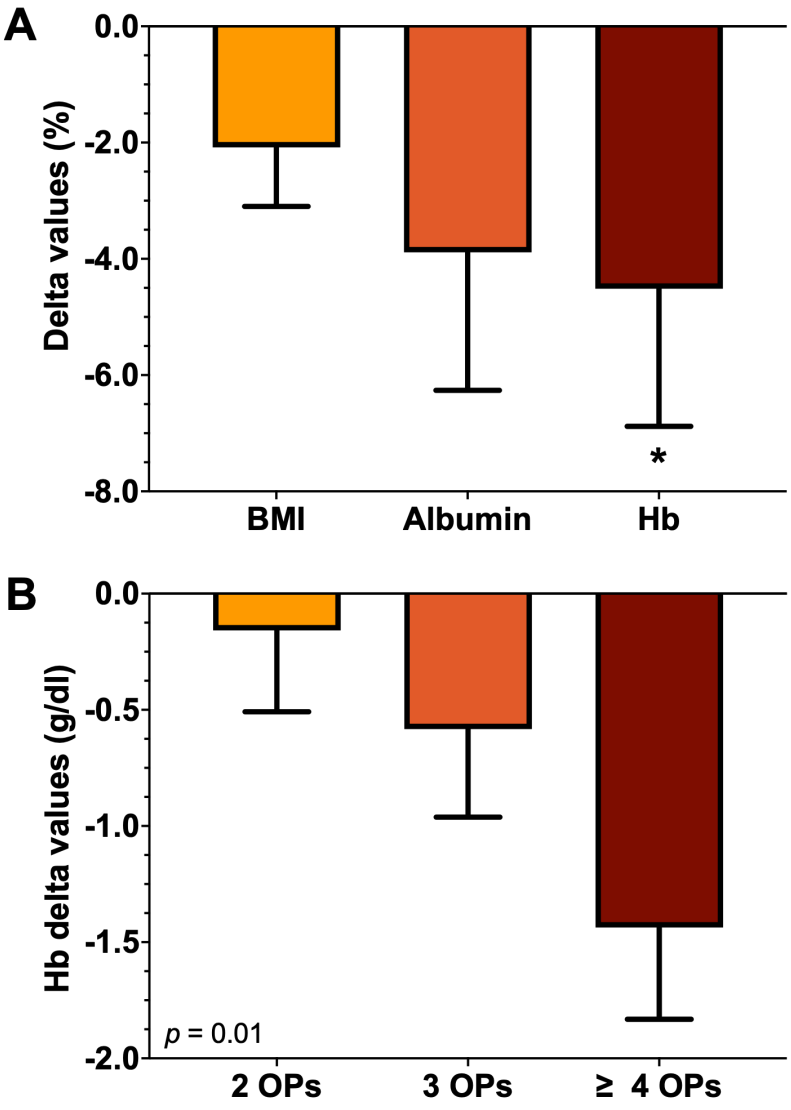

Abb. 7: Veränderungen der Ernährungsparameter im Verlauf der Erkrankung werden als Deltawerte dargestellt, die als Differenz zwischen den Werten vor der ersten und der letzten Operation berechnet werden. Negative Werte bedeuten eine Abnahme, während positive Werte eine Zunahme im Laufe der Zeit anzeigen. (A) Die Veränderung der Ernährungsparameter wird als Deltawert in Prozent des Ausgangswertes dargestellt. (B) Die Veränderung der Hämoglobinwerte in Abhängigkeit von der Anzahl der Tumorresektionen ist als absoluter Deltawert (g/dl) dargestellt (B). *$p < 0,05$.

Die multivariable COX-Regression identifizierte das Vorliegen einer präoperativen Anämie als unabhängigen prognostischen Faktor für das Gesamtüberleben nach Resektion sowohl von Primärtumoren als auch von Rezidiven (s. Abb. 8).

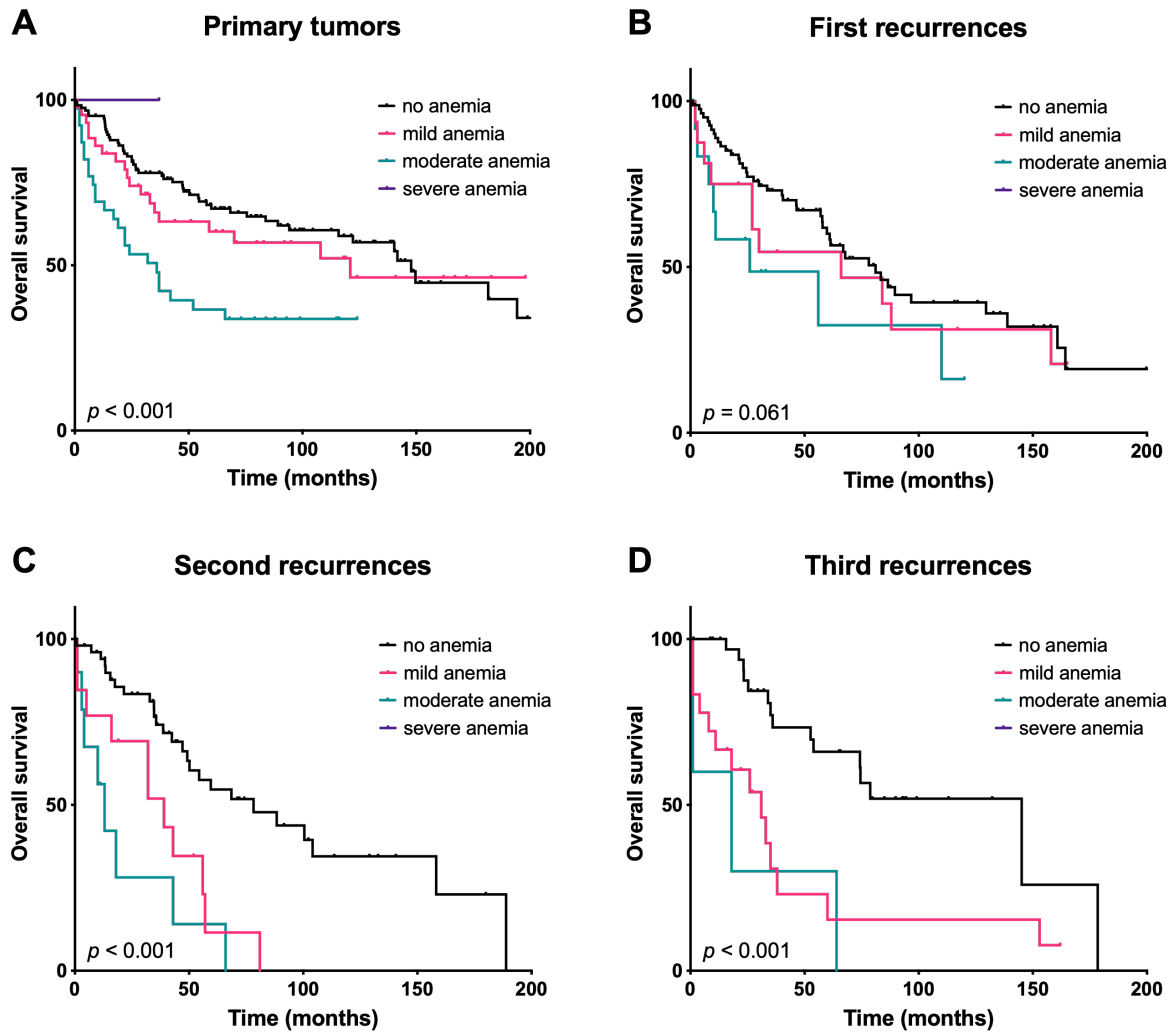

Abb. 8: Kaplan-Meier-Kurven mit Log-Rank-Test für das Gesamtüberleben nach Resektion des Primärtumors (A) sowie nach Resektion des ersten (B), zweiten (C) und dritten Tumorrezidivs (D) in Abhängigkeit vom präoperativen Hämoglobinwert. Einteilung der Anämie nach WHO: leicht: Hb 11,0 - 11,9 g/dl bei Frauen; Hb 11,0 - 12,9 g/dl bei Männern; mittelschwer: Hb 8,0 - 10,9 g/dl; schwer: Hb < 8,0 g/dl.

3.5 Einfluss (multipler) RPS-Resektionen auf die postoperative Lebensqualität

Mit den aktuellen Therapiestrategien bei RPS werden beachtliche Überlebenszeiten bei weiterhin hohen Rezidivraten erzielt. Dies kann jedoch dazu führen, dass im Verlauf der Erkrankung mehrere ausgedehnte Operationen – zum Teil mehrfache multiviszerale Resektionen (MVR) – notwendig werden. Zudem sind aufgrund des persistierenden Rezidivrisikos, welches auch nach fünf Jahren nicht abfällt, regelmäßige Nachsorgen lebenslang notwendig.[9] Obwohl diese Faktoren besondere physische und psychische Herausforderungen mit sich bringen, gibt es nur wenige Daten über die Auswirkungen auf die gesundheitsbezogene Lebensqualität (hrQoL) von RPS-Patienten. Sowohl die PROSa-Studie[62] als auch die SURVSARC-Studie[63] untersuchten die gesundheitsbezogene Lebensqualität bei Patienten mit Knochen- und Weichteilsarkomen und berichteten über signifikante Unterschiede in der gesundheitsbezogenen Lebensqualität in Abhängigkeit von Tumorhistologie und -lokalisation. Für RPS liegen jedoch bisher nur wenige Daten aus relativ kleinen Patientenkohorten vor.[62–66] Analysen auf der Basis einer italienischen Kohorte mit 58 Patienten zeigten eine adäquate und sich verbessernde Lebensqualität nach RPS-Resektion im ersten postoperativen Jahr.[64] Andere Analysen retrospektiver Kohorten weisen darauf hin, dass die postoperative Lebensqualität anfänglich noch starken Schwankungen und Veränderungen unterliegt und dass eine Nachbeobachtungszeit von mindestens zwei Jahren erforderlich ist, um die langfristige postoperative Lebensqualität zu beurteilen.[63,65,66] Weder die Auswirkungen mehrfacher Operationen auf die Lebensqualität noch das psychische Wohlbefinden (MWB) und die Angst vor dem Fortschreiten der Erkrankung wurden bisher bei RPS-Patienten mittels spezifischer Fragebögen untersucht. Unser Ziel war es daher, die mittels Patient Reported Outcomes (PROs) berichtete hrQoL nach Resektion und Re-Resektion eines RPS im Hinblick auf physische sowie emotionale und soziale Komponenten zu analysieren.

Nach positivem Ethikvotum (S-593/2020) und Registrierung der Studie am *Deutschen Register Klinischer Studien* (DRKS00023223) wurden alle noch lebenden Patienten, die aufgrund eines RPS (Primärerkrankung, Lokalrezidiv und/oder Fernmetastasen) im Zeitraum zwischen 10/2001 und 12/2020 an der Universitätsklinik Heidelberg operiert wurden zur Studienteilnahme eingeladen. Die Erhebung der Lebensqualität erfolgte mit fünf bereits validierten Fragebögen zur allgemeinen gesundheitsbezogenen Lebensqualität von Krebspatienten (EORTC QLQ-C30),[67] zum psychischen Wohlbefinden (WEMWBS),[68] zur Progredienzangst (FoP-Q-SF),[69] zu Symptomen einer posttraumatischen Belastungsstörung (PC-PTSD)[70] und zu einigen zusätzlichen körperlichen Symptomen (PRO-CTCAE).[71] Außerdem wurde die aktuelle Lebensqualität auf einer 10-stufigen Likert-Skala erfragt. Um

den Zusammenhang zwischen klinischen/demographischen Parametern und den verschiedenen Aspekten der hrQoL zu untersuchen wurden multivariable lineare Regressionsanalysen durchgeführt. Ergänzend wurden in Einzelfällen Spearman-Korrelationen berechnet.

Mit einer Rücklaufquote von 71 % nahmen 127 Patienten mit RPS an dieser Studie teil. Die mediane Zeit zwischen Diagnosestellung und Studienteilnahme betrug ca. 6,5 Jahre. Die mittels EORTC QLQ-C30 erfasste hrQoL zeigte eine zufriedenstellende allgemeine Lebensqualität sowie einen zufriedenstellenden subjektiven Gesundheitszustand, welche sich nur unwesentlich von der deutschen Allgemeinbevölkerung unterschied.[67] Bei einem insgesamt guten psychischen Wohlbefinden zeigten die Ergebnisse des WEMWBS bei 18 Patienten (14 %) ein erhöhtes Risiko für das Auftreten einer Depressionen und laut dem Screening Fragebogen für eine mögliche posttraumatische Belastungsstörung (PTSD) erfüllten 28 Patienten (22 %) die Cut-off-Kriterien. Bei 21 Patienten (17 %) wurde eine mäßige Progredienzangst festgestellt, während nur 3 Patienten (2 %) Anzeichen einer ausgeprägten Progredienzangst aufwiesen. In diesem Zusammenhang sind auch Symptome wie Müdigkeit oder Schlafstörungen zu nennen, die im Vergleich zur deutschen Allgemeinbevölkerung häufiger auftraten.[67,72] Ebenso fanden sich Einschränkungen im Bereich der emotionalen und sozialen Funktionalität.[67,72] Die Belastung durch primär körperliche Symptome war dagegen gering. Abdominelle Beschwerden traten mit Ausnahme von Diarrhoen nicht häufiger auf als in der deutschen Allgemeinbevölkerung.[67,72]

Die mediane Lebensqualität wurde mit 7 (Median: 6–8) ermittelt und wies eine signifikante Korrelation mit dem EORTC-QLQ-C30-Score für globale Gesundheit/QoL ($r_s = 0,75$) auf. Hohe Bewertungen der Lebensqualität zeigten starke Zusammenhänge mit körperlichen ($r_s = 0,74$), rollenbezogenen ($r_s = 0,67$) und emotionalen Funktionen ($r_s = 0,51$) sowie moderate Korrelationen mit Müdigkeit ($r_s = -0,65$) und Schmerzen ($r_s = -0,48$). Abdominelle Symptome und die kumulative Komplikationsbelastung hatten hingegen nur geringe oder keine Auswirkungen auf die Lebensqualität ($r_s < -0,4$) (s. Abb. 9).

Patienten und Patientinnen, die mehr als zwei Operationen durchlaufen hatten, wiesen signifikant häufiger Symptome wie Durchfall ($p < 0,001$) oder Ödeme ($p = 0,006$) auf. Allerdings waren weder das Auftreten eines Rezidivs noch die Anzahl der durchgeführten Operationen mit einer erhöhten Wahrscheinlichkeit für Progressionsangst oder einem beeinträchtigten psychischen Wohlbefinden assoziiert ($p > 0,05$). Eine MVR hatte keinen Einfluss auf die EORTC-QLQ-C30- und PTCD-Scores oder das MWB. Allerdings wurde bei Pankreasresektionen vermehrt das Auftreten von Diarrhöen beobachtet ($p = 0,002$). Des Weiteren wurde eine Verschlechterung der globalen Gesundheit/QoL ($p = 0,003$) und der

körperlichen Leistungsfähigkeit (p = 0,018) in Zusammenhang mit einer Strahlentherapie beobachtet.

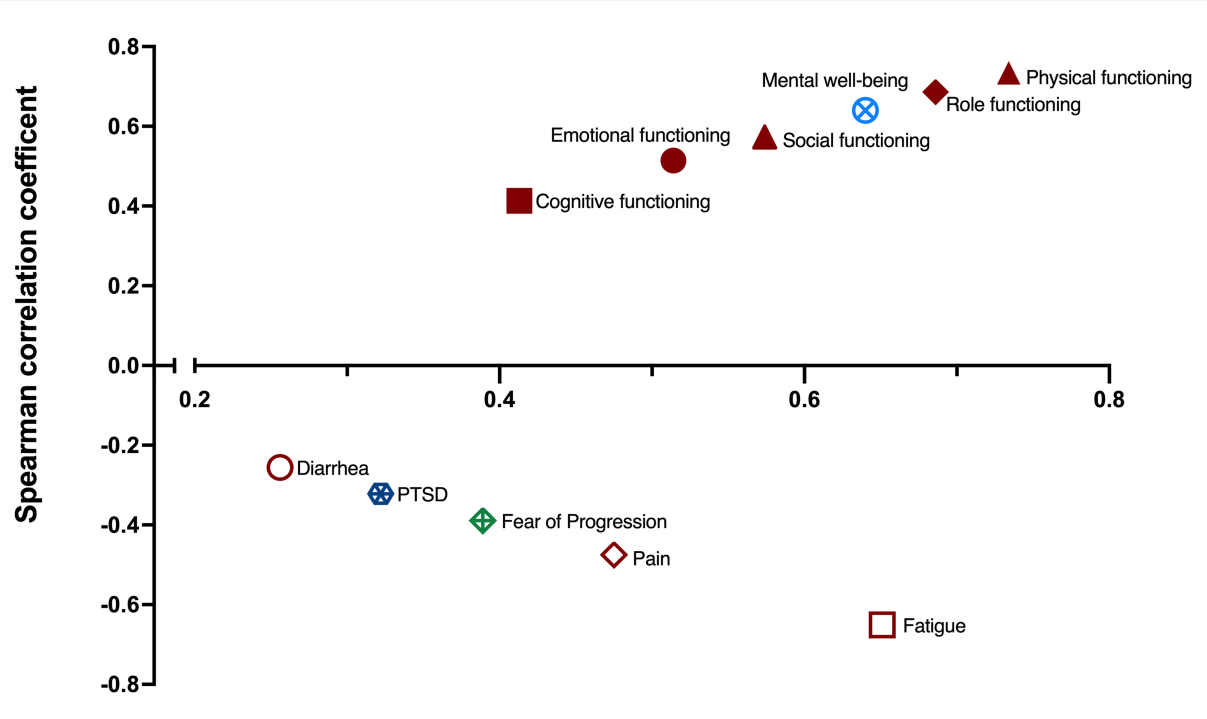

Abb. 9: Korrelation spezifischer Symptome/hrQoL-Ratings mit Ratings der aktuellen Lebensqualität, ermittelt mittels Spearman'sche Rangkorrelationen. Die in Rot dargestellten Symptome/Ratings wurden mit dem EORTC QLQ-C30 erhoben. Das MWB (hellblau) wurde mit dem WEMWBS, das mögliche Vorliegen einer PTSD (dunkelblau) wurde mit dem PC-PTSD und die Progredienzangst (hellgrün) wurde mit dem FoP-Q-SF-Fragebogen erfasst.

4. Diskussion der eigenen Arbeit

In Anbetracht der bereits dargelegten Herausforderungen in der Therapie und Forschung bei RPS erbringen retrospektive, monozentrische Analysen wie die vorliegenden einen signifikanten Beitrag zur RPS-Forschung. Die präsentierten Ergebnisse einer großen Kohorte stellen in vielen Bereichen die umfassendste Analyse zu spezifischen Fragestellungen dar. Dennoch sind solche Untersuchungen mit methodischen Limitationen verbunden. Retrospektive Analysen bergen das Risiko einer Selektionsverzerrung und einer unvollständigen Datenerfassung. Ebenso sollten bei kleinen Stichprobengrößen, insbesondere in Subgruppenanalysen, signifikante Ergebnisse mit Vorsicht interpretiert werden. In Bezug auf die Übertragbarkeit ist bei Daten aus einem einzigen Zentrum ebenfalls eine mit besonderer Sorgfalt durchgeführte Interpretation signifikanter Ergebnisse erforderlich. Unsere Kohorte ist jedoch konsistent zu großen RPS-Patientenkollektiven hinsichtlich Tumor- und Patientencharakteristika, Operationsstrategien, postoperativer Morbidität und Rezidivraten,[3,4,17] was insgesamt für die Repräsentativität unserer Ergebnisse spricht.

Die endgültige Klärung vieler der aufgeworfenen Fragen erfordert letztlich multizentrische, randomisierte, kontrollierte Studien. Deren kurzfristige Durchführung ist jedoch unter den gegebenen strukturellen Bedingungen unwahrscheinlich. Retrospektive Studien wie diese bieten daher derzeit die bestmögliche Evidenz für viele Forschungsfragen.[73] Ein erhebliches Potenzial zur Klärung offener Fragen bietet die Erhöhung der Patientenzahlen in zukünftigen Studien durch gemeinsame Anstrengungen, wie sie von der Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) gefördert werden. Die zunehmende Verfügbarkeit von prospektiven, multinationalen, multizentrischen Datensätzen, wie beispielsweise das Retroperitoneal Sarcoma Register (RESAR) der TARPSWG,[74] verspricht, zukünftige Forschungsbemühungen erheblich voranzutreiben.

Im Folgenden werden die individuellen Ergebnisse der einzelnen Studien in Bezug auf die aktuelle Literatur diskutiert.

4.1 Bedeutung der IORT und hoher kumulativer Strahlendosen bei RPS

Bei dieser Studie handelt es sich um die bis dato größte RPS-Kohorte, bei der die Rolle der intraoperativen Strahlentherapie systematisch erfasst und untersucht wurde. Zusammenfassend scheint die Durchführung einer IORT das onkologische Outcome nicht zu beeinflussen. Es konnte weder ein Zusatznutzen einer IORT noch einer kumulativen Strahlendosis ≥ 60 Gy bezogen auf das Lokalrezidiv-freie Überleben nachgewiesen werden. Bisherige Studien die einen möglichen Vorteil der IORT auf das LR-freie Überleben zeigten, beinhalteten nur wenige Patienten und die Effekte waren nur in der univariaten Analyse signifikant und konnten in multivariablen Analysen nicht bestätigt werden.[51–53] Einige Studien zeigten vielversprechende Lokalrezidivraten nach Durchführung einer IORT, jedoch wurden keine Kontrollgruppen ohne IORT berücksichtigt.[75–77]

Die Rolle der Strahlentherapie, die bis zur Erscheinung der STRASS-Studie[39] einen festen Bestandteil der multimodalen RPS-Therapie darstellte, ist aktuell umstritten. Subgruppen-Analysen, für die die Studie primär nicht gepowert war, suggerieren einen Vorteil einer neoadjuvanten Radiatio bezogen auf das LR-freie Überleben in der Subgruppe der G1 und G2 Liposarkome, weswegen in dieser Studie die Rolle der IORT ebenfalls explizit in Liposarkomen untersucht wurde. Jedoch zeigte sich auch hier kein Benefit einer IORT oder einer kumulativen Strahlendosis ≥ 60 Gy. Da die Subgruppe der Liposarkome heterogene Tumore umfasst, wäre es interessant, die Wirksamkeit der EBRT und IORT in Abhängigkeit vom histologischen Subtyp und Tumorgradings weiter prospektiv und randomisiert zu untersuchen. Solche Analysen würden jedoch große und einheitliche Patientenkohorten und -subgruppen erfordern, was angesichts der Heterogenität und der Seltenheit der Krankheit schwer zu erreichen ist.

Um Strukturungleichheiten zwischen den einzelnen Subgruppen möglichst gering zu halten, führten wir ein Propensity-Score-Matching durch. Wichtig ist hervorzuheben, dass diese Methode das Problem der Selektionsverzerrung zwar reduziert, aber nicht vollständig löst. Beispielsweise wurde die anfängliche Entscheidung, eine Resektion mit oder ohne IORT in Bereitschaft durchzuführen, präoperativ getroffen und die Gründe für diese Entscheidung können mit den Parametern einer Propensity-Score-Matching-Analyse nicht vollständig abgedeckt werden. Tatsächlich könnte das Risiko eines Lokalrezidivs präoperativ in der IORT-Bereitschaftsgruppe höher eingeschätzt worden sein als bei Patienten, die ohne IORT-Bereitschaft reseziert wurden. Diese Mängel können offensichtlich nur durch eine prospektive, randomisierte Studie behoben werden. Bis solche Daten verfügbar sind, erweitert diese gegenwärtige retrospektive Analyse einer relativ großen Patientenkohorte, die ein

angemessenes Propensity-Score-Matching ermöglicht, die Erkenntnisse aus früheren retrospektiven Analysen.

4.2 Bedeutung der Kompartmentresektion bei RPS

Wir konnten in dieser Studie zeigen, dass die Kompartmentresektion (CR) ein unabhängiger prognostischer Faktor für ein verbessertes DSS bei primären LPS zu sein scheint. Insbesondere scheint bei primären G3-LPS die CR mit einem verbesserten FMFS einherzugehen, was zu dem mit CR assoziierten verbesserten DSS bei G3-LPS beitragen könnte. Bei LMS-Patienten wurde ein solcher Zusammenhang jedoch nicht beobachtet.

Damit stehen unsere Ergebnisse nicht ganz im Einklang mit den ersten Studien, die das Konzept der CR etablierten und zeigten, dass diese bei RPS-Patienten im Vergleich zum damaligen Standardverfahren, der kompletten Tumorentfernung mit Mitnahme der Nachbarorgane nur bei eindeutigen Infiltrationszeichen, mit einem verbesserten Gesamtüberleben und LRFS assoziiert ist.[20,21,78] Diese Kohorten wurden jedoch nach Zeiträumen analysiert, in denen die CR in bestimmten Zeiträumen häufiger durchgeführt wurde, aber nicht nach der tatsächlichen Durchführung einer CR stratifiziert.[21,78] Darüber hinaus wurden in diesen Studien verschiedene RPS-Entitäten zusammen analysiert.[20,21,78] Wenn Subgruppenanalysen erfolgten, wurde entweder das Grading für alle RPS-Entitäten oder RPS-Entitäten ohne Berücksichtigung des Tumorgrades separat untersucht.[20,21,78]

Bei primären LPS konnte kein statistisch signifikanten Unterschied hinsichtlich des LRFS anhand von Kaplan-Meier-Analysen oder multivariabler COX-Regression festgestellt werden. Obwohl wir über fünf Jahre keine geringere LR-Rate in der CR-Gruppe beobachten konnten, war das mediane Zeitintervall zwischen der ersten Tumorresektion und der Diagnose eines Rezidivs bei Patienten, die sich einer CR unterzogen, deutlich länger. Ein längeres Intervall zwischen der Diagnose eines Tumorrezidivs und der ersten Operation gilt als unabhängiger Prädiktor für ein verbessertes Gesamtüberleben bei primärem LPS,[32,79] was erklären könnte, warum die CR in unserer Kohorte mit primärem LPS dennoch mit einem verbesserten DSS assoziiert ist.

In Grading-stratifizierten Subgruppenanalysen bei primärem LPS scheint die CR insbesondere bei primären G3-LPS mit einem günstigen DSS und FMFS, aber nicht mit einem verbesserten LRFS assoziiert zu sein. Unsere Daten deuten darauf hin, dass auch die Bildung von Fernmetastasen durch eine frühzeitige radikale chirurgische Behandlung in Form einer CR verhindert werden kann, was zu einem verbesserten DSS führen könnte. Diese Ergebnisse und Schlussfolgerungen sind jedoch aufgrund der geringen Stichprobengröße mit Vorsicht zu interpretieren. Das Fehlen eines Zusammenhangs zwischen CR und LRFS bei G3-LPS unterstreicht die Notwendigkeit, diese Ergebnisse in größeren, vorzugsweise prospektiven Kohorten zu validieren. Darüber hinaus sollten diese Ergebnisse in den Kontext der laufenden

STRASS-2-Studie gestellt werden, in der die Rolle der neoadjuvanten Chemotherapie bei primären LMS- und G3-LPS-Tumoren untersucht wird.[74]

Für LMS-Patienten konnten wir keine Verbesserung des DSS, LRFS oder FMFS durch die Durchführung einer CR feststellen. In diesem Zusammenhang muss jedoch erwähnt werden, dass die analysierte LMS-Kohorte insgesamt nur 46 Patienten (27,9 % der Kohorte) umfasste und unsere Ergebnisse möglicherweise nicht auf alle LMS-Patienten verallgemeinert werden können. Nichtsdestotrotz ist unsere Studie die erste, die zeigt, dass LMS nicht von einer CR im Vergleich zu einer En-bloc-Tumorresektion mit infiltrierten Organen zu profitieren scheinen.

Neben den bereits erwähnten Limitationen durch den retrospektiven Charakter der Studie sowie den teilweise kleinen Stichprobengrößen, stellt die lange Nachbeobachtungszeit eine weitere Einschränkung dar, da Fortschritte in der RPS-Behandlung im Laufe der Jahre die onkologischen Ergebnisse beeinflusst haben könnten und somit unsere Ergebnisse verzerren. Wir haben jedoch versucht, diese Verzerrung so weit wie möglich zu reduzieren, indem wir nach der Art der Operation und nicht dem Zeitpunkt der Operation stratifiziert haben sowie eine multivariable Analyse zur Korrektur von Störfaktoren verwendet haben. Dennoch ist die Interpretation der multivariablen Regressionsanalyse begrenzt und auch hier ist eine Validierung in größeren, idealerweise multizentrischen und prospektiv untersuchten Kohorten erforderlich.

Insgesamt liefert diese Studie unseres Wissens die erste Evidenz für histologieorientierte chirurgische Ansätze bei RPS. Unsere Ergebnisse deuten darauf hin, dass insbesondere Patienten mit primärem LPS von einer CR in Form eines verbesserten DSS profitieren, während die Durchführung einer CR die onkologischen Ergebnisse bei Patienten mit primärem LMS nicht verbessert. Diese Ergebnisse unterstützen die Annahme, dass ein personalisierter chirurgischer Ansatz für die RPS-Behandlung von entscheidender Bedeutung ist.

4.3 Ergebnisse nach Resektion mehrfach rezidivierender RPS

Diese Studie umfasst eines der größten Kollektive mit primärem und mehrfach rezidivierten RPS, anhand derer der Einfluss mehrfacher Rezidivresektionen auf das Gesamtüberleben analysiert wird. Das Auftreten von Lokalrezidiven, Fernmetastasen oder beidem führt zu einem reduzierten Gesamtüberleben und ist mit einer erhöhten Wahrscheinlichkeit eines weiteren Tumorrezidivs verbunden. In Übereinstimmung mit den Ergebnissen von MacNeill et al.[32] identifizierten wir ein verlängertes Intervall bis zum Auftreten von LR/DM und die chirurgische Resektion von LR/DM als prognostische Faktoren, die auf ein verbessertes Gesamtüberleben nach Auftreten eines ersten Rezidivs (LR oder DM) hinweisen. Dies galt sowohl für die gesamte Patientenkohorte als auch für die LPS- und LMS-Subgruppen. Wichtig ist jedoch, dass unsere Daten darauf hindeuten, dass das Überleben nicht nur durch die Resektion des ersten, sondern auch durch die Resektion des zweiten LR verlängert werden kann. Obwohl unsere Ergebnisse keinen signifikanten Vorteil der chirurgischen Resektion des dritten und vierten LR erkennen lassen, war das mediane Überleben nach Resektion des dritten LR mehr als doppelt so lang wie bei Patienten ohne Resektion. Die unvollständige Resektion des ersten, zweiten und dritten LR war signifikant mit einem schlechteren Überleben assoziiert, was ebenfalls die Annahme untermauert, dass die Patienten von der Resektion nachfolgender Resektionen profitieren. Es gibt sogar Studien die nahe legen, dass Patienten von einem chirurgischen Debulking profitieren können,[57,80,81] während andere Studien keinen Unterschied in den Ergebnissen zwischen reinen Biopsien oder R2-Resektionen beschreiben.[82–84]

Es muss natürlich berücksichtigt werden, dass die Daten und Schlussfolgerungen dieser Studie einem Selektionsbias unterliegen. Beispielsweise haben Patienten mit isoliertem LR oder DM oder Patienten mit langsam wachsenden Tumoren ohne Multifokalität eine höhere Wahrscheinlichkeit, eine makroskopisch vollständige Resektion zu erreichen. Ein beträchtlicher Anteil der Patienten mit irresektablem oder multifokalem LR/DM und externer Behandlung des Primärtumors wurde möglicherweise nicht in unserer Abteilung vorgestellt, während Patienten mit resektablem LR oder DM häufig zur Rezidivbehandlung in unser Zentrum überwiesen wurden. Trotz der hier und oben aufgeführten Limitationen handelt es sich unseres Wissens um die größte Fallserie, die das onkologische Outcome nach Entwicklung eines zweiten, dritten und vierten Rezidivs analysiert und die aktuellen Empfehlungen unterstützt, dass RPS-Patienten von einer chirurgischen Resektion profitieren, wenn eine vollständige Resektion technisch möglich und angesichts des Performance-Status der Patienten vertretbar ist.[41]

4.4 Erfassung und zeitliche Variation des Ernährungsstatus und präoperativer Anämien bei retroperitonealen Weichteilsarkomen

Bei dieser Studie handelt es sich um die erste Arbeit, die den Ernährungs- und Anämiestatus von Patienten mit RPS retrospektiv über den Krankheitsverlauf untersucht und dabei einen Schwerpunkt auf multiviszerale und wiederholte Tumorresektionen legt.

Die Evaluation des Ernährungszustands anhand von Albumin und BMI ergab in unserer Kohorte keine Fälle schwerer Mangelernährung. Diese Ergebnisse stehen im Gegensatz zu früheren Studien, die Raten von Mangelernährung bei Patienten mit RPS von 46–52 % dokumentierten.[60,61] In unserer Kohorte traten Hypoalbuminämien mit einer Prävalenz von weniger als 5 % seltener auf als in anderen Studien mit 16 %.[60,85] Diese Diskrepanz könnte die Ursache dafür sein, dass in dieser Arbeit kein Zusammenhang zwischen erniedrigtem Albuminspiegeln und erhöhter Morbidität oder verlängerten Krankenhausaufenthalten, wie in früheren Arbeiten beschrieben, festgestellt wurde.[60,61,85] Eine weitere Erklärung könnte in der unterschiedlichen Erfassung des Ernährungszustands liegen: Aufgrund des retrospektiven Designs dieser Studie wurden standardisierte präoperative Parameter ausgewertet, die möglicherweise nicht ideal für eine umfassende Beurteilung des Ernährungsstatus sind. Darüber hinaus ist der BMI, obwohl weit verbreitet, bei RPS möglicherweise kein zuverlässiger Indikator für den Ernährungszustand, da das Tumorgewicht das Körpergewicht erheblich beeinflussen kann. Zudem kann Adipositas Mangelernährung und katabole Zustände verschleiern.[86,87] Diese Erkenntnisse unterstreichen die Notwendigkeit, dass etablierte Methoden, wie Albumin- oder BMI-basierte Scores, möglicherweise nicht ausreichend sind, um den Ernährungszustand bei RPS adäquat zu beurteilen. Dies verdeutlicht die Notwendigkeit spezifischer Instrumente zur Bewertung des Ernährungsstatus bei RPS, insbesondere bei adipösen Patienten.

Jedoch war die Prävalenz von Anämien in unserer Kohorte auffallend hoch (40 %), was in starkem Kontrast zu den beschriebenen Anämieprävalenzen in der deutschen Allgemeinbevölkerung über 65 Jahre (4,3 %) und bei Krankenhauspatienten im Alter zwischen 50 und 80 Jahren (25 %) steht.[88,89] Das Vorliegen einer mikrozytären und/oder hypochromen Anämie, die auf einen Eisenmangel hinweisen kann, war in 20-40 % der Fälle vorhanden, was mit den Ergebnissen von Eisele et al. übereinstimmt, die zeigten, dass 29 % der Anämien in der deutschen Bevölkerung auf einen Eisenmangel zurückzuführen sind.[88] Unsere Ergebnisse zeigen auch, dass das präoperative Hämoglobin im Verlauf der Erkrankung signifikant abnimmt, was mit der Anzahl der durchgeführten Operationen korreliert. Ebenso war in dieser Kohorte der präoperative Hämoglobinwert ein unabhängiger prognostischer Faktor für das

Gesamtüberleben, wobei niedrigere präoperative Hämoglobinwerte nach Resektion von Primärtumoren und Rezidiven mit einem schlechteren Gesamtüberleben assoziiert waren. Das Vorliegen einer präoperativen Anämie wurde bereits mit einer höheren Komplikationsrate, einem längeren Krankenhausaufenthalt und einer erhöhten Mortalität in Verbindung gebracht.[89] In unserer Kohorte fanden wir keinen Zusammenhang zwischen niedrigen Hämoglobinwerten und dem Auftreten von postoperativen Komplikationen oder einem längeren Krankenhausaufenthalt, aber wir beobachteten eine höhere 30-Tage-Mortalität. Letztlich bleiben mögliche Zusammenhänge zwischen niedrigen Hb-Werten und einem schlechteren Überleben ungeklärt, sei es als Spiegelbild von Begleiterkrankungen, schlechterer Tumorbiologie, höherer Mortalität oder wahrscheinlich einer Kombination dieser Faktoren. Dennoch scheint die mögliche Verbesserung der Hb-Werte, insbesondere im Falle eines Eisenmangels, der bis zu 40 % ausmachen kann, ein vernünftiger therapeutischer Ansatz zu sein. Eine sorgfältige Überwachung der Hämoglobinwerte vor der Operation und während der Nachsorge ist von entscheidender Bedeutung, da wir im Verlauf der Erkrankung eine signifikante Abnahme der Hämoglobinwerte beobachtet haben. Dieser Ansatz ermöglicht eine frühe Diagnose der Anämie und einen rechtzeitigen Therapiebeginn, was möglicherweise zu besseren Patientenergebnissen und Überlebensraten beiträgt.

Aufgrund des retrospektiven Designs waren wir bei der Auswahl der Parameter zur Bewertung des Ernährungszustands eingeschränkt, wodurch möglicherweise andere relevante Indikatoren übersehen wurden. Insbesondere die Einbeziehung von Serumferritin und der Transferrinsättigung wäre für die Interpretation der Anämie präoperativ und im Verlauf der Erkrankung wertvoll gewesen. Das Fehlen umfassender Daten zu Komorbiditäten stellt eine weitere Einschränkung dar, da diese Faktoren die beobachteten Assoziationen zwischen Ernährungsparametern und Ergebnissen verzerren könnten. Trotz dieser Einschränkungen hat die Studie mehrere Stärken. Wir beschreiben die größte RPS-Kohorte zur Untersuchung des Ernährungszustandes und diese Studie ist die erste, die Veränderungen des Ernährungszustandes im Verlauf der Erkrankung untersucht. Obwohl unsere Studie keine signifikante Mangelernährung zeigte, beobachteten wir eine erhebliche Prävalenz präoperativer Anämien und identifizierten niedrigere präoperative Hämoglobinwerte als unabhängigen prognostischen Faktor für das Gesamtüberleben. Previtali et al. zeigten, dass ein präoperatives Ernährungsscreening und eine präoperative supportive Ernährung mit hohem Proteingehalt das Potenzial haben, eine bestehende Mangelernährung auszugleichen und postoperative Ergebnisse zu verbessern.[60] Ein ähnlicher Ansatz sollte für die Überwachung und das Management der Hämoglobinwerte bei RPS-Patienten in Betracht gezogen werden, um die Patientenergebnisse zu optimieren und möglicherweise die Überlebensraten zu verbessern.

4.5 Einfluss (multipler) Resektionen auf die postoperative Lebensqualität

Diese Studie liefert eine umfassende Analyse der Auswirkungen verschiedener klinisch-pathologischer und chirurgischer Faktoren auf die langfristige Lebensqualität in einer großen Kohorte von RPS-Patienten. Interessanterweise hatten in unserer Analyse weder die Durchführung einer MVR noch das Auftreten postoperativer Komplikationen einen signifikanten Einfluss auf die langfristige Lebensqualität der Patienten. Vergleichbare Ergebnisse wurden von Fiore et al. bei der Analyse der Lebensqualität von 58 italienischen Patienten im ersten Jahr nach Resektion eines primären RPS beobachtet.[64] Auch in der multizentrischen PATRONUS-Studie, in der die Lebensqualität nach großen abdominalen Tumoroperationen untersucht wurde, fand sich kein Zusammenhang zwischen postoperativen Komplikationen und der Einschätzung der Lebensqualität durch die Patienten.[90] Darüber hinaus hatten in unserer Analyse weder die Resektion bestimmter Organe noch die Anzahl der durchgeführten Operationen einen signifikanten Einfluss auf die körperliche Funktionsfähigkeit, den allgemeinen Gesundheitszustand, das psychische Wohlbefinden oder die Angst vor dem Fortschreiten der Erkrankung. Neuere Studien haben gezeigt, dass das Gesamtüberleben von RPS-Patienten durch die Resektion der häufig auftretenden Rezidive signifikant verlängert wird.[32,41] Die vorliegenden Ergebnisse bestätigen diesen chirurgischen Ansatz und zeigen, dass wichtige Aspekte der Lebensqualität durch mehrfache Resektionen offenbar nicht beeinträchtigt werden.

Auffallend ist jedoch, dass in unserer Kohorte Symptome wie Müdigkeit und das Vorhandensein von Schlafstörungen, welche beide mit einer schlechteren aktuellen Lebensqualität korrelieren, häufiger sind als in der Allgemeinbevölkerung. Ebenso zeigten sich Defizite im Bereich der emotionalen und sozialen Funktionsfähigkeit, während die Unterschiede in Bezug auf die körperliche Funktionsfähigkeit im Vergleich zur Allgemeinbevölkerung trivial waren. Unsere Daten legen nahe, dass eher psychosoziale und psychologische Aspekte als rein körperliche die Lebensqualität nach einer Resektion beeinflussen. Daraus kann gefolgert werden, dass sich die Nachsorge nicht nur auf körperliche Symptome, sondern auch auf die Bewältigung von Alltagsanforderungen und die soziale Anpassung konzentrieren sollte. Eine regelmäßige Erhebung der PROs in der Nachsorge kann dazu beitragen, Problembereiche früher zu erkennen, das Ansprechen sensibler Themen zu erleichtern und damit eine maßgeschneiderte, ganzheitliche Versorgung zu ermöglichen.[91] Dies könnte insbesondere bei chirurgischen Nachsorgeuntersuchungen der Fall sein, bei denen eher der onkologische Status und vor allem körperliche Einschränkungen im Vordergrund stehen.

Die Ergebnisse der vorliegenden Studie deuten darauf hin, dass die Anwendung einer Strahlentherapie mit schlechteren Werten für die körperliche Funktionsfähigkeit und den allgemeinen Gesundheitszustand verbunden ist. Diese Ergebnisse unterscheiden sich von früher veröffentlichten Daten zu diesem Thema, die keinen Zusammenhang zwischen Strahlentherapie und Lebensqualität bei RPS-Patienten zeigten.[64,66,92] Eine Sekundäranalyse der hrQoL-Daten aus der randomisierten STRASS-Studie, in der die präoperative Bestrahlung mit der alleinigen Operation verglichen wurde, wird weitere Erkenntnisse zu diesem Thema liefern. Die Übertragbarkeit der Ergebnisse unserer Kohorte auf die Gesamtheit der RPS-Patienten ist jedoch aufgrund des Rekrutierungszeitraums von 20 Jahren mit teilweise unterschiedlichen Therapieregimen eingeschränkt. Der lange Beobachtungszeitraum stellt auch noch aus weiteren Gründen eine wichtige Einschränkung dar. Änderungen und Verbesserungen der Therapie von RPS im Laufe der Jahre können sich ebenfalls auf die hrQoL auswirken und unsere Ergebnisse verfälschen. Eine wesentliche Limitation dieser Studie ist ebenfalls ihr retrospektives Design. Das Fehlen von Ausgangsdaten zur hrQoL erschwert die Interpretation. Darüber hinaus gibt es einen Survivorship Bias. So konnten Patienten, die kurz nach der Operation aufgrund einer aggressiven und fortgeschrittenen Erkrankung oder schwerer postoperativer Komplikationen starben, nicht in diese Analyse einbezogen werden. Ebenso besteht die Möglichkeit eines Response Bias. Durch die hohe Rücklaufquote von 71 % konnte dieser Effekt jedoch auf ein Minimum reduziert werden. Mit 127 Patienten ist dies die bisher größte verfügbare Kohorte von RPS-Patienten mit Daten zur Lebensqualität. Dennoch ist die Übertragbarkeit der Ergebnisse der multivariaten Regressionsanalyse begrenzt und eine Validierung in größeren, idealerweise multizentrischen Kohorten mit prospektivem Design erforderlich.

5. Zusammenfassung

Die vorliegende Arbeit widmet sich der systematischen Untersuchung zentraler Fragestellungen zur Behandlung und Nachsorge von Patienten mit retroperitonealen Weichteilsarkomen (RPS). Die hohe Rezidivrate sowie die Seltenheit und Heterogenität dieser Tumore stellen große Herausforderungen in der Therapie dar und erschweren die Erforschung dieser Erkrankung. Die vorliegende kumulative Habilitationsschrift hat zum Ziel, die Wirksamkeit unterschiedlicher Therapieansätze zu evaluieren, die Bedeutung von Rezidivresektionen zu beleuchten sowie die langfristigen Auswirkungen auf den Ernährungszustand und die Lebensqualität der Betroffenen zu analysieren.

Die in dieser Arbeit präsentierten Forschungsergebnisse tragen zur Schließung bestehender Wissenslücken bei. So wurde in der Analyse zur intraoperativen Strahlentherapie (IORT) festgestellt, dass diese keinen signifikanten Einfluss auf das lokoregionäre rezidivfreie Überleben oder das Gesamtüberleben hat. Ebenso konnte der Vorteil einer kumulativen Strahlendosis von ≥ 60 Gy auf das Lokalrezidiv-freie Überleben nicht nachgewiesen werden. Stattdessen erwiesen sich eine makroskopisch vollständige Tumorresektion, ein niedrigeres Tumorgrading und ein jüngeres Patientenalter als entscheidende positive prognostische Faktoren. Diese Ergebnisse unterstreichen die bestehende Kontroverse um eine IORT und weisen darauf hin, dass diese kein integraler Bestandteil in der Behandlung von RPS darstellen sollte.

Die Untersuchung zur Kompartmentresektion (CR) ergab demgegenüber klare Vorteile hinsichtlich der Behandlung primärer Liposarkome. In diesem Kontext führte die CR zu einer signifikanten Verlängerung des Zeitintervalls bis zum Auftreten eines Lokalrezidivs sowie zu einer Verbesserung des krankheitsspezifischen Überlebens. Für Leiomyosarkome konnten hingegen keine Vorteile einer CR nachgewiesen werden. Allerdings ist anzumerken, dass die CR mit einer gesteigerten postoperativen Morbidität verbunden ist. Diese Ergebnisse betonen die Relevanz einer differenzierten Indikationsstellung zur CR und unterstreichen die Bedeutung von chirurgischen Therapiestrategien, die sich an der Tumorhistologie orientieren.

Die vorliegende Studie zu Rezidivresektionen unterstreicht die prognostische Relevanz chirurgischer Interventionen bei erneuten Tumorrezidiven. Die Resektion eines ersten und auch zweiten Lokalrezidivs war mit einer verbesserten Überlebensrate assoziiert. Ein frühes Auftreten eines Rezidivs innerhalb von 12 Monaten nach der vorherigen Operation verschlechterte die Prognose signifikant. Gleiches galt für die Entwicklung von Fernmetastasen, deren Auftreten innerhalb von 12 Monaten nach der Primäroperation mit einem schlechteren Outcome assoziiert war verglichen zu einem späteren Auftreten. Diese

Erkenntnisse unterstreichen die zentrale Rolle einer konsequenten chirurgischen Therapie bei der Behandlung von Rezidiven und liefern wichtige Hinweise für die Langzeitüberwachung.

Die Analyse des Ernährungszustands bei RPS-Patienten ergab, dass nur eine geringe Anzahl der Patienten an einer Mangelernährung litt und der Ernährungszustand auch nach mehrfachen RPS-Resektionen als stabil einzustufen war. Hingegen wurde eine überdurchschnittlich hohe Prävalenz an präoperativen Anämien festgestellt, welche mit der Anzahl durchgeführter Operationen signifikant korrelierte. Das Vorliegen einer präoperativen Anämie war mit einer erhöhten 30-Tage-Mortalität assoziiert und wurde ebenfalls als unabhängiger prognostischer Faktor für das Gesamtüberleben identifiziert. Diese Erkenntnisse unterstreichen die Relevanz einer engmaschigen Überwachung und frühzeitigen Behandlung von präoperativen Anämien, um eine zielgerichtete Therapie zeitnah einleiten zu können und somit die Prognose von RPS-Patienten potenziell zu verbessern.

Die vorliegende Untersuchung zur Lebensqualität ergab, dass die Mehrzahl der Patienten trotz wiederholter Operationen eine gute allgemeine Lebensqualität aufwies. Jedoch traten im Vergleich zur Allgemeinbevölkerung vermehrt Symptome wie Müdigkeit und Schlafstörungen auf und RPS-Patienten zeigten Defizite im Bereich der emotionalen und sozialen Funktionalität. Das Vorliegen einer Progressionsangst sowie abdomineller Beschwerden war sehr selten und weder mit der Anzahl an Operationen noch mit dem Auftreten von Rezidiven assoziiert. Diese Erkenntnisse unterstreichen die Relevanz einer Beurteilung des psychosozialen Wohlbefindens im Rahmen der regelmäßig stattfindenden Nachsorge. Die Erfassung dieser Faktoren ermöglicht eine frühzeitige Identifikation von Bedarfslagen und die Implementierung angemessener Unterstützungsmaßnahmen, mit dem Ziel, die postoperative Versorgung zu optimieren.

Zusammenfassend liefert diese Arbeit wichtige Erkenntnisse für die Optimierung der Therapie und Nachsorge retroperitonealer Weichteilsarkome. Die Ergebnisse betonen die Bedeutung einer differenzierten Indikationsstellung bei der Kompartmentresektion und einer konsequenten chirurgischen Behandlung von Rezidiven. Darüber hinaus wird die Notwendigkeit verdeutlicht, langfristige Folgen wie Anämien und postoperative Einschränkungen auch im psychosozialen Bereich im Rahmen eines multidisziplinären Ansatzes zu adressieren. Diese Ergebnisse unterstreichen die Relevanz einer patientenzentrierten Nachsorge, die über rein onkologische Aspekte hinausgeht.

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8. Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit bzw. die mir zuzuordnenden Teile im Rahmen einer kumulativen Habilitationsschrift selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nicht veröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Ich versichere, dass ich für die nach §2 (3) der Habilitationsordnung angeführten bereits veröffentlichten Originalarbeiten als Erst- oder Seniorautor fungiere, da ich den größten Teil der Daten selbst erhoben habe, für das Design der Arbeiten verantwortlich bin und die Manuskripte maßgeblich gestaltet habe. Für alle von mir erwähnten Untersuchungen habe ich die in der „Satzung der Justus-Liebig-Universität zur Sicherung guter wissenschaftlicher Praxis“ niedergelegten Grundsätze befolgt. Ich versichere, dass alle an der Finanzierung der Arbeiten beteiligten Geldgeber in den jeweiligen Publikationen genannt worden sind. Ich versichere außerdem, dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Weise einer anderen Prüfungsbehörde vorgelegt wurde oder Gegenstand eines anderen Prüfungsverfahrens war. Mit der Überprüfung meiner Arbeit durch eine Plagiatserkennungssoftware bzw. ein internetbasiertes Softwareprogramm erkläre ich mich einverstanden.

Gießen, 15.04.2025

Franziska Willis

9. Anhang mit Originalarbeiten

1. **Willis, F.***, Schimmack, S.*, Uhl, M., Haefner, M. F., Mechtersheimer, G., Hinz, U., Schmidt, T., Debus, J., Fröhling, S. & Schneider, M. (2020). Significance of intraoperative radiation therapy and high cumulative radiation doses in retroperitoneal soft tissue sarcoma. *European Journal of Surgical Oncology*, *46*(5), 905-913

2. Musa, J.*, **Willis, F.***, Rompen I. F., Harnoss, J.-C., Grünewald, T. P. G., Al-Saeedi, M., Büchler, M. W. & Schneider, M. (2025). Histology-driven tailoring of surgical approaches in retroperitoneal soft tissue sarcoma: retrospective cohort study. *BJS Open*. 9(3):zraf050.

3. **Willis, F.**, Musa, J., Schimmack, S., Hinz, U., Mechtersheimer, G., Uhl, M., Schmidt, T., Fröhling, S., Büchler, M. W. & Schneider, M. (2021). Outcome after surgical resection of multiple recurrent retroperitoneal soft tissue sarcoma. *European Journal of Surgical Oncology*, *47*(8), 2189-2200.

4. **Willis, F.**, Trunk, A. M., Musa, J., Harnoss, J. M., Strowitzki, M. J., Engerer, C., Harnoss, J.-C., Al-Saeedi, M., Büchler, M. W. & Schneider, M. (2025). Temporal variation in nutritional status and preoperative anemia among patients with retroperitoneal soft tissue sarcoma: a retrospective longitudinal cohort study. *Langenbeck's Archives of Surgery*, *410*(1), 1-11.

5. **Willis, F.**, Buck, L., Musa, J., Hinz, U., Mechtersheimer, G., Seidensaal, K., Fröhling, S., Büchler, M. W. & Schneider, M. (2023). Long-term quality of life after resection of retroperitoneal soft tissue sarcoma. *European Journal of Surgical Oncology*, *49*(11), 106977.

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Significance of intraoperative radiation therapy and high cumulative radiation doses in retroperitoneal soft tissue sarcoma

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ABSTRACT

Introduction: In retroperitoneal soft tissue sarcoma (STS) local recurrence (LR) rates remain high despite more aggressive surgical approaches. Since wide resection margins cannot be achieved in all patients, application of intraoperative radiation therapy (IORT) has been frequently discussed. Still, the significance of IORT in multimodal treatment of retroperitoneal STS remains unclear.

Material and methods: Patients undergoing resection of primary or recurrent retroperitoneal STS at the University of Heidelberg Department of General, Visceral and Transplantation Surgery were retrospectively analyzed. Univariate Kaplan-Meyer and multivariate Cox regression analyses were performed to identify predictors of LR-free survival and to investigate the impact of IORT and high cumulative radiation doses. Analyses with propensity-score matched subgroups for IORT and cumulative radiation dose were performed to control for selection bias. Subgroup analyses for patients with retroperitoneal liposarcoma were likewise performed.

Results: 272 patients were identified. Recurrent tumors, histology of dedifferentiated liposarcoma or unclassified sarcoma and microscopically incomplete resection were associated with decreased LR-free survival. In liposarcoma, only recurrent and dedifferentiated tumors were confirmed as poor prognostic factors concerning LR. IORT and cumulative radiation doses exceeding 60 Gy did not influence LR rates (estimated 5-year LR-free survival: IORT: 39%, non-IORT: 46%; $p = 0.79$).

Conclusion: In this retrospective evaluation, additional application of IORT does not significantly influence oncological outcome in retroperitoneal soft tissue sarcoma. Randomized trials are needed to clarify the benefit of IORT.

Introduction

Retroperitoneal soft tissue sarcomas (STS) account for about 15% of all soft tissue sarcomas [1]. Local recurrence (LR) is common in retroperitoneal STS (50–80%) and associated with high mortality rates (5-year overall survival 40–65%) [2–5]. Factors influencing the LR rate comprise tumor entity, histological grading and surgical resection margins [6–8].

Despite more aggressive surgical approaches, LR rates in retroperitoneal STS remain high, and wide resection margins cannot be achieved in all patients [6–9]. Hence, there is a strong rationale for additive therapy. Several retrospective studies have suggested

Abbreviations: STS, soft tissue sarcoma; *LR*, local recurrence; *OS*, overall survival; *EBRT*, external beam radiation therapy; *IORT*, intraoperative radiation therapy; cRD, cumulative radiation dose; *DD-LPS*, dedifferentiated liposarcoma; *WD-LPS*, well-differentiated liposarcoma; *LMS*, leiomyosarcoma; *MPNST*, malignant peripheral nerve sheath tumor; *SFT*, intermediate malignancy: solitary fibrous tumor & desmoid fibromatosis.

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beneficial effects of external beam radiation therapy (EBRT) concerning LR [7,10–12], or concerning overall survival (OS) [10,11,13]. However, the only randomized trial (STRASS EORTC 62092), which compared preoperative EBRT plus surgery with curative-intent surgery alone in the treatment of non-metastatic retroperitoneal STS, failed to demonstrate any beneficial effects of preoperative radiation therapy concerning LR, with the exception of the retroperitoneal liposarcoma (LPS) subgroup [14]. In STS of the extremities, EBRT in an adjuvant setting applying doses exceeding 60 Gy positively influences LR rates [15]. Due to large resection sites and limited radiation tolerance of adjacent organs, adjuvant ERBT dosages in this range can rarely be achieved for retroperitoneal STS [16]. Therefore, the putative benefit of intraoperative radiation therapy (IORT) has drawn attention lately. However, current evidence is not conclusive. Some authors report a benefit regarding LR rates [12,17–20], whereas others failed to detect beneficial effects of IORT [21,22].

The aim of this retrospective analysis was to investigate the impact of IORT on LR rates, and to elaborate on its significance in multimodal therapy for retroperitoneal STS.

Patients and methods

Patients

Following approval by the ethics board of the University of Heidelberg (S-649/2012), we performed a retrospective analysis of all patients who underwent resection of primary or recurrent retroperitoneal STS between 10/2001 and 12/2016 at Heidelberg University Hospital, Department of General, Visceral and Transplantation Surgery. Patients with gastrointestinal stromal tumors and those with embryonal, pediatric or gynecological STS were excluded from the analysis.

To achieve tumor-free resection margins, resection of adjacent organs or tissues and multivisceral resections were performed as necessary [23–26]. Indications for IORT, EBRT or chemotherapy were determined on a case-by-case basis according to multidisciplinary tumor board review (see Fig. 1). IORT was applied as an electron beam radiation boost with doses between 10 and 15 Gy. The target volume included areas with close or positive resection margins as judged by the operating surgeon and radiation oncologist. Radiosensitive structures or organs at risk, such as the small intestine or ureter, were spared from radiation exposure by either removing them from the radiation field or lead shielding. Final decisions on IORT were made intra-operatively.

Statistical methods

Outcome parameters assessed in this study were LR-free survival and OS (see Supplement for precise definitions).

Survival and recurrence rates were estimated applying the Kaplan-Meier method. Statistical significance was tested with the log-rank test. Possible predictors used for univariate analysis were resection status, grading according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), tumor histology, tumor presentation, tumor size, radiation therapy (RT), application of IORT, EBRT, cumulative radiation doses (cRD), and patient age and sex (see Supplement Table 1) [2,4,7,11,27].

Multivariate Cox regression analyses including all potential predictors from the univariate Kaplan-Meier analysis (log rank: $p < 0.2$) were performed to identify independent prognostic factors. Patients with incomplete datasets were excluded. For analysis of LR-free survival, patients with residual tumor after surgery (R2) were excluded.

Propensity score-matched analyses were performed in order to analyze the effects of IORT and cRD, independently of patient- and tumor specific confounders. For each patient, a propensity score was generated using a multivariable logistic regression analysis, applying IORT (IORT *vs.* no IORT) or cRD (10–59 Gy vs. ≥60 Gy) as dependent variables. A 1:1 match was performed using the nearest neighbor-matching method. Uni- and multivariate analyses were performed as described above. Similar analyses were performed for the subgroup of patients with LPS.

SPSS (Version 22.0.0.0) was used for all statistical analyses. The level of statistical significance was set to $p \leq 0.05$ (two-tailed).

Results

Clinicopathological features

Between 10/2001 and 12/2016 a total of 1100 patients were

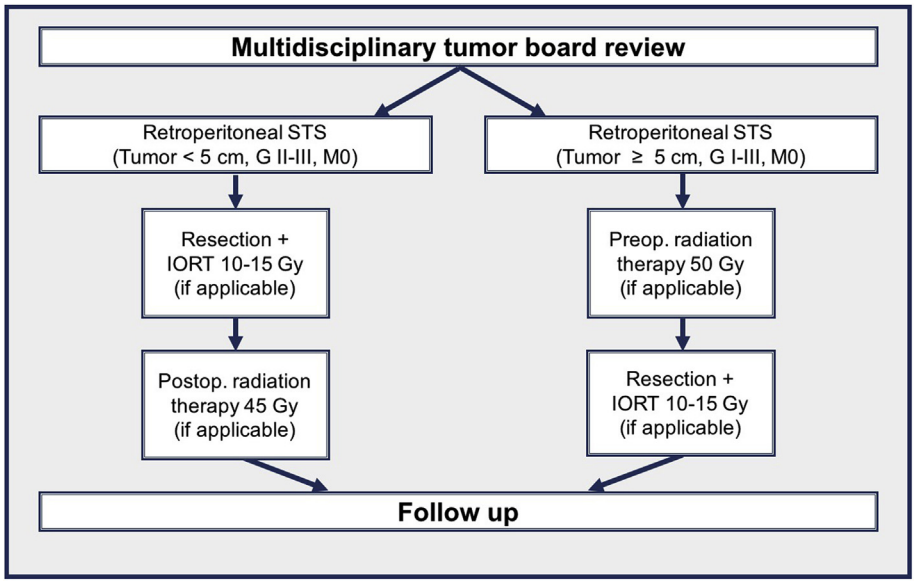


Fig. 1. Diagram depicting therapeutic procedures for retroperitoneal STS as applied in this study.

Table 1
Demographic, clinical and pathological characteristics.

Variable	Value	%/IQR[1]-range
Entire study population		
n	272	
Sex		
Male	147	54.0
Female	125	46.0
Age, yr (mean)	58.0 (13.4)	
Status of disease		
Primary tumor (P)	159	58.5
Local recurrence (LR)	113	41.5
Histology		
WD-Liposarcoma	37	13.6
DD-Liposarcoma	148	54.4
Leiomyosarcoma	39	14.3
Unclassified sarcoma	6	2.2
Other	29	10.7
Intermediate malignancy	13	4.8
Tumor Grade		
1	39	14.3
2	81	29.8
3	83	30.5
does not apply	69	25.4
Resection margins		
R0	90	33.1
R1	157	57.7
R2	25	9.2
Tumor Size, median (cm)	12.0	7.0–22.0
Number of resected organs		
0	40	14.7
1	62	22.8
2	66	24.3
3	46	16.9
4	30	11.0
5	13	4.8
6	7	2.6
7	4	1.5
8	3	1.1
9	1	0.4
Types of resected organs		
Kidney	97	35.7
Spleen	24	8.8
Liver	21	7.7
Left colon and/or rectum	74	27.2
Right colon	54	19.9
Small bowel	37	13.6
Duodenum/head of pancreas	14	5.1
Duodenum or duodeno-jejunal junction	4	1.5
Distal pancreas	26	9.6
Stomach	11	4.0
Psoas muscle	26	9.6
Abdominal wall muscles	11	4.0
Diaphragm	27	9.9
Adnexa and/or uterus	13	4.8
Testis and/or spermatic cord and/or vas deferens	5	1.8
Iliac artery and/or aorta	12	4.4
Iliac vein and/or inferior vena cava	30	11.0
Bladder	11	4.0
Ureter	41	15.1
Prostate	1	0.4
Lung	1	0.4
Bone	4	1.5
Other	68	25
OP time (min.), median	266.5	190.0–360.0
Blood loss (ml), median	600	300–1500
Radiation		
None/Pre/Post/Pre + Post	123/63/48/1	45.2/23.2/17.6/0.4
IORT (total)/IORT + EBRT/IORT alone	119/82/37	43.7/30.1/13.6
Median radiation dose (Gy): cumulative/IORT/Pre/Post	56/12/50/45	(15–62/12-15/50–54/45-50)
Irradiated patients with cumulative dose <60 Gy	86	31.6
Irradiated patients with cumulative dose >60 Gy	63	23.2
Chemotherapy		
Pre/Post/Pre + Post	7/12/3	2.6/4.4/1.1
Intensive Care		
ICU, median	0	0–1
IMC, median	0	0–2
Total, median	1	0–3
Days in inpatient care	14	10–22.8
Complications (Clavien-Dindo)		
1	12	4.4
2	13	4.8
3	35	12.9
4	9	3.3
5	10	3.7
Reintervention/Reoperation/both	15/31/6	5.5/11.4/2.2

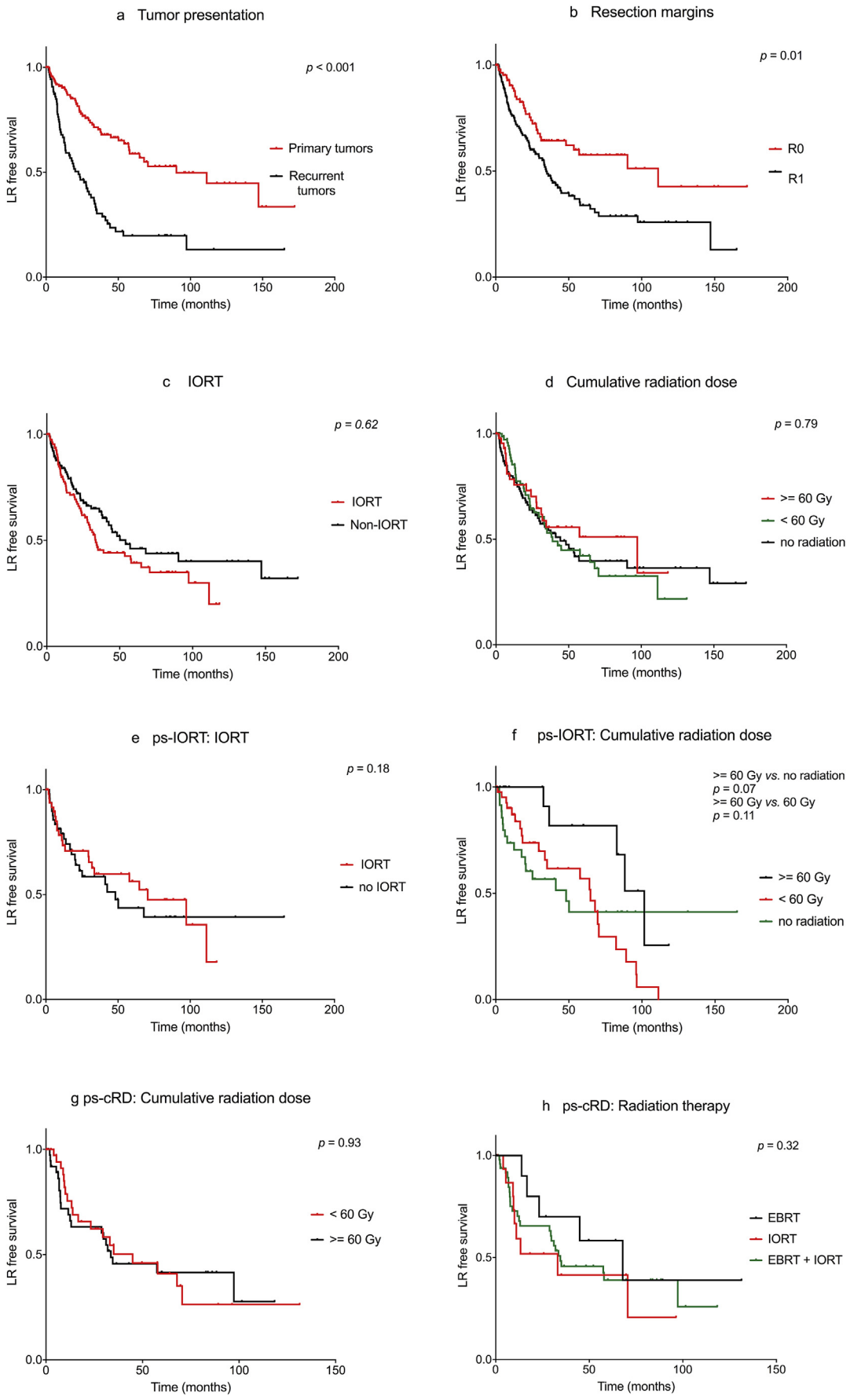
treated for STS at the University of Heidelberg Department of General, Visceral and Transplantation Surgery, and 272 patients who underwent resection of primary or recurrent retroperitoneal STS were considered for this analysis. Median follow-up was 33.6 months (interquartile range (IQR) 11.6–69.3). For surviving patients, median follow-up was 48.3 months (IQR: 21.4–84.5). 159 patients (59%) with primary tumors and 113 patients (41%) with recurrent tumors were included. The most frequent tumors were liposarcoma (185; 68%), followed by leiomyosarcoma (39; 14%). Gross macroscopic complete resection (R0/R1) was achieved in 247 patients (91%). 149 (55%) patients received additional RT and 22 (8%) additional chemotherapy. IORT was applied in 119 cases (44%). IORT was mainly applied because of intraoperatively uncertain resection margins (105; 88%). Other reasons comprised intraoperatively suspected R1- (11; 9%) or R2-resections (3; 3%). Indications for chemotherapy comprised residual tumor mass (8; 35%), presence of distant metastases (4; 17%), or adherence to study protocols in cases of study participation (3; 13%). For details see Table 1.

Local control

Median LR-free survival of all 272 patients was 44.3 ± 8.0 months (95% CI: 28.65–59.93). 3-year LR-free survival was 55% and 5-year LR-free survival was 43%. Prognostic factors associated with LR-free survival in univariate analysis were tumor grade ($p < 0.05$), tumor histology ($p < 0.001$), resection status ($p < 0.05$), and tumor presentation (primary *vs.* recurrent; $p < 0.001$): High tumor grade, dedifferentiated histology, R1 resection, and recurrent disease were associated with increased LR rates. Furthermore, the univariate analysis revealed tendencies towards reduced LR-free survival in male patients ($p = 0.06$) and in patients receiving IORT ($p = 0.15$).

In a multivariate Cox regression analysis, tumor presentation (Fig. 2a), resection status (Fig. 2b) and tumor histology remained independent factors predicting LR (Table 2). Specifically, dedifferentiated LPS and unclassified sarcoma were associated with increased likelihood of LR (Table 2). Already recurrent tumors as well as R1-resection were confirmed as poor prognostic factors concerning LR. In the multivariate model neither application of IORT nor cRD exceeding 60 Gy influenced LR-free survival (Table 2 and Fig. 2c and d).

In the subgroup of patients with primary tumors, both tumor histology ($p < 0.01$) and resection status ($p < 0.05$) remained prognostic factors concerning LR. Moreover, this subgroup analysis revealed a trend towards improved LR-rates in patients receiving preoperative RT as compared to those undergoing postoperative RT


a Tumor presentation
p < 0.001
Primary tumors
Recurrent tumors
b Resection margins
p = 0.01
R0
R1
c IORT
p = 0.62
IORT
Non-IORT
d Cumulative radiation dose
p = 0.79
>= 60 Gy
< 60 Gy
no radiation
e ps-IORT: IORT
p = 0.18
IORT
no IORT
f ps-IORT: Cumulative radiation dose
>= 60 Gy vs. no radiation
p = 0.07
>= 60 Gy vs. 60 Gy
p = 0.11
>= 60 Gy
< 60 Gy
no radiation
g ps-cRD: Cumulative radiation dose
p = 0.93
< 60 Gy
>= 60 Gy
h ps-cRD: Radiation therapy
p = 0.32
EBRT
IORT
EBRT + IORT
LR free survival
Time (months)

or no RT at all, albeit these findings did not reach significance (postoperative *vs.* preoperative RT: HR 2.36, $p = 0.09$; no RT *vs.* preoperative: HR 2.31, $p = 0.07$) (Table 2).

Propensity score matched analyses to assess effects of IORT and cRD

Using propensity scores, 52 patients who received IORT were matched with 52 comparable patients without IORT (Table 3). According to Cox regression analysis, only the resection status represented an independent prognostic factor in this subgroup (ps-IORT), with R1-margins being associated with reduced LR-free survival (HR 3.79, $p < 0.001$; Table 2). Notably, application of IORT did not have a statistically significant impact on LR-free survival ($p = 0.18$; Table 2; Fig. 2e). However, there was a trend towards higher LR rates in patients receiving no RT compared to those receiving cumulative radiation doses exceeding 60 Gy (HR: 6.62, $p = 0.07$; Table 2; Fig. 2f).

In most cases, cRD exceeding 60 Gy are only achievable by combining EBRT with IORT. To better assess the effects of cRD exceeding 60 Gy, we performed a second propensity score matched analysis, including 40 patients who received EBRT in combination with IORT (thus resulting in cRD $\geq$ 60 Gy), matched to 40 patients who received RT with cRD lower than 60 Gy (Table 3). In this subgroup (ps-cRD), multivariate analysis revealed only tumor presentation as a prognostic factor, with increased LR rates in patients with recurrent tumors (HR 3.61, $p < 0.001$; Table 2). Moreover, we observed a trend towards reduced LR-free survival in R1 resected tumors (HR 2.02, $p = 0.07$). Application of IORT ($p = 0.32$) and cRD ($p = 0.93$) did not reach statistical significance in the univariate analysis concerning LR-free survival in this patient subgroup ($p = 0.32$; Fig. 2g and h) and were therefore not considered in the multivariate model.

Subgroup analyses for patients with liposarcoma

Since the STRASS trial [14] revealed that patients with retroperitoneal LPS seem to benefit from preoperative RT, we performed additional analyses considering only patients with retroperitoneal LPS (WD-LPS and DD-LPS; n = 164). In this subgroup, tumor histology ($p < 0.01$) and tumor presentation ($p < 0.01$) were prognostic factors concerning LR. However, R0 resection, IORT or high cRD were not associated with improved LR rates (Table 2).

For primary LPS, tumor histology ($p < 0.001$), tumor grade ($p < 0.01$) and resection status ($p = 0.10$) as well as sex ($p = 0.09$) were significant or close to significant prognostic factors in the univariate analysis. None of these factors remained as an independent prognostic factor for LR in the multivariate model.

Above-mentioned propensity-score matched analyses were likewise extended to the subgroup of LPS-patients (ps-IORT: n = 70, ps-cRD: n = 52), revealing that neither IORT nor cRD exceeding 60 Gy were prognostic factors concerning LR.

Overall survival

Median OS in the entire cohort of retroperitoneal STS was 78.13 ± 15.80 months (95% CI: 47.16–109.09). 3-year OS was 68%, and 5-year OS was 56%.

In multivariate analysis, only R2 resection ($p = 0.01$), histopathological tumor grade ($p < 0.05$) and older age ($p < 0.05$) were confirmed as prognostic factors concerning impaired OS (Table 4). Application of IORT ($p = 0.21$) and sequence of RT (neoadjuvant versus adjuvant versus no radiation, $p = 0.49$) were not associated with improved OS rates in univariate analysis, and were therefore not included in the multivariate model.

Morbidity and mortality

52 of 272 patients (19%) developed complications necessitating invasive therapeutic procedures, and 10 patients (3.7%) died during hospitalization. 30-day mortality was 3%.

In the subgroup matched by IORT, 11 (21%) of patients without and 12 (23%) patients with IORT underwent an invasive therapeutic procedure due to postsurgical complications, and in the non-IORT group 2 patients (2%) died. 30-day mortality was 3.8% in the non-IORT group and 1.9% in the IORT group.

Discussion

To our knowledge, this study comprises one of the largest patient populations treated with IORT for retroperitoneal STS described in the literature. Moreover, it is the first analysis investigating the effects of IORT and cRD applying propensity score matched control groups.

There is evidence that cRD exceeding 60 Gy are necessary to positively influence LR rates in extremity STS [28]. Importantly, in retroperitoneal STS, doses exceeding 55 Gy are unlikely to be reached by EBRT alone due to potential toxicity towards adjacent organs [20]. Therefore, cRD exceeding 60 Gy were only achieved in patients subjected to full-dose EBRT in combination with IORT, whereas patients who received less than 45 Gy were treated with IORT alone and/or reduced EBRT. However, our present findings did not confirm any beneficial effects of IORT or cRD exceeding 60 Gy concerning LR and OS.

Previous studies have reported decreased LR rates after IORT in combination with EBRT, however, the number of patients treated with IORT was mostly limited, and these effects could not be confirmed in multivariate analyses [12,18,19]. There are, likewise, several studies describing favorable local control in larger patient samples treated with IORT and EBRT (5-year local control 50–70%), however, with limitations related to included control groups [6,9,20,29–31]. Consistent with our present findings, results reported by Ballo et al. revealed no positive effects of EBRT in combination with IORT on LR rates in univariate analysis, nor were LR rates improved by cRD exceeding 50 Gy in a sample of 81 patients of whom 18 were treated with IORT [21]. In a phase I-II study by the Italian Sarcoma Group, which evaluated the feasibility and safety of preoperative chemo-radiation, 14 out of 83 patients additionally received IORT without statistically significant effects concerning progression-free and overall survival [22]. In our present study, beneficial effects of IORT or high cRD were neither detectable in the entire patient population, nor in propensity score matched subgroups designed to minimize selection bias.

Fig. 2. Kaplan-Meier curves, indicating local recurrence free survival.
a) Impact of tumor presentation in entire study population (estimated 5-year LR-free survival: primary: 59%, recurrent: 20%).
b) Impact of resection margins in entire study population (estimated 5-year LR-free survival: R0: 58%, R1: 34%).
c) Impact of IORT in entire study population (estimated 5-year LR-free survival: IORT: 39%, no IORT: 46%).
d) Impact of cumulative radiation dose in entire study population (estimated 5-year LR-free survival: $\geq$ 60 Gy: 51%, <60 Gy: 42%, no radiation: 40%).
e) Impact of IORT in subgroup ps-IORT (estimated 5-year LR-free survival: IORT: 56%, no IORT: 45%.
f) Impact of cumulative radiation dose in subgroup ps-IORT (estimated-5-year LR free survival: $\geq$ 60 Gy: 72%, <60 Gy: 59%, no radiation: 34%).
g) Impact of cumulative radiation dose in subgroup ps-cRD (estimated 5-year LR-free survival: $\geq$ 60 Gy: 42%, <60 Gy: 41%).
h) Impact of radiation sequence in subgroup ps-cRD (estimated 5-year LR-free survival: EBRT: 58%, IORT: 42%, EBRT + IORT: 39%).

Table 2
Local recurrence according to multivariate Cox model in all patients (top), in primary tumors (upper middle), and in propensity score matched subgroups for IORT (ps-IORT; lower middle) and for cRD (ps-IORT; bottom).

All patients		Hazard Ratio (HR)	95% confidence interval	*p*-value
Sex	female *vs.* male	0.91	0.58–1.44	0.688
Tumor presentation	Locally recurrent *vs.* primary	2.59	1.61–4.18	**< 0.001*****
Tumor grade				0.093
	G2 *vs.* G1	0.64	0.29–1.41	0.266
	G3 *vs.* G1	1.10	0.49–2.45	0.823
Resection status	R1 *vs.* R0	2.03	1.16–3.55	**0.014***
Histology				**0.002****
	WD-LPS *vs.* DD-LPS	0.29	0.11–0.78	**0.014***
	LMS *vs.* DD-LPS	0.52	0.21–1.31	0.165
	Unclassified *vs.* DD-LPS	7.48	1.51–37.04	**0.014***
	Other *vs.* DD-LPS	0.72	0.33–1.57	0.404
	Intermediate malignancy *vs.* DD-LPS	2.89	0.37–22.70	0.316
IORT	IORT *vs.* no IORT	0.89	0.55–1.42	0.613
Primary tumors		**Hazard Ratio (HR)**	**95% confidence interval**	***p*-value**
Sex	female *vs.* male	0.60	0.30–1.23	0.164
EBRT				0.149
	No radiation *vs.* preoperative	2.31	0.94–5.67	***0.069***
	Postoperative vs. preoperative	2.36	0.87–6.39	***0.092***
Tumor grade				0.195
	G2 *vs.* G1	0.94	0.15–5.75	0.945
	G3 *vs.* G1	1.82	0.32–10.17	0.494
Resection status	R1 *vs.* R0	3.29	1.26–8.07	**0.014***
Histology				**0.003****
	WD-LPS *vs.* DD-LPS	0.16	0.02–1.50	0.108
	LMS *vs.* DD-LPS	0.54	0.20–1.46	0.221
	Unclassified *vs.* DD-LPS	10.27	1.76–59.95	**0.010***
	Other *vs.* DD-LPS	0.42	0.14–1.28	0.126
ps-IORT		**Hazard Ratio (HR)**	**95% confidence interval**	***p*-value**
Resection status	R1 *vs.* R0	3.79	1.68–8.51	**0.001****
Tumor grade				0.068
	G2 *vs.* G1	0.52	0.18–1.50	0.227
	G3 *vs.* G1	1.28	0.40–4.14	0.680
Tumor presentation	Locally recurrent *vs.* primary	1.85	0.95–3.62	***0.072***
Histology				0.159
	WD-LPS *vs.* DD-LPS	0.27	0.07–1.02	***0.053***
	LMS *vs.* DD-LPS	0.64	0.20–2.00	0.483
	Unclassified *vs.* DD-LPS	4.48	0.51–39.69	0.178
	Other *vs.* DD-LPS	0.58	0.21–1.64	0.303
IORT	IORT *vs.* no IORT	0.48	0.16–1.39	0.176
EBRT				0.440
	Preoperative EBRT *vs.* no EBRT	1.31	0.36–4.79	0.680
	Postoperative EBRT *vs.* no EBRT	1.96	0.64–6.01	0.239
Cumulative Radiation dose				0.187
	No radiation *vs.* > 60 Gy	6.62	0.83–52.89	***0.074***
	<60 Gy *vs.* > 60 Gy	2.51	0.81–7.78	0.111
ps-cRD		**Hazard Ratio (HR)**	**95% confidence interval**	***p*-value**
Tumor presentation	Locally recurrent *vs.* primary	3.61	0.95–4.29	**< 0.001*****
EBRT				0.676
	IORT alone *vs.* preoperative	1.45	0.63–3.39	0.387
	Postoperative vs. preoperative	1.23	0.58–2.60	0.582
Resection status	R1 *vs.* R0	2.02	0.95–4.29	**0.067**
LPS		**Hazard Ratio (HR)**	**95% confidence interval**	***p*-value**
Tumor presentation	Locally recurrent *vs.* primary	2.32	1.32–4.09	**0.004****
Resection status	R1 *vs.* R0	1.76	0.90–3.46	***0.098***
Tumor grade				0.248
	G2 *vs.* G1	0.46	0.19–1.19	0.111
	G3 *vs.* G1	0.62	0.24–1.59	0.317
IORT	IORT *vs.* no IORT	1.19	0.70–2.04	0.517
Histology	WD-LPS *vs.* DD-LPS	0.19	0.06–0.57	**0.003****
Tumorsize				0.510
	<5 cm vs. > 20 cm		0.48–3.19	0.652
	5–10 cm vs. > 20 cm		0.47–1.88	0.848
	<10–20 cm vs. 20 cm		0.78–2.86	0.226

The efficacy of IORT should be evaluated in relation to additionally performed EBRT with regard to cRD. Surgery is the mainstay of therapy, however, in cases where anatomical tumor extension precludes complete surgical clearance, the benefit of additional RT seemed to be established. Several studies reported beneficial effects of RT on LR and even OS in large retrospective cohort samples [7,10,11,13,32,33]. Most centres favored preoperative EBRT over postoperative EBRT due to better manageable regional radiation fields, reduced toxicity to adjacent organs and the chance to reduce tumor volume [12,16,20,34–36]. In this

Table 3
Demographic, clinical and pathological characteristics in propensity score matched subgroups.

Variable	Value (%/IQR[a])	Value (%/IQR[a])	*p*-value	Value (%/IQR[a])	Value (%/IQR[a])	*p*-value
	Non-IORT	**IORT**		**10–59 Gy**	**≥ 60 Gy**	
n	**52**	**52**		**40**	**40**	
Sex			1.00[b]			**0.039**[b]
Male	26 (50.0)	26 (50.0)		19 (47.5)	22 (55.0)	
Female	26 (50.0)	26 (50.0)		21 (52.5)	18 (45.0)	
Age, yr (mean)	57.1 (13.5)	59.1 (11.4)	0.382[c]	59.4 (12.8)	57.1 (9.5)	0.333[c]
Status of disease			0.537[b]			0.248[b]
Primary tumor (P)	33 (63.5)	36 (69.2)		28 (70.0)	22 (55.0)	
Local recurrence (LR)	19 (36.5)	16 (30.8)		12 (30.0)	18 (45.0)	
FU (months)	32.1 (12.5–69.6)	38.5 (10.5–83.1)		40.2 (12.6–80.3)	52.2 (13.3–82.8)	
FU if alive (months)	36.4 (24.4–69.55)	60.0 (23.9–96.4)		58.4 (11.15–119.01)	65.3 (34.9–88.9)	
Histology			0.640[d]			0.634[d]
WD-Liposarcoma	7 (13.5)	9 (17.3)		5 (12.5)	5 (12.5)	
DD-Liposarcoma	28 (53.8)	25 (48.1)		20 (50.0)	22 (55.0)	
Leiomyosarcoma	12 (23.1)	9 (17.3)		7 (17.5)	8 (20.0)	
Unclassified sarcoma	1 (1.9)	0		0	0	
Other	4 (7.7)	9 (17.3)		8 (20.0)	4 (10.0)	
Intermediate malignancy	0	0		0	1 (2.5)	
Tumor grade			0.382[c]			0.820[c]
1	7 (13.5)	12 (23.1)		6 (15.0)	8 (20.0)	
2	22 (42.3)	22 (42.3)		15 (37.5)	15 (37.5)	
3	23 (44.2)	18 (34.6)		19 (47.5)	17 (42.5)	
Resection margins			0.837[b]			1.000[b]
R0	19 (36.5)	57 (32.7)		12 (30.0)	13 (32.5)	
R1	33 (63.5)	35 (67.3)		28 (70.0)	27 (67.5)	
Tumor size, median (cm)	11.5 (7.5–25.75)	12.87 (7.0–21.87)	0.780[d]	12.0 (7.0–20.8)	10.0 (5.6–18.8)	0.290[d]
OP time (min.), median	242 (180–360)	300 (227–385)	0.060[c]	309 (254–439)	323 (241–361)	0.654[c]
Blood loss (ml), median	550 (300–1475)	600 (362.5–1500)	0.747[c]	800 (400–1550)	900 (400–1425)	0.995[c]
Number of resected organs (median)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.918[c]	2 (1.0–3.8)	2.5 (2.0–4.0)	0.616[c]
Radiation			**<0.001**[d]			**<0.001**[d]
None/Pre/Post	36 (69.2)/11 (21.2)/5 (9.6)	0/15 (28.8)/21 (640.4)		0/11 (27.5)/11 (27.5)	0/24 (60.0)/16 (40.0)	
IORT/IORT + EBRT/IORT alone	–	52 (100)/36 (69.2)/16 (30.8)		29 (72.5)/11 (27.5)/11 (27.5)	40 (100)/40 (100)/0	
Median radiation dose (Gy): cumulative/IORT/Pre/Post	50 (49.25–54.75)	58.50 (15.00-62-00)		47.50 (15.00–54.00)	62.00 (60.25–66.00)	
Irradiated patients with cumulative dose <60 Gy	14 (26.9)	26 (50)		40 (100)	0	
Irradiated patients with cumulative dose >60 Gy	2 (3.8)	26 (50)		0	40 (100)	
Chemotherapy			0.887[d]			0.256[d]
Pre/Post/Pre + Post	2 (3.8)/4 (7.7)/0	2 (3.8)/1 (1.9)/1 (1.9)		3 (7.5)/1 (2.5)/0	0/0/1 (2.5)	
Intensive Care			0.476[c]			0.550[d]
ICU, median	0 (0–1)	0 (0–1)		0 (0–1)	0 (0–1)	
IMC, median	0 (0–2)	0 (0–2)		0 (0–2)	0 (0–1)	
Total, median	1 (0–3)	0.5 (0–2.25)		1 (0–3)	1 (0–2)	
Days in inpatient care	15 (10–24.8)	10 (10–24.8)		15 (10.3–27.0)	12 (10–22.5)	
Complications			0.973[d]			0.348[d]
Reintervention/Reoperation/both	0/9 (17.3)/2 (3.8)	5 (9.6)/7 (13.5)/0		1 (2.5)/9 (22.5)/0	4 (10.0)/3 (7.5)/0	
Exitus	2 (1.7)	0		2 (5.0)	0	

[a] *IQR* interquartile range.
[b] Fisher exact test.
[c] Mann-Whitney-U test.
[d] Chi-squared test.

Table 4
Overall survival according to multivariate Cox model in all patients.

		Hazard Ratio (HR)	**95% confidence interval**	***p*-value**
Age	>50 years *vs.* < 50 years	1.98	1.04–3.79	**0.038***
Tumor presentation	Locally recurrent *vs.* Primary	1.09	0.67–1.75	0.706
Tumor grade				**0.038***
	G2 *vs.* G1	2.39	0.85–6.73	0.099
	G3 *vs.* G1	3.57	1.24–10.26	0.018
Resection status				**0.010****
	R0 *vs.* R2	0.38	0.18–0.83	**0.015***
	R1 *vs.* R2	0.35	0.18–0.69	**0.003****
Histology				0.502
	WD-LPS *vs.* DD-LPS	0.84	0.34–2.08	0.708
	LMS *vs.* DD-LPS	1.20	0.60–2.38	0.603
	Unclassified *vs.* DD-LPS	1.72	0.22–13.39	0.606
	Other *vs.* DD-LPS	0.53	0.21–1.37	0.192
	Intermediate malignancy *vs.* DD-LPS	3.96	0.48–32.67	0.201

context, recently presented results from the randomized STRASS trial (EORTC 62092/STRASS), which compared preoperative RT (50.4 Gy) followed by surgery versus surgery alone in retroperitoneal STS, provided important new insights into the role of RT in STS therapy. The study failed to demonstrate beneficial effects of preoperative RT for retroperitoneal STS. However, in the subgroup of LPS, 3-year abdominal recurrence-free survival was significantly improved in patients receiving preoperative RT (71.6% vs. 60.4%), whereas in leiomyosarcoma (LMS) and high grade sarcoma preoperative RT was not associated with improved LR rates [14].

It appears convincing that local therapies such as RT or IORT are more effective in LPS than LMS, since LMS is frequently associated with distant rather than local failure [8,37,38]. In our collective, however, IORT or cRD exceeding 60 Gy were associated with improved LR-free survival neither in the entire cohort of LPS patients, nor in primary LPS, nor in propensity-score matched groups. In synopsis, it can thus be concluded that application of IORT does not seem to influence oncological outcome. Since the subgroup of LPS comprises heterogenous tumors, it would be interesting to further analyze the effect of RT and IORT depending on histologic subtype or grade. However, such analyses would mandate large and uniform cohorts of patients and patient subgroups, which is difficult to achieve given the heterogeneous STS treatment landscape and rareness of the disease. Of note, in the entire cohort and all subgroup analyses recurrent disease was associated with decreased LR-free survival. This emphasizes the notion that the initial therapeutic attempt is most crucial concerning oncological outcome. In this context, further follow-up and studies are needed to evaluate the value of preoperative RT and IORT especially in the subgroup of retroperitoneal LPS. Still, to finally elucidate the significance of IORT prospective randomized trials would be necessary.

Interestingly, microscopic complete resection (R0) was associated with a decreased likelihood of LR rates compared to microscopic incomplete resection (R1). Gross macroscopic incomplete resection (R2) is a well-established prognostic factor for poor LR and OS rates [2,4,7,8,39]. The influence on R1-margins, however, is controversial, since most authors differentiate between gross macroscopic complete and incomplete resetion only [2,4,7,11,27,40]. Consistent with our findings, Tan et al. reported increased LR rates after R1-resection in a large retrospective analysis of 675 patients [8]. However, considering the size, large surface area, and anatomic relations of retroperitoneal STS it is difficult to reliably assess the microscopic margins of resected tumors [41].

Major limitations of our study reside in its retrospective, single-centered nature and in moderate follow-up times. Moreover, relatively small patient subgroups, which are due to the overall rareness and heterogeneity of the disease, call for careful interpretation of significant findings. Importantly, the use of a propensity score matched analysis does reduce, but not entirely solve the problem of selection bias in this retrospective analysis. For instance, an initial decision to perform resection with or without IORT in standby was made preoperatively, and reasons underlying this decision cannot be fully covered with the parameters of a propensity score matched analysis. Indeed, the risk of LR may have been preoperatively judged as higher in the IORT-standby group compared to patients who underwent resection without IORT in standby. These shortcomings can, obviously, only be resolved with a prospective, randomized trial. However, until such data become available, our present retrospective analysis of a rather large patient collective, which does allow for decent propensity score matching, extends insights from previous retrospective analyses. Notably, our results concerning predictors of OS (grading, macroscopically incomplete resection) and of local recurrence (tumor histology, tumor presentation) are consistent with results from other retrospective patient cohorts [7,8,11,34,40], indicating that our sample of patients is indeed valid and representative of the disease.

Conclusion

We analyzed the effects of IORT and high cRD on LR-free survival in patients with primary or recurrent retroperitoneal STS. Propensity score-matched analyses were performed to control for possible confounders. While surgery remains the central component of curative treatment, the benefit of additional IORT to achieve increased radiation doses in regions of close or positive resection margins remains questionable. Therefore, randomized trials are needed to provide further insight into this problem.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.12.014.

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Original Article

Histology-driven tailoring of surgical approaches in retroperitoneal soft tissue sarcoma: retrospective cohort study

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Abstract

Background: Histology-driven tailoring of surgical approaches for retroperitoneal soft tissue sarcoma is currently under debate. Compelling evidence assessing the role of histology-dependent extent of resection is lacking. The aim of this study was to assess outcomes of patients with primary retroperitoneal liposarcoma (LPS) or leiomyosarcoma (LMS) according to whether comprehensive (formerly 'compartmental') resection (CR) was performed.

Methods: A retrospective study was conducted on data from patients undergoing surgical resection for LPS and LMS at Heidelberg University Hospital (2002–2019). Parameters were compared between groups with and without CR, with subgroup analyses for grading (LPS). Kaplan–Meier and Cox regression analyses were used to identify predictors of disease-specific survival (DSS), local recurrence-free survival, and distant metastasis-free survival.

Results: In total, 119 patients with primary LPS and 46 patients with primary LMS were identified. DSS was improved in patients with LPS with CR ($P = 0.049$), and both DSS ($P = 0.040$) and distant metastasis-free survival ($P = 0.041$) were improved in the subgroup of patients with primary G3 LPS. In contrast, CR in patients with LMS was not associated with improved DSS, local recurrence-free survival, or distant metastasis-free survival. CR was associated with more severe postoperative complications ($P = 0.021$) and a longer hospital stay ($P = 0.013$) in patients with LPS, longer operation times ($P < 0.010$) in both patients with LPS and LMS, and increased blood loss ($P = 0.008$) in patients with LMS.

Conclusion: CR is associated with improved DSS in patients with primary LPS, which is not the case in patients with primary LMS. Given the association between CR and increased perioperative morbidity, surgical strategies for retroperitoneal soft tissue sarcoma should be individualized according to the underlying histology.

Introduction

Retroperitoneal soft tissue sarcomas (RPS) comprise a histologically heterogeneous group of malignant tumours that primarily affect patients around their sixth decade of life, with an annual incidence rate of 0.76 cases per 100 000 individuals[1–3]. Retroperitoneal liposarcoma (LPS) is the most frequent (45–55%), comprising well differentiated LPS (WDLPS, G1; 15–24%) and dedifferentiated LPS (DDLPS, G2/3; 16–21%), followed by retroperitoneal leiomyosarcoma (LMS; 21–26%)[2,4]. RPS with different histology exhibit distinct clinical phenotypes, creating specific clinical challenges that account for tumour-related mortality[5]. Local recurrence frequently occurs in both WDLPS and DDLPS, whereas additional metastatic spread is often seen in G3 DDLPS, which worsens prognosis[5,6]. In LMS, patient prognosis is predominantly determined by distant metastases, with local recurrence being less frequent than in LPS[5,6].

The mainstay of treatment for RPS is gross macroscopic tumour resection including adjacent organs[7–12]. Modifying surgical approaches according to tumour type, grading, and clinical features (tumour biology) is increasingly being recommended[6,13]. Retroperitoneal WDLPS and G2 DDLPS predominantly exhibit a tendency for local recurrence, with WDLPS posing virtually no risk of metastatic spread and G2 DDLPS presenting only a low risk of distant metastases[6,13]. Differentiating WDLPS from normal retroperitoneal adipose tissue can be challenging, whereas G2 DDLPS are generally more readily distinguishable[6,13]. However, due to intratumour heterogeneity, marginal G1 components in G2 and G3 DDLPS are also difficult to distinguish from normal retroperitoneal adipose tissue. Therefore, comprehensive (formerly 'compartmental') resection (CR) has been proposed as an extended surgical strategy to enhance the likelihood of achieving negative surgical margins[6,13]. CR was originally defined as the systematic resection of uninvolved contiguous organs surrounding the tumour to ensure free surgical margins, and typically comprises *en bloc* resection of the hemicolon, kidney, and part of the psoas, as well as additional adjacent organs as necessary[14]. Although metastatic spread is more likely to

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determine oncological outcomes in retroperitoneal G3 DDLPS than in WDLPS or G2 DDLPS, local recurrence remains a significant concern, with a 5-year local recurrence rate of 33% and a distant metastasis rate of 44%[15]. Therefore, CR is still considered appropriate for these tumours, because local recurrence remains a predominant form of disease recurrence, necessitating aggressive surgical strategies to maximize local control[13]. In contrast, in LMS, tumour margins tend to be clearly distinguishable from surrounding tissues, which is why resection of adherent structures while leaving the remainder of the compartment intact has been discussed as an appropriate surgical treatment[6,13]. However, current recommendations concerning histology-driven surgical approaches rely on a few retrospective studies, which did not systematically assess the role of CR as an independent prognostic factor for oncological outcome depending on tumour histology[14,16,17].

The primary aim of the present study was to investigate the impact of CR based on tumour histology, as well as tumour biology and clinical presentation. This approach aims to provide a more comprehensive understanding of the significance of CR in the treatment of RPS to potentially refine surgical strategies to improve patient outcomes.

Methods

Following approval by the Ethics Board of the University of Heidelberg (S-649/2012), a retrospective analysis was performed of all patients who underwent resection of primary retroperitoneal LPS and LMS between January 2002 and December 2019 at the Department of General, Visceral, and Transplantation Surgery, Heidelberg University Hospital. Patients were analysed based on clinicopathological parameters and clinical outcomes with a particular emphasis on the conduction of CR.

The variables assessed were age at diagnosis, sex, grading according to Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), tumour size, number of organs resected, conduction of CR, resection status (R0/R1 or R2), postoperative complications (as assessed by Clavien–Dindo classification and the comprehensive complication index [CCI][18]), intraoperative blood loss, requirement for blood transfusions, operation time, duration of hospital stay, reoperations, (re-)interventions (defined as non-surgical, but invasive, procedures, such as computed tomography-guided drainage placement), 30-day and 90-day mortality, the application of radiotherapy or systemic therapy, disease-specific survival (DSS), local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), the crude cumulative incidence of local recurrences, and the crude cumulative incidence of distant metastases.

Microscopic surgical margins were assessed in a reference centre by senior pathologists experienced in retroperitoneal sarcomas on conventional haematoxylin- and eosin-stained slides; in case of doubt, additional analyses were performed, including chromogen *in situ* hybridization for the *MDM2* gene and/or immunohistochemical staining for MDM2 and/or cyclin dependent kinase 4 (CDK4). With regard to tumour grading, the term 'not applicable' was used for patients who had undergone neoadjuvant treatment because, following such treatment, the pathology report does not generally include tumour grading, which is determined by the examining pathologist and the particular characteristics of the tumour.

DSS was defined as the interval between the date of surgery and the date of death due to RPS. LRFS and DMFS were defined as the interval between the date of surgery and the date of occurrence of a local recurrence or distant metastasis, respectively. Local recurrence was defined as tumour recurrence in the retroperitoneum or abdomen, excluding liver metastases. Liver metastases and all other metastases were defined as distant metastases. For surviving patients, follow-up was censored at the date of last disease assessment.

CR was defined as ipsilateral hemicolectomy, nephrectomy, and resection of the fascia or psoas muscle as a minimum, sometimes with additional adrenal resection, splenectomy, (partial) pancreatectomy, and resection of the inferior vena cava, iliac vessels, and other organs, if involved. The concept of CR was gradually implemented upon increasing evidence in the field, enabling retrospective investigation of a CR *versus* no CR group (*Table S1*). In the remaining 25–30% of patients who did not undergo CR in recent years, the extent of the resections was less due to individual patient factors, as determined at the discretion of the operating surgeon.

To identify significant differences between categorical and metric variables according to CR, χ^2 and Mann–Whitney *U* tests were performed. Kaplan–Meier analyses with log-rank statistics were used for survival analyses. DSS, LRFS, and DMFS are presented as the median with 95% confidence interval (c.i.) after 5 years of follow-up, along with 3-year and 5-year survival rates. For analysis of the crude cumulative incidence of local recurrences and distant metastases, death was treated as a competing event and the Fine–Gray test was used to test for statistical significance[19].

Multivariable Cox regression analyses were performed to identify independent prognostic factors for DSS, LRFS, and DMFS. Patient age was modelled as a continuous variable, all other variables were modelled as categorical variables using dummy variables. In respect of number of events, backwards step-wise variable selection was used[20]. For analyses of LRFS, patients with macroscopically incomplete resection (R2) were excluded. Analyses were performed for primary LPS and primary LMS separately. Due to different LPS recurrence patterns depending on tumour grade, subgroup analyses were performed for primary G2 LPS and G3 LPS. There was an insufficient number of patients with primary G1 LPS to enable subgroup analysis.

SPSS (Version 29.0.2.0) was used for all statistical analyses. The level of statistical significance was set to $P < 0.05$ (two-tailed).

Results

Patient characteristics and clinicopathological features

In total, 370 patients with RPS were operated at the University of Heidelberg between 2002 and 2019. Of these patients, 290 presented with LPS or LMS; 165 exhibited primary disease (119 primary LPS and 46 primary LMS) and were included in the present study.

The cohort comprises 119 patients with primary LPS (72.1%; 26 WDLPS (21.9%), 51 G2 DDLPS (42.9%), 29 G3 DDLPS (24.4%), and 13 without grading after neoadjuvant therapy (10.9%)) and 46 patients with LMS (27.9%; 18 G2 LMS (39.1%), 19 G3 LMS (41.3%), and 9 without grading after neoadjuvant therapy (19.6%)). The general clinicopathological characteristics of patients with primary LPS and LMS stratified according to the conduction of CR are presented in *Table 1*.

Of the patients with primary LPS, those who underwent CR were significantly older at diagnosis ($P = 0.039$) and had a greater median number of resected organs ($P < 0.001$) as well as a

Table 1 Clinical and histological characteristics of the primary LPS and LMS cohorts according to whether CR was performed

	LPS			LMS		
	No CR	CR	P*	No CR	CR	P*
No. of patients	54	65		24	22	
Age at diagnosis (years), median (i.q.r.)	55.0 (50.5–66.0)	61.0 (53.5–72.0)	0.039	57.0 (51.5–68.8)	56.5 (49.3–68.3)	0.560
Sex			0.421†			0.553†
Male	31 (57.4%)	42 (64.6%)		9 (37.5%)	11 (50.0%)	
Female	23 (42.6%)	23 (35.4%)		15 (62.5%)	11 (50.0%)	
Tumour grading			0.257†			0.045†
G1	13 (24.1%)	13 (20.0%)				
G2	19 (35.2%)	32 (49.2%)		12 (50.0%)	6 (27.3%)	
G3	16 (29.6%)	13 (20.0%)		10 (41.7%)	9 (40.9%)	
Not applicable	6 (11.1%)	7 (10.8%)		2 (8.3%)	7 (31.8%)	
Tumour size (cm), median (i.q.r.)	21.8 (11.0–31.4)	20.0 (13.0–27.5)	0.519	9.5 (6.5–13.3)	11.5 (6.4–14.5)	0.488
No. of resected organs, median (i.q.r.)	2.0 (1.0–3.0)	4.0 (3.0–5.0)	<0.001†	2.0 (1.0–3.0)	3.5 (3.0–4.0)	<0.001†
Resection status			0.019†			0.509†
R0/R1	48 (88.9%)	65 (100.0%)		22 (91.7%)	22 (100.0%)	
R2	6 (11.1%)	0 (0.0%)		2 (8.3%)	0 (0.0%)	
Systemic therapy			0.112†			0.927†
No	50 (92.6%)	64 (98.5%)		22 (91.7%)	20 (90.9%)	
Before surgery	0 (0.0%)	0 (0.0%)		1 (4.2%)	1 (4.5%)	
After surgery	1 (1.9%)	1 (1.5%)		1 (4.2%)	1 (4.5%)	
Before and after surgery	3 (5.6%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Radiation therapy			0.113†			0.322†
No	36 (66.7%)	34 (52.3%)		15 (62.5%)	5 (22.7%)	
Before surgery	7 (13.0%)	24 (36.9%)		7 (29.2%)	13 (59.1%)	
After surgery	11 (20.4%)	6 (9.2%)		2 (8.3%)	4 (18.2%)	
Before and after surgery	0 (0.0%)	1 (1.5%)		0 (0.0%)	0 (0.0%)	
Complications (Clavien–Dindo ≥III)	7 (13.0%)	20 (30.8%)	0.021†	6 (25.0%)	6 (27.3%)	0.861†
CCI score, median (i.q.r.)	26.2 (8.7–37.2)	29.6 (12.2–37.1)	0.466	26.2 (8.6–100.0)	42.6 (21.8–55.2)	0.971
(Re-)intervention	2 (3.7%)	10 (15.4%)	0.035†	2 (8.3%)	3 (13.6%)	0.564†
Reoperation	5 (9.3%)	9 (13.8%)	0.439†	2 (8.3%)	5 (22.7%)	0.175†
(Re-)intervention and Reoperation	0 (0.0%)	1 (1.5%)	0.360†	0 (0.0%)	0 (0.0%)	
30-day mortality	1 (1.9%)	3 (4.6%)	0.405†	4 (16.7%)	0 (0.0%)	0.045†
90-day mortality	3 (5.%)	3 (4.6%)	0.815†	4 (16.7%)	1 (4.5%)	0.187†
Operation time (min), median (i.q.r.)	225.0 (133.8–225)	270.0 (205.0–349.0)	0.006	225.0 (167.5–309.5)	352.5 (282.0–514.3)	0.002
Blood loss (ml), median (i.q.r.)	500.0 (300.0–500.0)	800.0 (325.0–1500.0)	0.149	700.0 (300.0–1650.0)	1475.0 (925.0–2700.0)	0.008
Transfusion	15 (27.8%)	19 (29.2%)	0.861†	10 (41.7%)	15 (68.2%)	0.085†
Length of hospital stay (days), median (i.q.r.)	10.0 (8.75–16.25)	21.8 (11.0–31.4)	0.013	15.0 (10.0–19.5)	15.50 (12.0–26.5)	0.197†
Follow-up duration (months), median (i.q.r.)	70.5 (21.7–121.7)	49.2 (24.7–92.5)	0.256	34.4 (12.9–89.9)	26.8 (16.2–63.3)	0.838
Follow-up duration if alive (months), median (i.q.r.)	87.3 (69.9–144.0)	63.6 (35.8–99.1)	0.005	97.7 (32.6–127.1)	52.2 (23.7–68.2)	0.142

(Re-)intervention refers to non-surgical, but invasive, procedures, such as computed tomography-guided drainage placement. *Mann–Whitney *U* test, except † χ^2 test. LPS, retroperitoneal liposarcoma; LMS, retroperitoneal leiomyosarcoma; CR, comprehensive resection; i.q.r., interquartile range; CCI, comprehensive complication index (patients with complications only).

greater number of macroscopically complete tumour resections ($P = 0.019$) compared with those who did not undergo CR (*Table 1*).

Of the patients with primary LMS, those who underwent CR had fewer G2 tumours and a greater number of patients in whom tumour grading was not applicable ($P = 0.045$), likely due to higher rates of preoperative radiation, compared with patients who did not undergo CR (*Table 1*). Patients who underwent CR had an increased median number of resected organs ($P < 0.001$) (*Table 1*).

Postoperative morbidity and mortality associated with CR

Of the patients with primary LPS, those who underwent CR experienced more severe postoperative complications (Clavien–Dindo ≥III; $P = 0.021$), accordingly requiring significantly more (re-)interventions ($P = 0.035$), and had longer durations of hospital stay ($P = 0.013$) compared with those who did not undergo CR (*Table 1*). However, when complications occurred, the severity as assessed by the CCI, did not differ significantly between the two treatment groups (*Table 1*). In addition, patients who underwent CR had longer operation times ($P = 0.006$) (*Table 1*).

Among patients with primary LMS, there were no significant differences in the occurrence of postoperative complications or in the length of hospital stay between those who did and did not undergo CR (*Table 1*). However, as for patients with primary LPS, operation times were longer ($P = 0.002$) and intraoperative blood loss was higher ($P = 0.008$) for patients with LMS who underwent CR (*Table 1*). Notably, among patients with primary LMS, 30-day mortality was significantly higher for those who did not undergo CR than for those who did undergo CR ($P = 0.045$) (*Table 1*).

DSS, LRFS, and DMFS in patients with primary LPS

Median DSS was not reached during the follow-up period, precluding its calculation. With CR, 3-year and 5-year DSS was 85 and 79%, respectively, compared with 70 and 67% without CR (*Fig. 1a*, *left panel*). In multivariable Cox regression analyses, CR was an independent prognostic factor and significantly associated with improved DSS ($P = 0.049$) independent of patient age, tumour grading, and resection status (*Table 2*). Similarly,

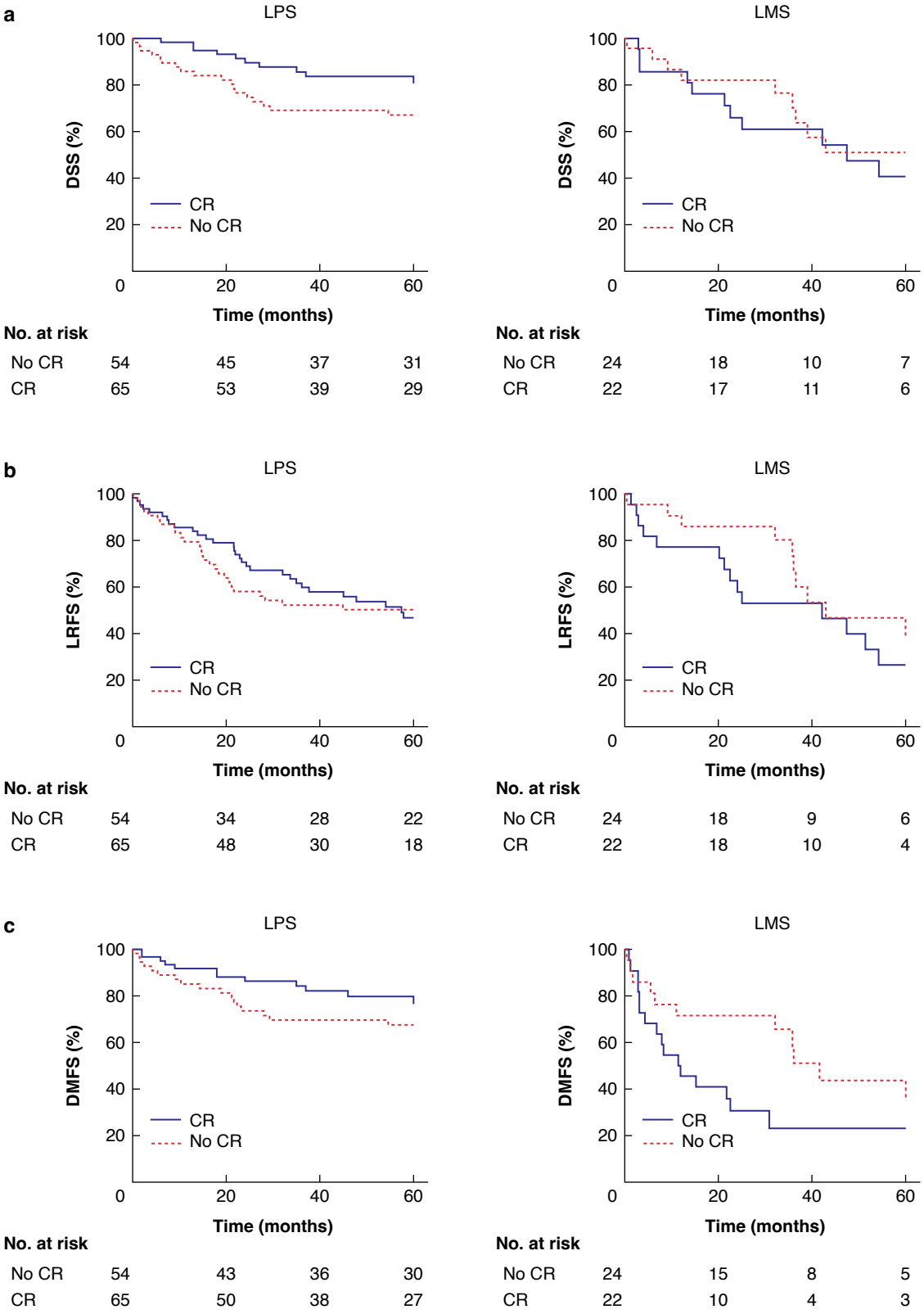

Fig. 1 Kaplan–Meier curves for 5-year DSS, LRFS, and DMFS in patients with LPS or LMS, with or without CR

a DSS, **b** LRFS, and **c** DMFS in primary LPS (left-hand panels) or LMS (right-hand panels). Significance levels between the CR and no CR groups were determined by log-rank tests and multivariable Cox regression. **a** $P = 0.058$ (log-rank test) and $P = 0.049$ (multvariable Cox regression) for LPS; no significant difference (log-rank test and multivariable Cox regression) for LMS. **b** No significant difference (log-rank test and multivariable Cox regression) for LPS and LMS. **c** No significant difference (log-rank test and multivariable Cox regression) for LPS; $P = 0.71$ (log-rank test) and no significant difference (multivariable Cox regression) for LMS. LPS, retroperitoneal liposarcoma; LMS, retroperitoneal leiomyosarcoma; CR, comprehensive resection; DSS, disease-specific survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival.

Table 2 Multivariable Cox regression analysis for 5-year DSS, LRFS, and DMFS for patients with LPS and LMS

	LPS		LMS	
	HR	P	HR	P
DSS				
Age at first diagnosis	1.06 (1.02–1.1)	0.006		
Resection status (R0/R1 *versus* R2)			0.14 (0.01–1.39)	0.093
Comprehensive resection (yes *versus* no)	0.46 (0.21–1.00)	0.049	1.87 (0.73–4.83)	0.195
Tumour grade		0.074		0.254
G1 *versus* G3	0.09 (0.01–0.72)	0.023		
G2 *versus* G3	0.55 (0.24–1.27)	0.161	3.63 (0.70–18.85)	0.125
N/A *versus* G3	0.37 (0.10–1.40)	0.144	3.61 (0.76–17.13)	0.106
LRFS				
Age at first diagnosis	1.01 (0.99–1.04)	0.295	1.01 (0.98–1.04)	0.477
Comprehensive resection (yes *versus* no)	0.89 (0.50–1.59)	0.687	1.68 (0.73–3.89)	0.222
Tumour grade		0.002		
G1 *versus* G3	0.08 (0.02–0.36)	0.001		
G2 *versus* G3	0.87 (0.47–1.65)	0.678		
N/A *versus* G3	0.21 (0.05–0.95)	0.042		
DMFS				
Age at first diagnosis	1.05 (1.01–1.09)	0.012	0.98 (0.95–1.01)	0.163
Resection status (R0/R1 *versus* R2)				
Comprehensive resection (yes *versus* no)	0.58 (0.28–1.21)	0.148	2.21 (0.97–5.06)	0.060
Tumour grade		0.092		0.456
G1 *versus* G3	0.09 (0.01–0.70)	0.021		
G2 *versus* G3	0.69 (0.31–1.53)	0.362	1.80 (0.53–6.17)	0.348
N/A *versus* G3	0.41 (0.11–1.52)	0.182	2.08 (0.66–6.52)	0.210

Values in parentheses are 95% confidence intervals. LPS, retroperitoneal liposarcoma; LMS, retroperitoneal leiomyosarcoma; DSS, disease-specific survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; N/A, not applicable.

younger age ($P = 0.006$) and G1 *versus* G3 grading ($P = 0.023$) were associated with improved DSS (*Table 2*).

Median LRFS was not reached during the follow-up period, precluding its calculation. With CR, 3-year and 5-year LRFS was 61 and 49%, respectively, compared with 57 and 55% without CR (*Fig. 1b*, *left panel*). Multivariable Cox regression analyses revealed that CR was not associated with improved LRFS (*Table 2*). Tumour grading was the only independent prognostic factor for LRFS in primary LPS ($P = 0.002$). The median interval to local recurrence was significantly longer in patients who underwent CR than in those who did not (25 (i.q.r.: 15.0–54.0) *versus* 15.5 (i.q.r.: 8.8–25.3) months, respectively; $P = 0.023$).

Median DMFS was not reached during the follow-up period, precluding its calculation. With CR, 3-year and 5-year DMFS was 83 and 75%, respectively, compared with 70 and 68% without CR (*Fig. 1c*, *left panel*). In multivariable Cox regression analyses, CR was not independently associated with improved DMFS (*Table 2*). Younger age ($P = 0.012$) and G1 *versus* G3 tumour grading ($P = 0.021$) were independently associated with improved DMFS (*Table 2*).

When 5-year DSS, LRFS, and DMFS for primary G2 and G3 LPS were analysed separately, CR was found to be an independent prognostic factor for improved DSS in G3 tumours, but not in G2 tumours (*Fig. 2a*; *Table S2*); this was also true for DMFS (*Fig. 2c*; *Table S2*), but not LRFS (*Fig. 2b*; *Table S2*). Consistent with these findings, when depicting local recurrences and distant metastases as crude cumulative incidence rates with death as a competing event, a lower crude cumulative incidence of distant metastases in the CR compared with no CR group was found only for primary G3 LPS ($P < 0.001$) (*Fig. S1*).

CR has increasingly been implemented over the recent years. Kaplan–Maier and multivariable Cox regression analyses were performed separating patients according to the time period (TP1: 2002–2007; TP2: 2008–2013; TP3: 2014–2019) when the operation was performed. In these analyses, 5-year DSS increased significantly over time (log-rank $P = 0.021$) in LPS (*Fig. S2a*, *left panel*). Consistent with these findings, in LPS, the time period when the operation was performed showed a tendency to be an independent prognostic factor for DSS in multivariable analysis ($P = 0.054$), whereby comparison of TP1 and TP3 specifically was an independent prognostic factor for DSS (T1 *versus* T3: hazard ratio (HR) 3.51, $P = 0.018$) (*Table S3*). There were no significant differences in 5-year LRFS rates over the time in LPS (*Fig. S2b*, *left panel*) and, consistent with these findings, the time period when the operation was performed was not an independent prognostic factor in multivariable analyses (*Table S3*). However, 5-year DMFS increased significantly over the time in LPS (log-rank $P = 0.039$) (*Fig. S2c*, *left panel*). In multivariable analyses, the time period when the operation was performed reached borderline significance as an independent prognostic factor for DMFS in LPS ($P = 0.050$) and was statistically significant when comparing TP1 *versus* TP3 (HR 3.21, $P = 0.025$) and TP2 *versus* TP3 (HR 2.87, $P = 0.029$) separately (*Table S3*).

DSS, LRFS, and DMFS in patients with primary LMS

Median DSS was not reached during the follow-up period, precluding its calculation. The 3-year and 5-year DSS with CR was 61 and 41%, respectively, compared with 70 and 51% without CR (*Fig. 1a*, *right panel*).

With CR, the median LRFS was 42.2 months (95% confidence interval (c.i.) 13.5 to 70.8 months), and the 3-year and 5-year LRFS was 53 and 27%, respectively (*Fig. 1b*, *right panel*). Without CR, the median LRFS was 42.9 months (95% c.i. 15.5 to 70.4), and the 3-year and 5-year LRFS without CR was 73 and 46%, respectively (*Fig. 1b*, *right panel*).

With CR, the median DMFS with CR was 11.4 months (95% c.i. 3.1 to 19.8 months), and the 3-year and 5-year DMFS with CR was 23 and 23%, respectively (*Fig. 1c*, *right panel*). Without CR, the median DMFS was 41.6 months (95% c.i. 31.9 to 51.3

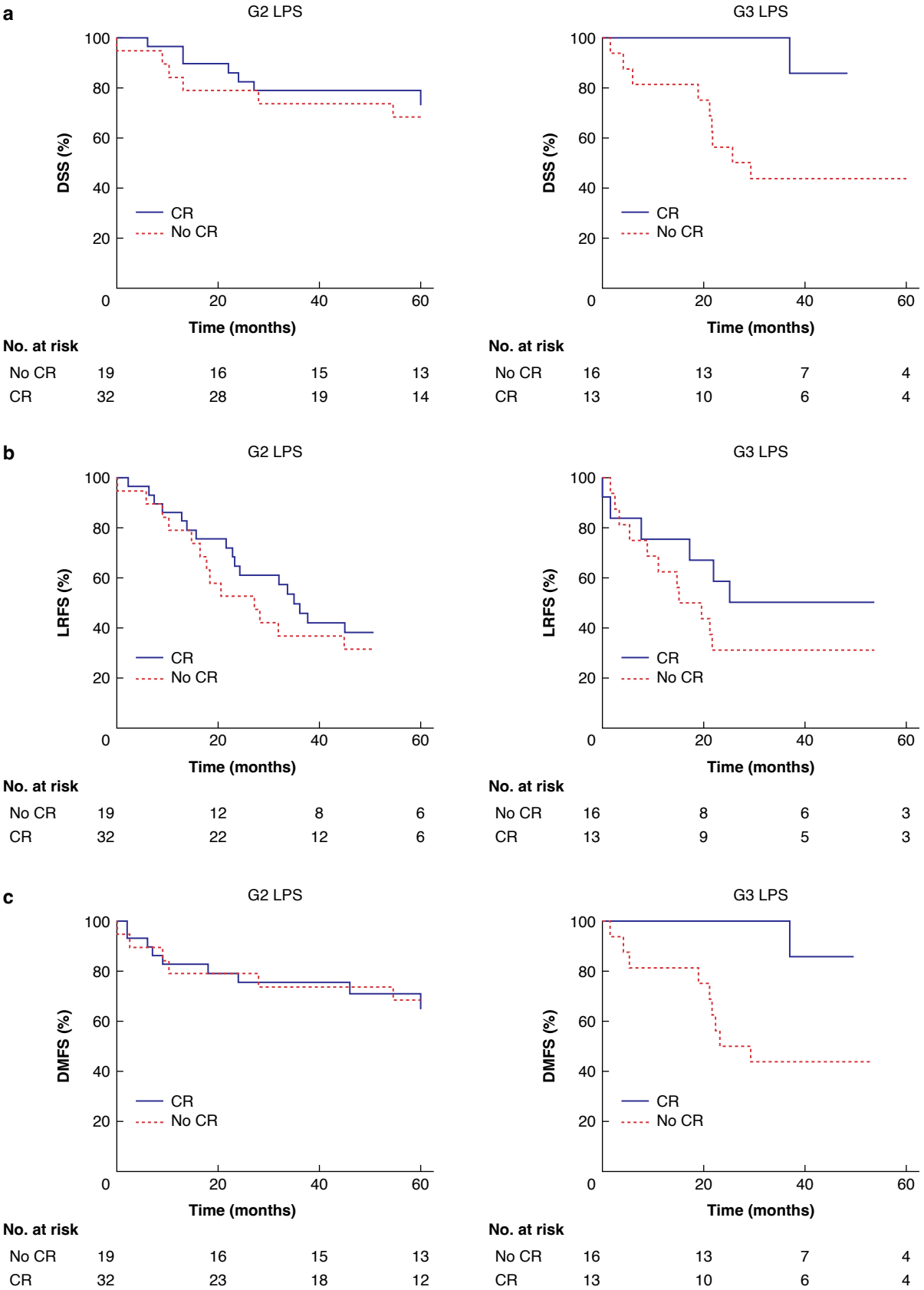

Fig. 2 Kaplan–Meier curves for subgroup analyses of 5-year DSS, LRFS, and DMFS for primary G2 and G3 LPS, with or without CR

a DSS, **b** LRFS, and **c** DMFS in primary G2 (left-hand panels) and G3 (right-hand panels) LPS. Significance levels between the CR and no CR groups were determined by log-rank tests and multivariable Cox regression. **a** No significant difference (log-rank test and multivariable Cox regression) for G2 LPS; $P = 0.025$ (log-rank test) and $P = 0.040$ (multivariable Cox regression) for G3 LPS. **b** No significant difference (log-rank test and multivariable Cox regression) for G2 and G3 LPS. **c** No significant difference (log-rank test and multivariable Cox regression) for G2 LPS; $P = 0.027$ (log-rank test) and $P = 0.041$ (multivariable Cox regression) for G3 LPS. LPS, retroperitoneal liposarcoma; LMS, retroperitoneal leiomyosarcoma; CR, comprehensive resection; DSS, disease-specific survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival.

months), and the 3-year and 5-year DMFS was 58 and 44%, respectively (*Fig. 1c*, *right panel*).

In multivariable Cox regression analysis, CR was not associated with improved DSS, LRFS or DMFS (*Table 2*). No independent prognostic factors for survival outcomes were identified (*Table 2*).

There was no significant association between the time point when the operation was performed and 5-year DSS, LRFS, and DMFS in univariate log rank and multivariable Cox regression analyses (*Fig. S2c*, *right panels*; *Table S3*).

Discussion

This retrospective single-centre study of 165 patients with primary retroperitoneal LPS and LMS demonstrated that CR is an independent prognostic factor for improved DSS in patients with primary LPS. In patients with primary G3 LPS, CR seems to be linked to improved DMFS, which may contribute to improved DSS associated with CR. In contrast, such associations were not observed in LMS.

Given the distinct underlying tumour biology and corresponding clinical presentation of different types of RPS, histology-driven surgical approaches have recently been recommended[6,13]. However, these recommendations are based on a few retrospective studies that did not systematically assess the role of CR as an independent prognostic factor for oncological outcome depending on tumour type and histology[14,16,17]. These pioneering studies, which established the concept of CR, revealed that CR is associated with improved overall survival and LRFS in RPS compared with standard procedures such as simple complete excision of the tumour or *en bloc* resection of the tumour with tumour-infiltrated organs in grade 1 and 2 RPS[14,16,17]. However, these study cohorts were analysed according to specific time periods during which resections were performed (with CR being more frequent within specific periods), but not stratified according to the use of CR[16,17]. Furthermore, the cohorts were based on mixed RPS cohorts with different histologies[14,16,17]. When subgroup analyses were included, either grading across all RPS entities or RPS entities without considering tumour grade have been investigated separately[14,16,17].

In contrast with previous reports that have shown an impact of CR on LRFS in RPS[14,16,17], the present study did not detect a statistically significant difference regarding LRFS in primary LPS using either Kaplan–Meier or multivariable Cox regression analyses. Local recurrences were not reduced in the CR group, but the median time interval between initial tumour resection and the diagnosis of recurrence was significantly longer in patients with primary LPS who underwent CR. Indeed, a prolonged interval between diagnosis of tumour recurrence and the initial operation is recognized as an independent predictor of improved overall survival in primary RPS[9,21], which may explain why CR was associated with improved DSS in the present cohort of patients with primary LPS.

Grading-stratified subgroup analyses of primary LPS performed in the present study revealed that CR appears to be associated with favourable DSS and DMFS, but not with LRFS in primary G3 LPS. In G3 LPS, the formation of distant metastases is a major determinant of prognosis[6]. These data suggest that upfront radical surgical treatment using CR may help prevent distant metastases, thereby contributing to improved DSS. However, these results and conclusions need to be interpreted with caution due to the small sample sizes in the respective subgroup analyses in this study. The lack of an association between CR and LRFS in G3 LPS further underscores the need for the validation of these findings in larger, preferably prospective, cohorts. In addition, these results should be contextualised within the ongoing STRASS-2 trial[22], which is investigating the role of neoadjuvant chemotherapy in primary LMS and G3 LPS tumours.

In patients with primary LMS, there was no improvement in DSS, LRFS, or DMFS when CR was performed. However, the primary LMS cohort only included 46 patients in total, and the findings may not be generalizable to all patients with primary LMS. The present study demonstrates that patients with primary LMS do not appear to benefit from CR compared with *en bloc* resection of the tumour and visibly infiltrated organs. These findings support current recommendations[6,13], which are based on LMS tumour biology and clearly distinguishable intraoperative tumour margins.

Personalization of surgical approaches regarding the extent of resection is of major clinical importance concerning surgical morbidity. The present study demonstrates that perioperative morbidity (intraoperative blood loss, number of severe complications, and length of hospital stay) is higher when performing CR. Although multivisceral resections in RPS are apparently not associated with inferior long-term quality of life[23], increased morbidity rates associated with CR make it crucial to identify subgroups of patients with RPS that truly benefit in terms of oncological outcome. Given this importance of personalized surgical management within a multimodality setting, the results of the present study support previous data, showing that sarcoma treatment should be conducted in specialized sarcoma centers[24].

This study has several limitations, the most important being its retrospective nature. Small sample sizes, especially in subgroup analyses, necessitate cautious interpretation of all significant findings. The long inclusion period presents another limitation, because advances in RPS treatment over the years may have influenced oncological outcomes and may bias the findings of this study. However, bias was reduced as much as possible through stratification by type of surgery as compared with timing of surgery (as in previous studies[16,17]), and by using multivariable analysis to correct for confounders. The interpretation of multivariable regression analysis is limited and validation in larger prospective multicentre cohorts is necessary. Given the rarity and heterogeneity of RPS, retrospective studies have historically served as a key source of comparative data[25]. Single-centre analyses necessitate cautious interpretation of findings, particularly regarding the generalizability of results. Nevertheless, this cohort aligns well with major RPS data sets in terms of tumour characteristics, patient demographics, postoperative morbidity, and recurrence rates, supporting the representativeness of the findings[2,26,27]. Increasing patient numbers in future studies through collaborative efforts, such as those facilitated by the Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG), holds considerable potential for clarifying unresolved questions. The growing availability of prospective multinational multicentre data sets, such TARPSWG's Retroperitoneal Sarcoma Registry (RESAR)[22], promises to significantly advance future research efforts.

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Author contributions

Julian Musa (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration,

Writing—original draft, Writing—review & editing), Franziska Willis (Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing—review & editing), Ingmar Rompen (Methodology, Software, Validation, Writing—review & editing), Julian-Camill Harnoss (Supervision, Validation, Writing—review & editing), Thomas G. P. Grünewald (Supervision, Validation, Writing—review & editing), Mohammed Al-Saeedi (Supervision, Validation, Writing—review & editing), Markus Büchler (Resources, Supervision, Validation, Writing—review & editing), and Martin Schneider (Conceptualization, Investigation, Project administration, Resources, Supervision, Validation, Writing—review & editing).

Disclosures

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

Data available upon reasonable request.

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Outcome after surgical resection of multiple recurrent retroperitoneal soft tissue sarcoma

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ABSTRACT

Introduction: Local recurrences (LR) and distant metastases (DM) are common in retroperitoneal soft tissue sarcoma (RPS). Longer time to recurrence and resection of the recurrent lesion have been identified as beneficial prognostic factors for overall survival (OS) upon first tumor relapse. However, prognostic factors concerning OS upon subsequent recurrences are scarcely defined. In this study, we aimed to identify prognostic factors for post-relapse outcome in multiple recurrent RPS.

Methods: Patients undergoing resection of primary and recurrent RPS at the University Hospital Heidelberg were retrospectively analyzed. Multivariable Cox regression analyses were performed to identify predictors of overall, LR- and DM-free survival. Subgroup analyses were performed for liposarcoma and leiomyosarcoma patients.

Results: 201 patients with primary disease, 101 patients with first, 66 patients with second and 43 patients with third LR as well as 75 patients with DM were analyzed. More than 12 months to recurrence and resection of recurrence were associated with improved OS after resection of first and second LR (5-year OS for first/second LR; resection: 64%/62%, no resection: 20%/46%). Gross macroscopic incomplete resection of first ($p < 0.001$), second ($p = 0.001$), and third recurrences ($p < 0.001$) was an independent prognostic factor for poor OS.

Conclusion: Development of LR and DM is frequent in RPS. Once a tumor relapsed, patients benefit from tumor resection not only in case of first, but also in case of subsequent recurrences.

Introduction

Retroperitoneal soft tissue sarcomas (RPS) account for about 15% of all soft tissue sarcomas [1]. Frequent recurrences, local as well as distant, are characteristic of RPS and are associated with high mortality (5-year overall survival 40–65%) [2–5]. RPS are therapeutically challenging, since tumor biology – reflected by tumor entity and grade - is the most important determinant for progression-free (PFS) and overall survival (OS) in primary tumors [6–11]. The only well-established prognostic factor for improved PFS and OS, which can be iatrogenically influenced, is complete gross macroscopic tumor resection [12–14]. Despite complete resection, approximately 50–60% of patients develop local or distant recurrences [14–16]. For recurrent RPS, the Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) identified a long time interval to tumor recurrence and resection of recurrence as beneficial prognostic factors concerning OS in the largest available cohort of patients with first relapse after resection of primary RPS [17]. However, after resection of the initial local recurrence (LR), crude cumulative incidence for the development of a subsequent LR or distant metastases (DM) was 58% and 16% in 5 years [17]. Evidence concerning prognostic factors for subsequent

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recurrences is limited, since only few retrospective analyses with small patient cohorts exist [18–21].

The aim of this study was to identify prognostic factors for post-relapse outcome of multi-recurrent RPS.

Patients and methods

Patients

Following approval by the ethics board of the University of Heidelberg (S-649/2012), we performed a retrospective analysis of all patients who underwent resection of primary, recurrent or metastasized RPS between 10/2001 and 12/2017 at Heidelberg University Hospital, Department of General, Visceral and Transplantation Surgery. Patients with gastrointestinal stromal tumors and those with embryonal, pediatric or gynecological RPS were excluded from the analysis.

To achieve tumor-free resection margins, resection of adjacent organs or tissues and multivisceral resections were performed as necessary [22,23]. Indications for additive chemo- and radiation therapy were determined on a case-by-case basis according to multidisciplinary tumor board review.

Statistics

Outcome parameters assessed in this study were OS, LR-free or DM-free survival. Local recurrence (LR) was defined as tumor recurrence in the retroperitoneum or abdomen, excluding liver metastases. Liver metastases and all other metastases were defined as distant recurrence. Seven or more abdominal nodes were defined as peritoneal sarcomatosis [24]. OS was defined as the date of surgery to the date of death. For alive patients, follow-up was censored at the date of last disease assessment. LR-free and DM-free survival were defined as the interval between the date of surgery and the date of LR and DM, respectively, or last follow-up.

Survival and disease relapse were estimated applying the Kaplan-Meier method. Overall, LR-free, and DM-free survival are presented as median with 95% confidence interval (CI) and as 3- and 5-year survival rates. Multivariate Cox regression analyses including all potential predictors from univariate Kaplan-Meier analyses (log rank: $p < 0.2$) were performed to identify independent prognostic factors for OS, LR, and DM. Possible predictors were resection status (R0 vs. R1 vs. R2), grading according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), histologic subtype, tumor size, radiation therapy (RT), systemic therapy (ST), multivisceral resection (MVR; resection of 3 or more organs), multifocality, and patient age and sex [2,4,13,15,25]. In cases with development of LR or DM, patient age and sex, grading and histology of the initial tumor, time interval to disease relapse (relapse within vs. after 12 months), resection, RT or ST of LR or DM and multifocality of the recurrence were considered.

Resection status, tumor grade, histology, RT, ST, MVR, multifocality, sex, time interval to LR or DM, and resection of LR or DM were modeled as categorical using dummy variables. For simplification liposarcoma subtypes were divided in a high-grade (G2 and G3) and low-grade (G1) group [14,26]. All other variables were modeled as continuous variables. In respect of number of events, we used forward and backwards step-wise variable selection [27].

Analyses were performed considering patients with primary tumors, first, second and third local recurrences. For analysis of LR-free survival, patients with macroscopically incomplete tumor resection (R2) were excluded. Analyses of DM were performed in patients with primary tumors only. Patients with incomplete datasets were excluded. In order to delineate prognostic factors for OS once tumor relapse occurred, subgroup analyses for patients who developed LR or DM after tumor resection at our institution were performed.

The same analyses were performed in the subgroups of liposarcoma (LPS) and leiomyosarcoma (LMS) patients as these are the predominant tumor entities in RPS, but show different relapse patterns [28]. For all LPS patients with resected LR, tumor growth rate was defined as the tumor size of the resected recurrence divided by the time from previous resection to LR. Since tumor growth rate was not available for all LPS patients it was not considered in multivariable analysis. Due to the relatively small number of LMS patients with few local recurrences, progression-free survival (PFS) was assessed as outcome parameter for analyses of disease recurrence.

SPSS (Version 22.0.0.0) was used for all statistical analyses. The level of statistical significance was set to $p \leq 0.05$ (two-tailed).

Results

Clinicopathological features and recurrence patterns

Demographic, clinicopathological, and treatment details are shown in Table 1. 332 patients who underwent resection of RPS at the University of Heidelberg Department of General, Visceral and Transplantation Surgery between 10/2001 and 12/2017 were identified. 201 patients with primary disease, 101 patients with first, 66 patients with second and 43 patients with third local recurrence as well as 75 patients with distant metastases were analyzed (Supplementary Fig. 1).

Recurrence rates and corresponding therapies are displayed in Table 2 and Supplementary Table 1. In 144 (43%) of all 332 patients the tumor relapsed locally; 75 patients (23%) developed DM, thereof 36 patients (11%) developed LR and DM after initial tumor resection at our institution (Supplementary Fig. 1). 82 patients (25%) developed multiple local recurrences. Incomplete tumor resection was more frequent in recurrent tumors than in primary tumors. Patients with LPS developed mainly LR (42,4% after resection of primary tumor), whereas DM were more frequent in LMS patients (53,5% after resection of primary LMS). In case of DM, the tumor mainly spread to lung and liver. In LPS, median tumor growth rate of the first LR was 0.17 (0.10–0.36) cm/month, of the second 0.56 (0.23–0.83) cm/month, of the third 0.44 (0.16–0.59) cm/month, and of the fourth 0.54 (0.25–1.31) cm/month.

Overall survival

Median OS in the entire cohort (EC) from first diagnosis was 147.8 months (95% CI: 94.5–201.4). 3-year OS was 75%, and 5-year OS was 67%. In patients with primary tumors median OS without tumor relapse was not reached yet, whereas for patients with development of LR, DM or both median OS was reduced (LR: 122.2 months [95% CI: 55.1–189]; DM: 42.2 months [95% CI: 31.9–52.4]; LR + DM: 24.4 months [18.9–30.0]). Interestingly, median OS increased with resection of subsequent LR, while median PFS remained constant (Table 2).

In the multivariable Cox model, initial grading, patient age as well as MVR were identified as independent predictors for OS in all primary tumors. Lower grading, younger age and no MVR were associated with improved OS. In patients with first, second and third recurrences R2 resection was associated with poor OS in multivariable Cox regression analysis (Table 3; Fig. 1 a-c). In the subset of patients who developed LR after tumor resection at our institution, surgical resection of LR was associated with improved OS not only after resection of first but also second LR (Table 4; Fig. 1 d-f). Furthermore, development of LR within 12 months after tumor resection was associated with significantly worse OS compared to

Table 1
Demographic, clinical and pathological characteristics.

	ALL PATIENTS		PRIMARY TUMORS		1st LR		2nd LR		3rd LR	
n (%)	332	(100)	201	(60.5)	101	(30.4)	66	(19.9)	43	(13.0)
AGE, median (IQR), y	58.0	(49.0–68.0)	57.0	(48.0–67.0)	60.0	(50.0–68.0)	60.0	(49.5–70.0)	62.0	(48.0–67.0)
SEX (%)										
Male	175	(52.7)	105	(52.2)	56	(55.4)	40	(60.6)	23	(53.5)
Female	157	(47.3)	96	(47.8)	45	(44.6)	26	(39.4)	20	(46.5)
TUMOR PRESENTATION (%)										
Primary tumors	194	(58.4)	194	(96.5)						
Local recurrence	110	(33.1)			96	(95.0)	62	(93.9)	40	(93.0)
Distant metastases	11	(3.3)								
Primary tumor and distant metastases	7	(2.1)	7	(3.5)						
Local recurrence and distant metastases	10	(3.0)			5	(5.0)	4	(6.1)	3	(7.0)
HISTOLOGY (%)										
DD- LPS	150	(45.2)	75	(37.3)	58	(57.4)	46	(69.7)	26	(60.5)
WD-LPS	40	(12.0)	25	(12.4)	9	(8.9)	5	(7.6)	9	(20.9)
Myxoid LPS	6	(1.8)	5	(2.5)	4	(4.0)	3	(4.5)	3	(7.0)
Pleomorphic LPS	4	(1.2)	1	(0.5)	2	(2.0)	1	(1.5)	1	(2.3)
LMS	58	(17.5)	43	(21.4)	8	(7.9)	3	(4.5)	1	(2.3)
NOS	22	(6.6)	15	(7.5)	8	(7.9)	3	(4.5)	0	(0.0)
Other	38	(11.4)	28	(13.9)	10	(9.9)	3	(4.5)	0	(0.0)
SFT	14	(4.2)	9	(4.5)	2	(2.0)	2	(3.0)	3	(7.0)
INITIAL TUMOR GRADE (%)										
G1	42	(12.7)	30	(14.9)	9	(8.9)	6	(9.1)	10	(23.3)
G2	97	(29.2)	66	(32.8)	35	(34.7)	24	(36.4)	13	(30.2)
G3	98	(29.5)	58	(28.9)	35	(34.7)	21	(31.8)	7	(16.3)
Does not apply	95	(28.6)	47	(23.4)	22	(21.8)	15	(22.7)	13	(30.2)
RESECTION STATUS (%)										
R0	113	(34.0)	71	(35.3)	39	(38.6)	19	(28.8)	13	(30.2)
R1	179	(53.9)	115	(57.2)	51	(50.5)	33	(50.0)	26	(60.5)
R2	40	(12.0)	15	(7.5)	11	(10.9)	14	(21.2)	4	(9.3)
TUMORSIZE, median (IQR), cm	12	(7.0–22.0)	14	(8.0–25.5)	7.20	(4.5–13.8)	7.25	(4.0–12.0)	7.25	(4.1–14.5)
MULTIFOCALITY (%)										
No	279	(84.0)	186	(92.5)	81	(80.2)	45	(68.2)	26	(60.5)
Yes	53	(16.0)	15	(7.5)	20	(19.8)	21	(31.8)	17	(39.5)
MVR (%)										
No	203	(61.1)	104	(51.7)	76	(75.2)	58	(87.9)	35	(81.4)
Yes	129	(38.9)	97	(48.3)	25	(24.8)	8	(12.1)	8	(18.6)
RADIATION THERAPY (%)										
No	174	(52.4)	108	(53.7)	46	(45.5)	40	(60.6)	26	(60.5)
Preoperative	75	(22.6)	53	(26.4)	15	(14.9)	10	(15.2)	2	(4.7)
Postoperative	52	(15.7)	31	(15.4)	15	(14.9)	8	(12.1)	4	(9.3)
Pre- & postoperative	1	(0.3)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
EBRT alone	47	(14.2)	38	(18.9)	10	(9.9)	7	(10.6)	0	(0.0)
IORT alone	30	(9.0)	8	(4.0)	25	(24.8)	8	(12.1)	11	(25.6)
EBRT + IORT	81	(24.4)	47	(23.4)	20	(19.8)	11	(16.7)	6	(14.0)
SYSTEMIC THERAPY (%)										
No	287	(86.4)	174	(86.6)	87	(86.1)	57	(86.4)	40	(93.0)
Preoperative	12	(3.6)	5	(2.5)	6	(5.9)	2	(3.0)	1	(2.3)
Postoperative	21	(6.3)	16	(8.0)	5	(5.0)	4	(6.1)	2	(4.7)
Pre- & postoperative	12	(3.6)	6	(3.0)	3	(3.0)	3	(4.5)	0	(0.0)
FOLLOW-UP, median (IQR), months										
From OP	35.5	(13.1–75.1)	36.9	(13.1–81.3)	29.4	(11.2–75.6)	69.8	(23.0–112.9)	89.8	(35.4–154.7)
From first diagnosis	54.8	(24.3–105.8)	39.5	(16.0–84.3)	70.1	(35.3–133.4)	89.0	(44.9–163.2)	124.3	(80.6–193.0)
From OP if alive	53.1	(24.1–88.3)	55.0	(26.3–92.9)	47.9	(24.8–111.9)	107.2	(77.3–167.0)	124.3	(85.0–180.7)
From first diagnosis if alive	74.1	(34.5–124.2)	58.0	(27.7–100.2)	92.9	(50.4–147.6)	107.2	(77.3–167.0)	124.3	(85.0–180.7)

LPS liposarcoma*; LMS* leiomyosarcoma*; LG-LPS* low grade liposarcoma; *HG-LPS* high grade liposarcoma; *WD-LPS* well differentiated liposarcoma; *DD-LPS* dedifferentiated liposarcoma; *NOS* undifferentiated sarcoma (not otherwise specified); *SFT* solitary fibrous tumor & other tumors with intermediate malignancy; *MVR* multivisceral resection; *EBRT* external beam radiation therapy*; IORT* intraoperative radiation therapy.

patients with later development of LR (Table 4; Fig. 1 g-i). Similarly, resection of DM and a time interval greater than 12 months until development of DM were prognostic factors for improved OS in patients who developed DM after initial resection (Table 4).

Consistent with findings from the entire cohort, patient age and MVR were identified as prognostic factors for OS in primary LPS. There was a trend towards reduced OS in high-grade compared to low-grade LPS but this did not reach statistical significance. Again, R2 resection of first, second and third LR was an independent prognostic factor for poor OS (Table 3; Fig. 2 a-c). In the subset of patients who developed LR after resection of LPS at our institution, resection of first and second LR was associated with improved OS (Table 4, Fig. 2 d-f). Development of LR within the first 12 months after initial LPS resection was associated with reduced OS in first, second and third LR (Table 4, Fig. 2 g-i). In patients with resection of first and second LR a LR growth rate less than 0.9 cm/months was associated with improved OS in univariable analysis.

For patients with primary LMS, the multivariable analysis did not reveal any prognostic factors for OS (Table 3). In the subset of patients with tumor relapse, resection of recurrent tumors and intervals greater 12 months to relapse were beneficial prognostic factors concerning OS (Table 4).

In our cohort (regarding all patients as well as LPS and LMS subgroups), radiation or systemic therapy of primary or recurrent

Table 2
Patterns of recurrence and therapy of recurrent tumors in the entire cohort, and for LPS and LMS subgroups.

	Entire cohort								LPS								LMS	
	PRIMARY TUMORS		1ST LR		2ND LR		3RD LR		ALL LPS		PRIMARY TUMORS		1ST LR		2ND LR		3RD LR		ALL LMS	
RELAPSE PATTERN																				
No relapse (%)	105	(52.2)	41	(40.6)	17	(25.8)	12	(27.9)	90	(45.0)	58	(54.7)	31	(42.5)	13	(23.6)	11	(28.2)	22	(38.6)
Development of (further) LR only (%)	46	(22.9)	41	(40.6)	39	(59.1)	27	(62.8)	85	(42.5)	35	(33.0)	34	(46.6)	34	(61.8)	24	(61.5)	4	(7.0)
Development of DM only (%)	29	(14.4)	3	(3.0)	2	(3.0)	0	(0)	4	(2.0)	3	(2.8)	0	(0)	2	(3.6)	0	(0)	24	(42.1)
Development of DM and LR (%)	21	(10.4)	16	(15.8)	8	(12.1)	4	(9.3)	21	(10.5)	10	(9.4)	8	(11.0)	6	(10.9)	4	(10.3)	7	(12.3)
INTERVAL TO RELAPSE																				
Interval to (further) LR, median (IQR), months	27.8	(9.1 −55.9)	13.6	(6.2 −32.7)	11.8	(4.9 −27.69	6.6	(3.5 −24.5)	20.5	(7.5 −41.2)	26.7	(13.0 −57.8)	12.7	6.1–29.4)	13.7	(5.4 −27.5)	6.3	(3.3 −24.5)	28.8	(8.1 −50.8)
Interval to DM, median (IQR), months	27.8	(6.6 −68.8)	26.8	(9.3 −75.6)	31.9	(9.4 −54.4)	33.4	(11.1 −54.5)	48.5	(13.0 −75.0)	38.1	(16.5 −82.4)	26.7	(9.6 −69.1)	34.2	(11.2 −54.5)	33.4	(11.0 −56.9)	12.5	(2.9 −34.8)
Interval to progression (DM or LR), median (IQR), months	21.4	(5.1 −50.8)	13.3	(5.6 −32.7)	10.0	(4.4 −20.3)	6.6	(3.5 −24.5)	30.8	(7.4 −41.09	25.7	(10.9 −57.5)	12.7	(6.1 −29.4)	11.0	(4.8 −20.2)	6.3	(3.3 −24.5)	11.0	(2.7 −32.4)
RESECTION OF LR																				
Complete resection[a] (%)	38	(56.7)	39	(68.4)	28	(59.6)	26	(83.9)	71	(66.4)	29	(64.4)	31	(73.8)	26	(63.4)	24	(92.9)	3	(27.3)
Incomplete resection[b] (%)	4	(10.5)	6	(15.8)	4	(14.3)	4	(15.4)	10	(14.1)	2	(6.9)	7	(22.6)	4	(15.4)	4	(16.7)	0	(0)
No resection (%)	29	(43.3)	19	(33.3)	19	(40.4)	5	(16.1)	36	(33.6)	16	(35.6)	11	(26.2)	15	(36.6)	4	(7.1)	8	(72.7)
SURVIVAL DATA																				
Median OS from surgery (IQR), months	121.5	(60.7 −182.3)	66.3	(42.6 −89.9)	152.8	(77.4 −228.2)	178.46	(−)[c]	80.6	(58.5 −102.7)	122.2	(69.8 −174.6)	57.7	(29.4 −86.1)	104.1	(24.4 −183.8)	178.46	(−)[c]	51.8	(37.4 −66.1)
Median OS after development of recurrence (IQR), months	39.3	(24.3 −54.4)	48.0	(38.4 −57.6)	59.8	(37.1 −82.4)	81.2	(37.1 −125.2)	44.7	(25.8 −63.6)	26.0	(0–73.3)	48.0	(29.6 −66.4)	59.8	(39.9 −79.6)	81.2	(22.3 −140.0)	40.0	28.7 −51.2)
Median PFS after recurrence (IQR), months	14.6	(0–199.9)	15.1	(9.1 −21.1)	9.0	(2.1 −16.0)	12.5	(6.8 −18.2)	15.6	(11.6 −19.5)	16.0	11.5 −20.4)	15.1	(10.5 −19.6)	8.9	(1.0 −16.9)	10.1	(5.5 −14.79	9.0	(0–38.4)
Median OS after resection of recurrence (IQR), months	89.6	(19.3 −69.2)	78.3	(16.9 −139.7)	64.4	(8.7 −120.1)	81.2	(49.1 −113.3)	75.1	(34.5 −115.8)	57.4	(0–119.5)	78.3	(21.5- (135.1)	64.4	(8.50 −120.3)	81.2	(29.3 −113.1)	46.3	(45.6 −47.1)
Median OS without resection of recurrence (IQR), months	12.5	(7.9 −17.0)	8.4	(0.0 −57.9)	13.5	(0.3 −26.7)	32.8	(0–74.4)	10.1	(5.2 −15.0)	10.1	(3.2 −17.0)	6.1	(1.53 −10.7)	19.3	(0–39.4)	6.74	(−)[c]	31.0	(6.4 −55.6)

IQR interquartile range; *OS* overall survival; *PFS* progression-free survival; [a] gross macroscopic complete resection (R0/R1); [b] gross macroscopic incomplete resection (R2); [c]cannot be estimated by less than 50% of events.

Table 3
Predictors of overall survival according to univariable (log-rank) and multivariable (COX) analysis in all patients (entire cohort, *top*), and in the LPS (*middle*) and LMS subgroups (*bottom*).

Overall survival																
Entire cohort																
	PRIMARY TUMORS				1ST LR				2ND LR				3RD LR			
	p-value (log-rank)	HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)	HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)	HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)	HR	95% CI	*p*-value (Cox)
Age	0.007	1.06	1.04 −1.09	<0.001	0.307				0.011	1.03	1.00 −1.07	0.033	0.095	1.05	0.99−1.10	0.094
Sex	0.356				0.959				0.816				0.634			
Tumor histology	0.025				0.164			0.081	0.563				0.603			
LG-LPS vs. HG-LPS						1.88	0.48 −7.41	0.366								
LMS vs. HG-LPS						1.44	0.28 −7.39	0.665								
NOS vs. HG-LPS						0.06	0.01 −0.51	0.010								
Other vs. HG-LPS						2.13	0.46 −9.87	0.332								
Tumor grade	<0.001	0.00		0.004	0.041			0.006	0.740				0.058			
G1 vs. G3		0.27	0.11 −0.66	0.004		0.12	0.01 −1.10	0.061								
G2 vs. G3		0.50	0.28 −0.89	0.019		0.30	0.14 −0.67	0.003								
Tumor size	0.774				0.742				0.220				0.586			
Resection status	<0.001			0.095	0.001			<0.001	<0.001			0.001	0.024			<0.001
R1 vs. R0		0.52	0.28 −0.95	0.032		1.64	0.65 −4.10	0.291		1.26	0.47 −3.38	0.650		0.63	0.14−2.94	0.556
R2 vs. R0		0.89	0.32 −2.48	0.822		21.29	5.65 −80.26	<0.001		5.72	1.91 −17.11	0.002		111.56	8.80 −1414.73	<0.001
MVR yes vs. no	0.006	2.23	1.30 −3.84	0.004	0.883				0.016	2.01	0.77 −5.27	0.157	0.110			
Multifocality yes vs. no	0.059				0.938				0.969				0.039	0.18	0.04−0.83	0.028
st yes vs. no	<0.001	2.72	1.30 −5.69	0.008	0.446				0.036				0.584			
RT	0.864				0.736				0.415				0.302			
EBRT vs. no RT																
IORT vs. no RT																
EBRT + IORT vs. no RT																
LPS subgroup																
	PRIMARY TUMORS				1ST LR				2ND LR				3RD LR			
	p-value (log-rank)	HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)	HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)	HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)	HR	95% CI	*p*-value (Cox)
Age	0.012	1.06	1.03 −1.10	0.001	0.104	1.03	1.01 −1.07	0.021	0.014	1.04	1.00 −1.07	0.060	0.038	1.07	1.01−1.13	0.034
Sex	0.032				0.456				0.504				0.464			
LG-LPS vs. HG-LPS	0.006	0.35	0.12 −1.02	0.054	0.857				0.702				0.482			
Tumor size					0.578				0.456				0.406			
Resection status	0.030			0.010	<0.001			0.001	<0.001			0.001	0.020			<0.001
R1 vs. R0		0.55	0.22 −1.36	0.197		1.40	0.61 −3.24	0.430		1.01	0.35 −2.92	0.981		0.51	0.08−3.31	0.484
R2 vs. R0		2.66	0.81 −8.75	0.108		13.98	3.32 −58.89	<0.001		5.96	1.77 −20.16	0.004		92.60	6.42 −1334.87	0.001
MVR yes vs. no	0.002	2.94	1.36 −6.38	0.006	0.600				0.029	1.68	0.59 −4.82	0.333	0.220			
Multifocality yes vs. no	0.297				0.269				0.834				0.097	0.25	0.05−1.22	0.087
ST yes vs. no	<0.001				0.006	1.03	0.33 −3.20	0.954	0.068				0.562			
RT	0.808				0.261				0.273				0.208			
EBRT vs. no RT																
IORT vs. no RT																

(*continued on next page*)

Table 3 (*continued*)

EBRT + IORT vs. no RT				
LMS subgroup				
	PRIMARY TUMORS			
	p-value (log-rank)	HR	95% CI	*p*-value (Cox)
Age	0.941			
Sex	0.306			
Tumor grade	0.987			
G1 vs. G3				
G2 vs. G3				
Tumor size	0.341			
Resection status	0.276			
R1 vs. R0				
R2 vs. R0				
MVR yes vs. no	0.612			
Multifocality yes vs. No	0.963			
st yes vs. No	0.229			
RT	0.006			0.107
EBRT vs. no RT		0.84	0.28 −2.50	0.746
IORT vs. no RT		19.37	1.66 −226.40	0.018
EBRT + IORT vs. no RT		1.05	0.40 −2.73	0.921

LPS liposarcoma; *LMS* leiomyosarcoma; *LG-LPS* low grade liposarcoma; *HG-LPS* high grade liposarcoma; *NOS* undifferentiated sarcoma (not otherwise specified); *MVR* multivisceral resection; *ST* systemic therapy; *RT* radiation therapy; *IORT* intraoperative radiation therapy. Missing values due to stepwise variable selection in cases of low number of events.

tumors was not associated with improved OS (Tables 3 and 4).

Local control

Median LR-free survival of all 292 patients with gross macroscopic complete resection after resection at our institution was 29.7 months (95% CI: 24.0–35.5). 3-year LR-free survival was 45% and 5-year LR-free survival was 32%. LR-free survival was reduced if patients already presented with recurrent disease (primary tumors: 111.3 months [95% CI: 50.2–172.4.]; recurrent tumors: 18.1 months [95% CI: 9.3–26.9]).

In multivariable Cox regression analysis for all primary tumors, tumor histology ($p = 0.028$) and MVR ($p = 0.037$) were independent factors predicting LR. Specifically, LR was significantly less frequent in LMS compared to high-grade LPS (HR 0.27; $p = 0.009$). Neither multifocal disease nor tumor size were associated with increased LR rates in patients with primary or recurrent tumors (Supplementary Table 2).

In all patients with LPS, median LR-free survival after resection at our institution was 26.2 months (95% CI: 19.4–33.1). 3-year LR-free survival was 39% and 5-year LR-free survival was 29%. Consistent with findings from the entire cohort, LR-free survival was reduced if patients already presented with recurrent disease (primary tumors: 57.9 months [95% CI: 21.8–93.9.]; recurrent tumors: 16.6 months [95% CI: 10.0–23.2]).

Low-grade LPS were less likely to develop LR compared to high-grade LPS (primary tumors: HR = 0.16; $p = 0.003$; 1st LR: HR = 0.23; $p = 0.021$). MVR was a negative prognostic factor for LR in primary tumors (HR = 2.52; $p = 0.016$) and second recurrences (HR = 6.43; $p = 0.003$) (see Supplementary Table 2).

Distant control

In the entire cohort of 332 patients median DM-free survival after initial resection at our institution was 46.1 months (95% CI: 31.5–60.6). 3-year DM-free survival was 53% and 5-year DM-free survival was 58%. In Cox regression analysis, histology ($p < 0.027$) and MVR ($p < 0.001$) were independent prognostic factors for primary tumors. Compared to HG-LPS, LMS displayed an increased likelihood of DM (HR = 4.12; $p = 0.002$) (Supplementary Table 2).

Median progression-free survival (PFS) of all 57 LMS patients after initial resection at our institution was 13.2 months (95% CI: 5.2–21.0). 3-year PFS was 21% and 5-year PFS was 12%. In primary LMS, only MVR was associated with reduced PFS (HR = 5.16; $p = 0.008$) (Supplementary Table 2).

Discussion

Based on a single center collective of patients with primary and multiple recurrent RPS, this study comprises one of the largest available analyses of prognostic factors for OS after surgical resection of multiple recurrences.

Development of tumor recurrences in form of local recurrence (LR), distant metastases (DM) or both leads to reduced overall survival (OS) and is associated with an increased likelihood of further tumor relapse. In line with findings by MacNeill et al. [17], we identified an extended interval to LR/DM and surgical (re-) resection of LR/DM as prognostic factors, indicating improved OS after development of a first recurrence (LR or DM). This was true for the entire patient cohort, as well as for the LPS- and LMS-subgroups. Importantly, however, our data suggest that survival can be prolonged not only by resection of first, but also by resection of second LR. Though our data do not reveal a significant benefit of surgical resection upon third and fourth LR, median OS after

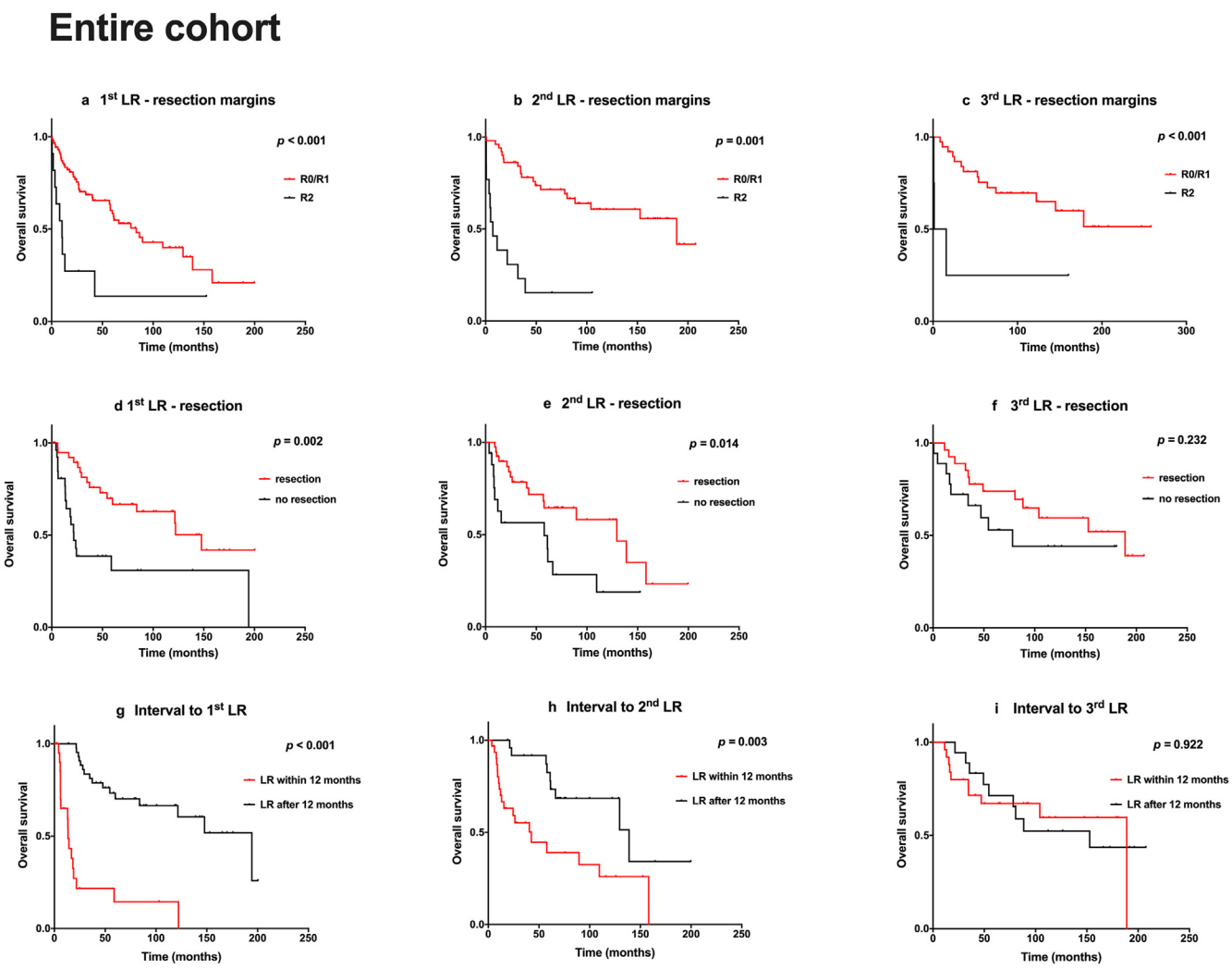

Fig. 1. *Kaplan-Meier curves with log-rank test, indicating overall survival after development of first, second and third local recurrences (LR) in the entire patient cohort (a-c) and in the subgroup of patients with preceding resection at our institution (d-i).* (a) Significance of resection margins (R0/R1 versus R2) concerning OS upon resection of 1st LR (estimated 5-year OS: R0/R1: 59%, R2: 14%). (b) Significance of resection margins (R0/R1 versus R2) upon resection of 2nd LR (estimated 5-year LR free survival: R0/R1: 72%, R2: 15%). (c) Significance of resection margins (R0/R1 versus R2) upon 3rd LR (estimated 5-year OS: R0/R1: 76%, R2: 25%). (d) Significance of resection (versus no resection) of 1st LR (estimated 5-year OS: resection: 67%, no resection 31%). (e) Significance of resection (versus no resection) of 2nd LR (estimated 5-year OS: resection: 65%, no resection: 57%). (f) Significance of resection (versus no resection) of 3rd LR (estimated 5-year OS: resection: 74%, no resection: 60%). (g) Significance of interval until 1st LR (within 12 months versus after 12 months; estimated 5-year OS: within 12 months: 14%, after 12 months: 70%). (h) Significance of interval until 2nd LR (within 12 months versus after 12 months; estimated 5-year OS: within 12 months: 45%, after 12 months: 83%). (i) Significance of interval until 3rd LR (within 12 months versus after 12 months; estimated 5-year OS: within 12 months: 67%, after 12 months: 71%).

resection of third LR was more than twice as long as in patients without resection. Incomplete resection of first, second and third LR was significantly associated with worse OS, further corroborating the notion that patients benefit from resection of subsequent recurrences. Interestingly, resection of three or more organs, which was frequently necessary to achieve gross macroscopic tumor free resection margins, was associated with reduced OS as well as LR- and DM-free survival in primary and recurrent tumors. However, this most likely reflects aggressive tumor biology causing more advanced tumors, which can only be controlled by extended resection [29].

Obviously, it has to be considered that these data and conclusions are susceptible to selection bias. For instance, patients with isolated LR or DM, or patients with slow growing tumors and without multifocal LR are at an increased likelihood of achieving gross macroscopic complete resection.

In our cohort multifocality increased with consecutive recurrences. However, multifocal presentation of LR was no predictor for reduced OS and resection of LR was associated with improved OS independently of uni- or multifocal tumor presentation. Anaya et al. reported that more than seven tumors represent a poor predictor for OS, and that complete resection is less likely for multifocal tumors [24]. Yet, if complete resection can be achieved, patients still seem to benefit from surgery [8]. There even is some evidence that patients may benefit from surgical debulking [9,18,30], whereas other studies describe no difference in outcomes between biopsy only or R2 resections [6,31,32].

In our cohort, additional radiation or systemic therapy was not associated with improved OS in primary as well as in recurrent tumors. On the contrary, systemic therapy of primary tumors was associated with reduced OS. These findings, however, are most likely biased since at our center, systemic therapy for RPS is only applied in cases with metastasized or advanced disease [33,34] and poor survival is rather associated with aggressive tumor biology than additional chemotherapy. Additional RT has been proposed as a beneficial prognostic factor for LR-free survival and even OS

Table 4
Predictors of overall survival in patients with tumor recurrences (preceding resection at our institution) according to univariable (log-rank) and multivariable (COX) analysis. *Top:* Data from patients with local recurrence (LR) of all tumor entities. *Middle:* Data from patients with LR from the LPS subgroup. *Bottom left:* Data from patients with distant metastases (DM) of all tumor entities. *Bottom right:* Data from patients with relapse (LR and/or DM) from the LMS subgroup.

Overall survival									
Entire cohort									
	1ST LR				2ND LR			3RD LR	
	p-value (log-rank)	HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)	HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)
Age	0.027	1.05	1.02–1.09	0.005	0.319				0.063
Sex	0.057				0.876				0.153
Tumor histology	0.543				0.486				0.008
LG-LPS vs. HG-LPS									
LMS vs. HG-LPS									
NOS vs. HG-LPS									
Other vs. HG-LPS									
Tumor grade	0.010				0.149			0.999	0.020
G1 vs. G3						–	–	0.981	
G2 vs. G3						0.98	0.33–2.92	0.966	
Interval to LR <12 months vs. >12 months	<0.001	0.05	0.02–0.17	<0.001	0.003	0.33	0.13–0.86	0.023	0.922
Multifocality of LR yes vs. no	0.301				0.050	2.49	0.57–10.92	0.226	0.062
Resection of LR yes vs. no	0.002	2.51	1.15–5.46	0.021	0.014	3.64	1.03–12.84	0.045	0.232
RT of LR yes vs. no	0.205				0.299				0.299
ST of LR yes vs. no	0.007	0.31	0.09–1.06	0.062	–				–
LPS subgroup									
	1ST LR				2ND LR			3RD LR	
	p-value (log-rank)	HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)	HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)
Age	0.113	1.02	0.98–1.06	0.322	<0.001	1.04	0.99–1.08	0.103	0.013
Sex	0.024				0.399				0.107
Tumor grade	0.025				0.245				0.033
G1 vs. G3									
G2 vs. G3									
Interval to LR <12 months vs. >12 months	<0.001	0.11	0.05–0.28	<0.001	0.006	0.29	0.12–0.70	0.006	0.740
Multifocality of LR yes vs. no	0.365				0.971				0.130
Resection of LR yes vs. no	<0.001	3.69	1.43–9.56	0.007	0.001	2.70	1.06–6.83	0.037	0.358
RT of LR yes vs. no	0.365				–				–
ST of LR yes vs. no	–				–				–
Growthrate of LR <0.9 vs >0.9 Cm/months	<0.001				0.008				0.152

Entire cohort					LMS subgroup				
	1ST PRESENTATION OF DM							1ST RELAPSE	
	p-value (log-rank)	HR	95% CI	*p*-value (Cox)		*p*-value (log-rank)	HR	95% CI	*p*-value (Cox)
Age	0.334				Age		0.988		
Sex	0.237				Sex		0.547		
Tumor histology	0.651								
Tumor grade	0.056				Tumor grade		0.582		
G1 vs. G3					G1 vs. G3				
G2 vs. G3					G2 vs. G3				
Interval to DM <12 months vs. >12 months	0.002	0.31	0.11–0.82	0.019	Interval to relapse <12 months vs. >12 months		0.007	0.14	
Resection of DM yes vs. no	0.002	2.85	1.20–6.79	0.018	Resection of relapse yes vs. no		0.002	0.19	
RT of DM yes vs. no	0.731				RT of relapse yes vs. no		0.777		
ST of DM yes vs. no	0.102				ST of relapse yes vs. no		0.018	1.17	0.30–4.58

Overall survival						
Entire cohort						
3RD LR		4TH LR				
HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)	HR	95% CI	*p*-value (Cox)
1.03	0.97–1.09	0.326	0.054 0.596 0.156	1.03	0.98–1.09	0.212
0.00 0.00 1.05	0–0 0–0 0.27–4.07	0.998 0.989 0.948	0.050			
			0.075 0.086 0.144 – –	2.02	0.50–8.21	0.323
LPS subgroup						
3RD LR		4TH LR				
HR	95% CI	*p*-value (Cox)	*p*-value (log-rank)	HR	95% CI	*p*-value (Cox)
1.08	1.01–1.16	0.017	0.021 0.599 0.061	1.06	0.99–1.12	0.082
			0.111 0.037 0.270 – – 0.071	0.46	0.09–2.27	0.342
LMS subgroup						
1ST RELAPSE						
0.03–0.80 0.04–0.98	0.027 0.048					
0.822						

LPS liposarcoma; *LMS* leiomyosarcoma; *LG-LPS* low grade liposarcoma; *HG-LPS* high grade liposarcoma; *NOS* undifferentiated sarcoma (not otherwise specified); *MVR* multivisceral resection; *RT* radiation therapy; *ST* systemic therapy. Missing values due to stepwise variable selection in cases of low number of events.

[13,25,35–39]. Yet, the randomized STRASS trial (EORTC 62092), which compared preoperative RT followed by surgery versus surgery alone in RPS, failed to demonstrate overall beneficial effects of preoperative RT with exception of the LPS subgroup [40]. In our cohort of LPS patients we could not confirm these effects. However, this might be due to the small sample size, heterogenous mode of RT application (preoperative/postoperative with and without intraoperative boosts) and the retrospective nature of this study. In general, however, it appears convincing that local therapies are more effective in LPS than LMS and it seems plausible that tumors which tend to reoccur with DM might benefit from additional systemic treatment [41]. The prospective randomized STRASS 2 trial (NCT04031677), which investigates preoperative systemic therapy plus surgery versus surgery alone in primary high-grade dedifferentiated LPS and LMS will provide evidence on this topic. Nonetheless for recurrent tumors, and multiple recurrent tumors in particular, such kind of evidence can hardly be achieved as it would necessitate randomized-controlled trials comparing surgical as well as multimodal treatment approaches. Due to the rareness and heterogeneity of the disease this appears improbable, and it is more likely that retrospective studies will remain the source of comparative data on this topic [42].

Finally, surgery is the mainstay of curative treatment in RPS, and it appears that this applies not only for primary, but also for recurrent tumors. Yet, multiple re-operations may seriously diminish quality of life after curative therapy and careful patient selection, considering patient's performance status as well as tumor biology, is therefore mandatory [10,22,41,43–47]. In this context, RPS specific

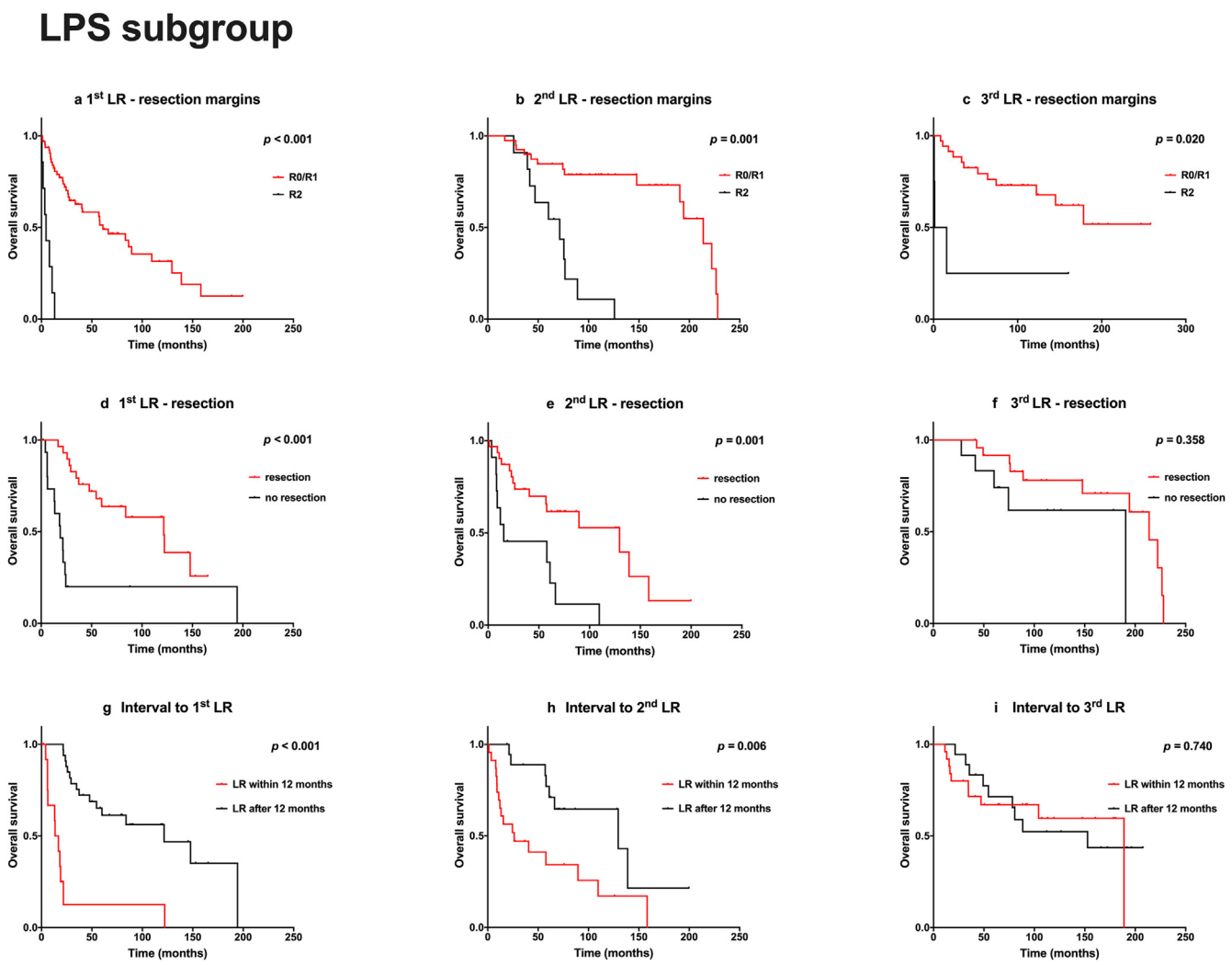

Fig. 2. *Kaplan-Meier curves with log-rank test, indicating overall survival after development of first, second and third local recurrences (LR) in the liposarcoma (LPS) subgroup (a-c) and in the LPS subgroup with preceding resection at our institution (d-i).* (a) Significance of resection margins (R0/R1 versus R2) concerning OS upon resection of 1st LR (estimated 5-year OS: R0/R1: 52%, R2: 0%). (b) Significance of resection margins (R0/R1 versus R2) upon resection of 2nd LR (estimated 5-year OS: R0/R1: 85%, R2: 64%). (c) Significance of resection margins (R0/R1 versus R2) upon resection of 3rd LR (estimated 5-year OS free survival: R0/R1: 80%, R2: 25%). (d) Significance of resection (versus no resection) of 1st LR (estimated 5-year OS: resection: 64%, no resection: 20%). (e) Significance of resection (versus no resection) of 2nd LR (estimated 5-year OS: resection: 62%, no resection: 46%). (f) Significance of resection (versus no resection) of 3rd LR (estimated 5-year OS: resection: 92%, no resection: 83%). (g) Significance of interval until 1st LR (within 12 months versus after 12 months; estimated 5-year OS: within 12 months: 9%, after 12 months: 61%). (h) Significance of interval until 2nd LR (within 12 months versus after 12 months; estimated 5-year OS: within 12 months: 34%, after 12 months: 77%). (i) Significance of interval until 3rd LR (within 12 months versus after 12 months; estimated 5-year OS: within 12 months: 71%, after 12 months: 76%).

nomograms to predict the individual risk of local or distant failure are an interesting tool to facilitate clinical decision making [42,48]. The advantage of nomograms is that not only tumor biology but also individual patient risk factors and previous treatments are considered. A well-established and externally validated nomogram by Gronchi et al. is available for primary tumors [29,49,50]. Nomograms likewise exist for first LR as well as DM, but have not yet been externally validated [14,29]. However, these nomograms only display the individual risk at a certain time point after surgery, and cannot incorporate the change in risk for DM or LR during the time course of the disease – as the risk of DM seems to plateau after 5 years, whereas the risk of LR persists [17,42]. Moreover, so far there are no nomograms predicting survival in patients with more than one LR [42]. Nevertheless, nomograms are a useful tool for personal risk assessment and should be integrated into clinical practice to support therapy decisions [42,48].

Major limitations of our present study reside in its retrospective, single-centered nature and its relatively small sample size regarding subgroup analyses, and call for careful interpretation of significant findings. Besides the selection bias residing from the retrospective design, additional bias exists concerning resection of recurrences. Indeed, a considerable fraction of patients with irresectable or multifocal LR or DM and external treatment of primary tumors may not have presented at our department, whereas patients with resectable LR or DM were often transferred to our tertiary care center.

Regardless, this is to our knowledge the largest case series, analyzing oncological outcome after the development of second, third and fourth recurrence, supporting current recommendations that RPS patients benefit from surgical resection, whenever

complete resection is technically possible and justifiable regarding patients' performance status [17,18,20,22,47,51].

CRediT authorship contribution statement

Franziska Willis: Conceptualization, Methodology, Formal analysis, Investigation, Visualization, Writing – original draft. **Julian Musa:** Quality control of data and algorithms, Writing – review & editing. **Simon Schimmack:** Investigation, Writing – review & editing. **Ulf Hinz:** Methodology, Validation, Formal analysis. **Gunhild Mechtersheimer:** Resources, Writing – review & editing. **Matthias Uhl:** Resources, Writing – review & editing. **Thomas Schmidt:** Writing – review & editing. **Stefan Fröhling:** Resources, Writing – review & editing. **Markus W. Büchler:** Resources, Supervision. **Martin Schneider:** Conceptualization, Validation, Visualization, Resources, Writing – review & editing, Supervision.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.04.040.

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Abbreviations

RPS: retroperitoneal soft tissue sarcoma
OS: overall survival
LR: local recurrence
DM: distant metastases
PFS: progression free survival
EC: entire cohort (all 332 patients)
LPS: liposarcoma
LMS: leiomyosarcoma
LG-LPS: low grade liposarcoma
HG-LPS: high grade liposarcoma
WD-LPS: well differentiated liposarcoma
DD-LPS: dedifferentiated liposarcoma
NOS: undifferentiated sarcoma (not otherwise specified)
SFT: solitary fibrous tumor & other tumors with intermediate malignancy
MVR: multivisceral resection
RT: radiation therapy
ST: systemic therapy
IORT: intraoperative radiation therapy

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RESEARCH

Temporal variation in nutritional status and preoperative anemia among patients with retroperitoneal soft tissue sarcoma: a retrospective longitudinal cohort study

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Abstract

Purpose Optimal management of retroperitoneal soft tissue sarcoma (RPS) often requires extensive tumor resections, frequently involving gastrointestinal organs. The impact of these procedures on the nutritional status and hemoglobin (Hb) levels of RPS patients remain unexplored. In this study, we aimed to evaluate preoperative nutritional status as well as the prevalence of anemia in RPS patients, and to investigate longitudinal changes throughout the disease course in order to identify potential strategies for prehabilitation.

Materials and methods Patients undergoing resection of primary and recurrent RPS at Heidelberg University Hospital were retrospectively analyzed. Changes in nutritional parameters and Hb levels throughout the disease course were analyzed using hierarchical linear regression models. Multivariable Cox regression analyses were performed to identify independent predictors of overall survival. Subgroup analyses were conducted for primary tumors, first, second and third recurrences.

Results Amongst 370 patients analyzed, comprising 219 with primary disease, we observed neither a significant prevalence of preoperative malnutrition nor notable changes in BMI or serum albumin levels throughout the disease course. Preoperative anemia affected up to 40% of RPS patients, and Hb levels significantly decreased over the course of the disease ($p=0.022$), particularly in correlation with the number of tumor resections performed ($p=0.010$). Low preoperative Hb levels were associated with increased 30-day mortality and they were identified as an independent prognostic factor for shorter overall survival in primary RPS as well as in second and third recurrences.

Conclusion Anemia screening should be performed preoperatively and during regular follow-ups to enable early-on therapy, thus potentially improving patient outcomes in RPS.

Keywords Retroperitoneal soft tissue sarcoma · Multivisceral resection · Overall survival · Nutritional status · Hemoglobin · Preoperative anemia

Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body mass index
CCI	Comprehensive Complication Index
CI	Confidence interval
CRP	C-reactive protein
DD-LPS	Dedifferentiated liposarcoma
DM	Distant metastases
FNCLLCC	Fédération Nationale Des Centres de Lutte Contre Le Cancer
Hb	Hemoglobin
HLM	Hierarchical linear models
IQR	Interquartile range

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LR	Local recurrence
LMS	Leiomyosarcoma
LoS	Length of stay
LPS l	Liposarcoma
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MVR	Multivisceral resection
NOS	Undifferentiated sarcoma (not otherwise specified)
OS	Overall survival
RPS	Retroperitoneal soft tissue sarcoma
SFT	Solitary fibrous tumor & other tumors with intermediate malignancy
WHO	World Health Organization

Introduction

Retroperitoneal soft tissue sarcomas (RPS) represent a rare and diverse subset of tumors, comprising approximately 1% of adult malignancies [1]. While average 5-year overall survival rates of 67% and 10-year overall survival rates of 46% can be achieved, high recurrence rates (ranging from 40 to 60%) beyond the five-year mark present an ongoing challenge [2–4]. Optimal management revolves around complete tumor resection, the cornerstone in treating both primary and recurrent tumors [5–7]. For liposarcoma, the most frequent histological subtype among RPS, compartmental resection has emerged as the standard surgical approach in an effort to minimize the likelihood of incomplete resection margins [8–10]. This approach entails the comprehensive removal of all adjacent organs and structures associated with the tumor, often requiring extensive multivisceral resections (MVR) [8–10]. MVR is likewise frequently performed in the treatment of other RPS entities [10, 11]. Consequently, patients with RPS undergo extensive surgical procedures, often requiring (partial) resection of organs of the digestive system [11, 12]. The impact of these operations on the nutritional status of RPS patients has not been investigated yet. Only few studies with a limited number of patients have investigated the role of preoperative nutritional status on postoperative outcomes in RPS, revealing high malnutrition rates (40–50%) [13–15]. However, changes of nutritional status due to disease recurrence and repeated operations remain unexplored.

The aim of this study was to assess the preoperative nutritional and anemia status in RPS patients, and to investigate alterations occurring throughout the course of the disease in order to delineate potential prehabilitation strategies.

Patients and methods

Patients

Following approval by the ethics committee of the University of Heidelberg (Approval No. S-649/2012), we conducted a retrospective analysis encompassing all patients who underwent surgical resection for primary, recurrent, or metastatic RPS between October 2001 and December 2019 at Heidelberg University Hospital, Department of General, Visceral, and Transplantation Surgery (tertiary care center). Patients with gastrointestinal stromal tumors and those with embryonal, pediatric, or gynecological soft tissue sarcomas were excluded from the study.

In all patients, the primary objective was to achieve macroscopically complete tumor resection, including en-bloc resection of adjacent organs (comprehensive resection) in case of liposarcoma histology [8–10]. All other entities were treated to achieve microscopically complete tumor resection margins. Decisions regarding the necessity of re-resection for recurrent tumors as well as the utilization of additional chemotherapy and radiation therapy were made on a case-by-case basis following review by a multidisciplinary tumor board. Postoperative complications were classified according to the Clavien-Dindo classification system and the Comprehensive Complication Index (CCI) [16]. To provide a comprehensive representation of the cumulative burden of postoperative complications over the entire course of the disease, CCI scores from each hospitalization were aggregated resulting in a cumulative CCI score with a minimum value of 0 and no predefined maximum threshold. To evaluate the preoperative nutritional status, preoperative Body Mass Index (BMI), preoperative albumin as surrogate parameter for protein status, and hemoglobin (Hb) as well as the mean corpuscular volume (MCV) and the mean corpuscular hemoglobin (MCH), were assessed. In case of multiple tumor resections at our department, the parameters mentioned above were assessed within two days before each operation. Hypoalbuminemia was defined as serum albumin < 30 g/l. Anemia was classified according to the WHO as Hb concentration of < 12.0 g/dl in women and < 13.0 g/dl in men. Anemia was categorized into mild (Hb 11.0–11.9 g/dl for women and Hb 11.0–12.9 g/dl for men), moderate (Hb 8.0–10.9 g/dl), and severe (Hb < 8.0 g/dl).

The study was registered at the German Clinical Trials Register (DRKS00034988).

Statistics

Hierarchical linear models (HLM) were performed to evaluate changes of nutritional parameters (hemoglobin, albumin, BMI), which were assessed repeatedly during the

course of the disease. For this purpose, for each patient with more than one tumor resection performed at our department, preoperative parameters before the initial and before the last surgery were taken into account. In addition, we investigated whether changes in these parameters were associated with the performance of MVR (defined as resection of three or more organs), the number of surgeries and the cumulative complication burden during the entire course of the disease. This was realized by introducing 2-way interaction terms. The estimations in the linear hierarchical models were computed as maximum likelihood estimators using the MIXED procedure in SPSS.

Multivariable linear regression models were used to test associations between nutritional parameters and the CCI as well as the length of hospital stay (LoS). To correct for non-normal/heteroskedastic residuals, wild bootstrapping with 2000 replications was performed [17]. Regression models were only calculated when the ANOVA indicated a good fit for the data ($p \leq 0.05$). In case of dichotomous dependent variables (transfusion of blood components) a logistic regression analysis was performed.

Overall survival (OS) was defined as the date of surgery to the date of death. For alive patients, follow-up was censored at the date of last disease assessment.

Survival was estimated applying the Kaplan-Meier method and is presented as median with 95% confidence interval (CI). Multivariable Cox regression analyses including all potential predictors derived from the univariate Kaplan-Meier analysis (log rank: $p < 0.1$) were performed to identify independent prognostic factors for OS. Possible predictors were resection status (R0/R1 vs. R2), grading according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), histologic subtype, tumor size, MVR, multifocality, patient age, and sex. For nutritional parameters only albumin and Hb were considered to avoid bias due to too many missing values regarding BMI.

Resection status, tumor grade, histology, MVR, multifocality and sex were modeled as categorical using dummy variables. Age, tumor size, albumin and Hb were modeled as continuous variables. In respect of number of events, we used forward and backwards step-wise variable selection [18].

Analyses were performed considering patients with primary tumors, first, second and third recurrences (see Fig. 1). Patients with incomplete datasets were excluded.

SPSS (Version 29.0.2.0) was used for all statistical analyses. The level of statistical significance was set to $p \leq 0.05$ (two-tailed).

Results

Clinicopathological features and nutritional status

A total of 370 patients who underwent resection of RPS at the University of Heidelberg Department of General, Visceral, and Transplantation Surgery between October 2001 and December 2019 were identified. The analysis included 219 patients with primary disease, 114 patients with first recurrences, 76 patients with second recurrences, and 58 patients with third recurrences (Fig. 1). Demographic, clinicopathological, and treatment details are presented in Table 1.

Details on nutritional status are provided in Table 2. Due to missing information regarding height and weight, BMI values were available for only 250 patients (69%). Among them, the majority was overweight or obese (137 patients, 55% of patients with available datasets), while underweight patients constituted a minority (13 patients, 5% of patients with available datasets). Similar distributions were observed for patients before resection of a primary tumor. However, with an increasing number of resections, the proportion of normal-weight and underweight patients showed an upward trend.

Concerning serum albumin levels, only a small proportion of patients exhibited values below the reference range. Concomitant serum CRP levels were low, excluding general inflammation as a potential cause for low serum albumin.

At primary presentation, 150 patients (41%) presented with low Hb values. Of those, 71 patients (19%) were diagnosed with moderate or severe anemia. Similar proportions apply to the subgroup of patients with primary tumors. In the entire cohort as well as all subgroups, the majority of these anemias were normochromic and normocytic. However, a notable proportion was microcytic and/or hypochromic (20–40%), suggesting potential iron deficiency (see Supplementary Table 1).

Alteration in nutritional parameters upon repeated resection of RPS

In patients undergoing repeated tumor resection, BMI and serum albumin exhibited no significant change over time (all $p > 0.05$). By contrast, hierarchical linear regression analysis (HLM) revealed a significant decrease of Hb values over the course of the disease ($\beta = -0.98 \pm 0.43$, $t = -2.3$, $df = 345$, $p = 0.022$, $r = 0.12$) (see Fig. 2a). Intriguingly, the decline in Hb was significantly associated with an increasing number of RPS resections ($\beta = 0.30 \pm 0.11$, $t = 2.3$, $df = 365$, $p = 0.010$, $r = 0.13$) (see Fig. 2b). However, decreasing Hb values were not associated with the performance of MVR or the cumulative complication burden (all $p > 0.05$).

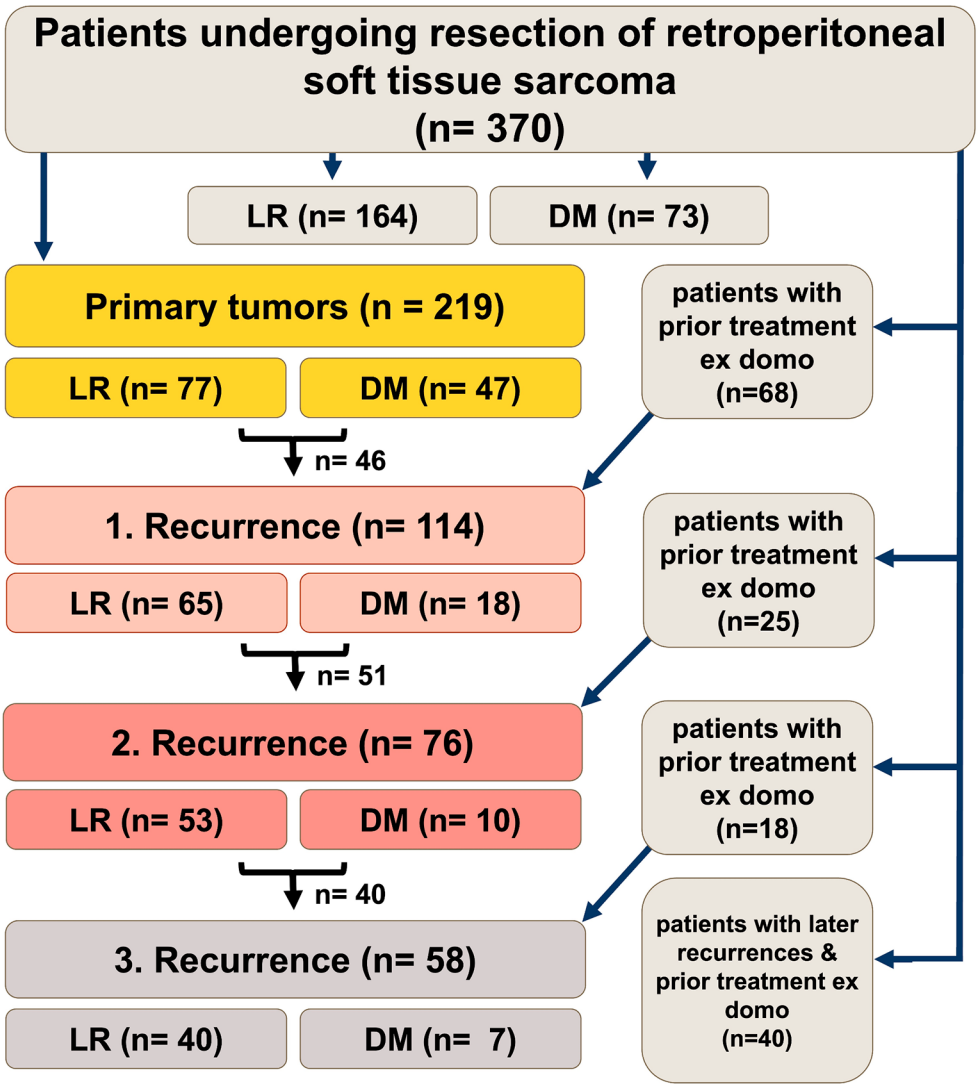

Fig. 1 Overview of patients included in this analysis. In total, 370 patients undergoing resection of retroperitoneal soft tissue sarcoma (RPS) were included. 164 patients developed local recurrence (LR), and 73 patients developed distant metastases (DM). 219 patients presented with primary disease. 151 patients underwent initial treatment of primary disease at other hospitals

Significance of preoperative nutritional and anemia status on morbidity, blood transfusion, and length of hospital stay

Multivariable linear regression models were employed to identify parameters associated with postoperative complications (CCI) and length of hospital stay (LoS) (see Supplementary Tables 2 and 3). In the entire cohort, only higher patient age at the time of the operation was found to be associated with an increased likelihood of postoperative morbidity (β: 0.26 ± 0.11; $p = 0.017$). A similar pattern of findings was observed in the analysis focusing on primary tumors alone (β: 0.25 ± 0.11; $p = 0.029$). Neither low albumin nor low Hb values were linked to the occurrence of postoperative complications. However, 30-day mortality was significantly higher in patients with preoperative anemia compared to patients with normal Hb-values after resection of a primary tumor (9.4% vs. 0.8%; $p = 0.004$). A similar trend was observed for resection of first and second recurrences, but did not reach statistical significance (first: 3.3% vs. 0.0%; $p = 0.100$; second: 14.3% vs. 1.9%; $p = 0.055$).

Concerning LoS, surrogate parameters for nutritional status showed no association with prolonged LoS in either the overall cohort or any subgroup analyses (all $p > 0.05$, see Supplementary Table 3).

Logistic regression models were used to investigate the impact of nutritional parameters on the necessity of perioperative transfusions of blood components (see Supplementary Table 4). As expected, the need for perioperative blood component transfusions within the entire cohort was significantly associated with lower preoperative Hb levels (OR: 0.702; 95% CI: 0.594–0.83; $p < 0.001$) and increased intraoperative blood loss (OR: 1.002; 95% CI. 1.001–1.002; $p < 0.001$). Similar associations were observed concerning the subgroup of primary tumors (Hb: OR: 0.669; 95% CI: 0.527–0.849; $p = 0.001$; blood loss: OR: 1.002; 95% CI: 1.001–1.002; $p < 0.001$). Notably, in the case of tumor recurrences, the transfusion of blood components was independent

Table 1 Demographic, clinical, and pathological characteristics

	ALL PATIENTS		PRIMARY TUMORS		1st recurrence		2nd recurrence		3rd Recurrence	
n	370		219		114		76		58	
AGE. median (IQR). years	58.5	(47.0–66.0)	57.0	(49.0–67.0)	59.0	(50.0-67.3)	60.0	(53.4–68.0)	61.5	(53.0–68.0)
SEX (%)										
Male	195	(52.7)	114	(52.1)	63	(55.3)	46	(60.5)	29	(50.0)
Female	175	(47.3)	105	(47.9)	51	(44.7)	30	(39.5)	29	(50.0)
TUMOR PRESENTATION (%)										
Primary tumors	219	(59.2)	219	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
Local recurrence	122	(33.0)	0	(0.0)	109	(95.6)	70	(92.1)	54	(93.1)
Distant metastases	11	(3.0)	0	(0.0)	3	(2.6)	4	(5.3)	1	(1.7)
Primary tumor and distant metastases	8	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Local recurrence and distant metastases	10	(2.7)	0	(0.0)	2	(1.8)	2	(2.6)	3	(5.2)
HISTOLOGY (%)										
DD LPS	178	(48.1)	89	(40.6)	72	(63.2)	58	(76.3)	40	(69.0)
WD LPS	49	(13.2)	33	(15.1)	12	(10.5)	5	(6.6)	11	(19.0)
LMS	65	(17.6)	46	(21.0)	8	(7.0)	3	(3.9)	3	(5.2)
NOS	22	(5.9)	14	(6.4)	7	(6.1)	3	(3.9)	0	(0.0)
Other	39	(10.5)	25	(11.4)	11	(9.6)	4	(5.3)	1	(1.7)
SFT	17	(4.6)	12	(5.5)	4	(3.5)	3	(3.9)	3	(5.2)
TUMOR GRADE (%)										
G1	47	(12.7)	34	(15.5)						
G2	107	(28.9)	75	(34.2)						
G3	103	(27.8)	61	(27.9)						
does not apply	113	(30.5)	49	(22.4)	114	(100.0)	76	(100.0)	58	(100.0)
RESECTION STATUS (%)										
R0/R1	327	(88.4)	206	(94.1)	106	(93.0)	63	(82.9)	53	(91.4)
R2	43	(11.6)	13	(5.9)	8	(7.0)	13	(17.1)	5	(8.6)
TUMORSIZE. median (IQR). cm	12.0	(7.0–20.0)	14.0	(8.5–24.0)	7.000	(4.2–12.0)	7.6	(4.8–12.0)	7.0	(3.5–15.6)
MULTIFOCALITY (%)	55	(14.9)	11	(5.0)	22	(19.3)	24	(31.6)	20	(34.5)
MVR (%)	153	(41.4)	109	(49.8)	29	(25.4)	14	(18.4)	10	(17.2)
BLOOD LOSS. median (IQR). ml	600	(300–1500)	700	(300–1500)	500	(200–1200)	450	(200–900)	300	(100–625)
TRANSFUSION (%)	127	(34.3)	78	(35.6)	31	(27.2)	14	(18.4)	9	(15.5)
CLAVIEN DINDO≥3 (%)	29	(23.2)	50	(22.8)	29	(25.4)	16	(21.1)	9	(15.5)
CCI. median (%) only w/ complications	33.7	(20.9–51.9)	29.6	(20.9–42.6)	33.5	(20.9–54.2)	33.7	(22.2–47.7)	37.1	(20.9–58.1)
30-DAY-MORTALITY (%)	14	(3.8)	9	(4.1)	1	(0.9)	4	(5.3)	1	(1.7)
FOLLOW-UP. median (IQR). months										
From OP	44.1	(16.9–89.2)	49.3	(19.0-98.8)	42.7	(16.9–85.4)	38.6	(13.4–71.1)	33.7	(17.4–75.5)
From first diagnosis	65.8	(27.6-128.6)	50.9	(21.9–102.0)	79.6	(40.2-147.7)	92.2	(60.2-160.4)	144.4	(80.7-199.7)

Table 1 (continued)

	ALL PATIENTS		PRIMARY TUMORS		1st recurrence		2nd recurrence		3rd Recurrence	
From OP if alive	73.3	(38.4-118.9)	80.9	(45.1–125.0)	56.8	(30.6-117.7)	42.7	(18.2–78.5)	43.0	(13.9–92.1)
From first diagnosis if alive	95.3	(50.2-146.4)	84.0	(49.3-131.3)	111.0	(68-153.7)	138.5	(73.5-170.7)	149.7	(93-200.1)

IQR interquartile range, *DD-LPS* dedifferentiated liposarcoma, *WD-LPS* well differentiated liposarcoma, *LMS* leiomyosarcoma, *NOS* undifferentiated sarcoma (not otherwise specified), *SFT* solitary fibrous tumor & other tumors with intermediate malignancy, *MVR* multivisceral resection (≥3 organs), *CCI* Comprehensive Complication Index

from preoperative Hb values, and manifested an association solely with intraoperative blood loss (first recurrence: OR: 1.001 95% CI: 1.000-1.002; $p=0.001$; second recurrence: OR: 1.003; 95% CI: 1.001–1.005; $p=0.002$). Neither preoperative albumin levels nor the performance of MVR had an impact on perioperative blood transfusions across any of the cohorts.

Impact of nutritional parameters on overall survival

The median overall survival (OS) for the entire cohort following initial presentation at Heidelberg University Hospital was 68.5 months (95% CI: 53.5–83.6). Specifically for primary tumors, the median OS was 121.5 months (95% CI: 74.2–168.8). Multivariable Cox regression analyses were conducted to explore the impact of nutritional parameters after the first to fourth tumor resection (see Table 3). Preoperative serum albumin levels did not exert an influence on OS regarding the resection of primary tumors or the resection of second and third recurrences (all $p>0.05$). Notably, only following the resection of the first recurrence low preoperative albumin levels were associated with reduced OS (HR = 0.89; 95% CI: 0.84–0.95; $p=0.001$). Importantly, in this subgroup, serum albumin was below the reference value in only 3 patients (2.6%). Interestingly, low Hb values were independently linked to reduced OS after the resection of primary tumors (HR = 0.87; 95% CI: 0.77–0.98; $p=0.020$), second recurrences (HR = 0.78; 95% CI: 0.62–0.97; $p=0.027$), as well as third recurrences (HR = 0.74; 95% CI: 0.55-1.00; $p=0.050$) (see Fig. 3). However, in patients with reduced Hb-values the etiology of anemia did not affect survival rates (see Supplementary Fig. 1).

Discussion

To our knowledge, this is the first study to retrospectively evaluate nutritional and anaemic status during the course of RPS, with a focus on multivisceral and repeated tumor resections.

Using albumin and BMI to assess nutritional status, we found no severe malnutrition in our patient cohort, which is in contrast to previous studies where malnutrition rates in RPS patients were as high as 46–52% [13, 14]. Hypoalbuminemia was less common in our cohort (< 5%) compared to other RPS cohorts (16%) [13, 19], which may explain the lack of association with increased morbidity or prolonged hospital stay reported in previous studies [13, 14, 19]. Another reason may be that the assessment of nutritional status in this analysis differed from the aforementioned studies. Due to its retrospective nature, this study evaluated standard preoperative parameters, which may

Table 2 Overview of parameters assessed for evaluation of nutritional status

n	ALL PATIENTS		PRIMARY TUMORS		1st recurrence		2nd recurrence		3rd Recurrence	
	370		219		114		76		58	
HEIGHT, median (IQR), cm	172.00	(164.0-180.0)	172.0	(165.0-180.0)	172.0	(164.0-180.0)	174.0	(165.0-183.0)	170.0	(164.0-181.0)
Missing values	113	(30.5)	62	(28.3)	37	(32.5)	14	(18.4)	5	(8.6)
WEIGHT, median (IQR), kg	76.0	(65.0–87.0)	76.0	(65.0-87.8)	74.5	(63.5–88.3)	75.0	(62.0–85.0)	70.0	(63.0–82.0)
Missing values	113	(30.5)	63.0	(28.8)	36.0	(31.6)	13.0	(17.1)	5.0	(8.6)
BMI, median (IQR), kg/m2	25.4	(22.6–28.2)	25.5	(22.5–28.8)	24.80	(22.8–28.8)	24.80	(22.2–27.7)	24.50	(21.3–27.1)
Underweight (%)	13	(3.5)	7	(3.2)	4	(3.5)	4	(5.3)	6	(10.3)
Normal weight (%)	104	(28.1)	61	(27.9)	37	(32.5)	29	(38.2)	26	(44.8)
Overweight (%)	93	(25.1)	55	(25.1)	24	(21.1)	21	(27.6)	15	(25.9)
Obesity I°(%)	29	(7.8)	21	(9.6)	8	(7.0)	7	(9.2)	5	(8.6)
Obesity II°(%)	11	(3.0)	8	(3.7)	4	(3.5)	1	(1.3)	1	(1.7)
Obesity III°(%)	4	(1.1)	2	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Missing (%)	116	(31.4)	65	(29.7)	37	(32.5)	14	(18.4)	1	(1.7)
ALBUMIN, median (IQR), g/l	43.4	(40.2–45.9)	43.5	(40.1–45.8)	44.9	(42.0-46.7)	43.9	(41.9–46.0)	44.0	(42.3–46.4)
Normal	311	(84.1)	181	(82.6)	95	(83.3)	65	(85.5)	49	(84.5)
Low (%)	16	(4.3)	9	(4.1)	3	(2.6)	1	(1.3)	0	(0.0)
Missing (%)	43	(11.6)	29	(13.2)	16	(14.0)	10	(13.2)	9	(15.5)
CRP, median (IQR), mg/l	6.3	(1.0-29.3)	8.7	(2.0-42.7)	2.0	(1.0-12.1)	3.0	(1.0-15.3)	2.0	(1.0-5.8)
Missing (%)	44	(12.0)	20.0	(9.1)	9.0	(7.9)	13.0	(17.1)	0.0	(0.0)
HEMOGLOBIN, median (IQR), g/dl	12.9	(11.4–14.2)	12.8	(11.3–14.1)	13.6	(12.2–14.7)	13.6	(12.3–14.4)	13.0	(12.2–14.3)
No anemia (%)	220	(59.5)	126	(57.5)	83	(72.8)	52	(68.4)	36	(62.1)
Mild anemia (%)	79	(21.4)	48	(21.9)	17	(14.9)	10	(13.2)	7	(12.1)
Moderate anemia (%)	69	(18.6)	44	(20.1)	14	(12.3)	14	(18.4)	15	(25.9)
Severe anemia (%)	2	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Missing (%)	0.0	(0.0)	0.0	(0.0)	0.0	(0.0)	0.0	(0.0)	0.0	(0.0)

IQR interquartile range, *BMI* body mass index

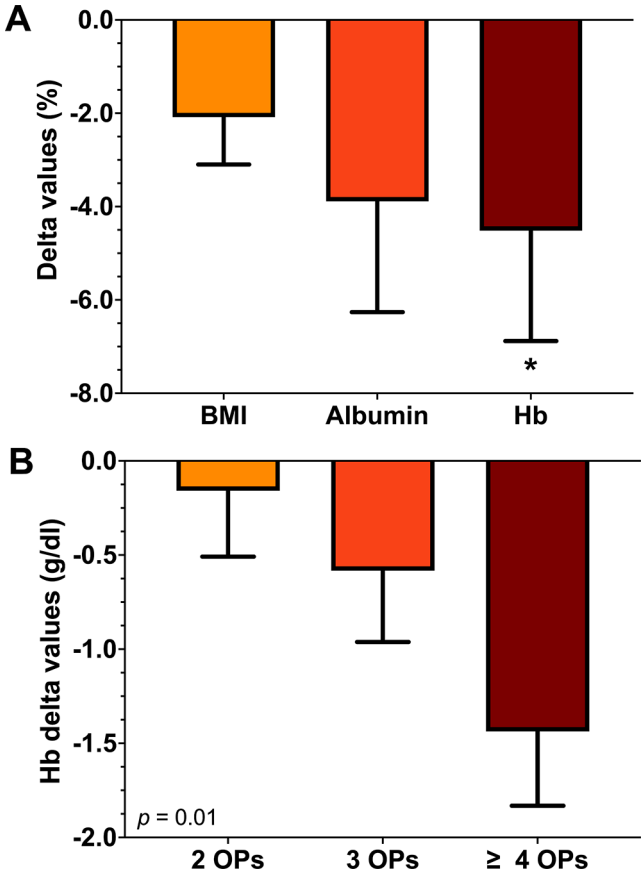

Fig. 2 Alterations in nutritional parameters *upon repeated resection of RPS* are illustrated as delta values, calculated as the difference between values before initial and final operations. Negative values indicate a decrease, while positive values indicate an increase over time. The transformation in nutritional parameters (**A**) is presented as delta values as a percentage of the initial value. The variation in hemoglobin values dependent on the number of tumor resections (**B**), is depicted as absolute delta values (g/dl) (**B**). *$p < 0.05$

not be ideal for a comprehensive assessment of nutritional status. Furthermore, BMI, although widely used, may not be a reliable reflection of nutritional status in RPS due to the weight of the tumor (up to 20 kg). In addition, obesity may mask malnutrition and catabolic states [15, 20]. Thus, current methods, including albumin or BMI-based scores, may not be sufficient to assess nutritional status in RPS, highlighting the need for RPS-specific tools, particularly in obese patients.

While the majority of patients in our cohort demonstrated normal albumin levels, a notable prevalence of anemia (40%) was observed, contrasting with the 4.3% rate in the general German population over 65 years old [21], as well as the approximately 25% rate in hospitalized patients admitted for surgery aged 50–80 years [22]. Of these anemic patients microcytic and/or hypochromic anemia, suggestive of iron deficiency, was present in 20–40% of patients, consistent with findings by Eisele et al., identifying 29% of anemias in the German population as attributable to iron deficiency [21]. Preoperative Hb values decreased over the disease course, which was independently associated with the number of resections performed but not with postoperative complications or MVR. Importantly, in our cohort, low preoperative Hb levels were identified as an independent prognostic factor for impaired overall survival after resection of primary tumors and recurrences, regardless of the etiology of anemia. Preoperative anemia has previously been associated with higher surgical complication rates, longer hospital stays and increased in-hospital mortality [22]. In our cohort, multiple regression analysis revealed no association between low Hb levels and complication rates or LoS, but higher 30-day mortality. Low preoperative Hb levels reportedly correlate with higher transfusion rates of blood components [22]. However, in our cohort, a correlation between preoperative anemia and the need for blood transfusions was only observed in primary tumors. This observation is consistent with findings by Wong et al., who showed that the need for blood transfusions in RPS patients depends predominantly on the complexity of the surgery and worse tumor biology than on preoperative anemia [23]. Interestingly, in gastric, colon, and bladder cancer, blood component transfusions have been associated with higher tumor recurrence rates [24–26]. Wong et al. did not observe worse overall or disease-free survival in RPS patients who received blood transfusions in multivariable analysis. However, as the authors observed strong associations between the need of transfusion of blood components and oncologic outcomes in univariate analysis, they argue that potential independent effects may be outweighed by tumor biology and comorbidity status [23]. Eventually, potential associations between low Hb values and impaired survival remain unexplained, whether as a reflection of comorbidity status, poor tumor biology, transfusion of blood components, higher in-hospital mortality, or, probably most likely, a combination of these factors. Nevertheless, improvement of Hb levels, especially in case of iron deficiency, which may constitute up to 40%, appears to be a prudent therapeutic approach. Vigilant monitoring of preoperative Hb levels as well as during follow-up is paramount, considering our observation of a substantial decline in Hb values during the course of the disease. This may facilitate prompt diagnosis of anemia, and allows for timely initiation of therapy, potentially contributing to improved patient outcomes and survival.

Major limitations of our present study reside in its retrospective nature, inherently carrying the risk of selection bias and incomplete data collection. As discussed above, we were constrained in the selection of additional parameters for assessing nutritional status, potentially overlooking relevant indicators. Moreover, the absence of comprehensive data on patient comorbidities likewise represents a study limitation.

Table 3 Predictors of overall survival in patients after resection of primary tumors and first to third tumor recurrences, according to univariable (log-rank) and multivariable (COX) analysis

OVERALL Survival

	PRIMARY TUMORS				1ST recurrence				2ND recurrence				3RD recurrence			
	***p*-value (log-rank)**	**HR**	**95% CI**	***p*-value (Cox)**	***p*-value (log-rank)**	**HR**	**95% CI**	***p*-value (Cox)**	***p*-value (log-rank)**	**HR**	**95% CI**	***p*-value (Cox)**	***p*-value (log-rank)**	**HR**	**95% CI**	***p*-value (Cox)**
AGE	<0.001	1.05	1.03–1.08	**<0.001**	0.060	1.02	1-1.05	0.081	0.073	1.01	0.98–1.03	0.714	0.341			
ASA SCORE ASA 3/4 vs. ASA 1/2	0.006	1.44	0.93–2.23	0.103	0.006	2.09	1.13–3.87	**0.019**	0.997				0.596			
TUMOR HISTOLOGY	<0.001			**0.001**	0.208				0.745				0.806			
WD-LPS vs. DD-LPS		1.02	0.26–3.95	0.981												
LMS vs. DD-LPS		2.70	1.53–4.76	**0.001**												
NOS vs. DD-LPS		1.95	0.81–4.72	0.137												
Other vs. DD-LPS		4.33	1.92–9.78	**<0.001**												
SFT vs. DD-LPS		0.84	0.1–7.12	0.870												
TUMOR GRADE	<0.001			**0.033**												
N.a. vs. G1		2.04	0.55–7.58	0.285												
G2 vs. G1		2.38	0.68–8.33	0.173												
G3 vs. G1		4.16	1.18–14.67	**0.027**												
TUMORSIZE	0.446				0.362				0.595				0.530			
MULTIFOCALITY yes vs. no	0.003	1.92	0.81–4.56	0.138	0.796				0.767				0.592			
MVR yes vs. no	0.002	1.96	1.21–3.17	**0.006**	0.308				0.002				0.669			
RESECTION STATUS R2 vs. R0/R1	<0.001	1.44	0.86–2.15	0.189	0.003	2.07	1.14–3.77	**0.018**	<0.001	2.42	1.34–4.37	**0.003**	<0.001			
HEMOGLOBIN	0.001	0.87	0.77–0.98	**0.020**	0.061	1.17	0.94–1.45	0.172	<0.001	078	0.62–0.97	**0.027**	0.001	0.74	0.55-1.00	**0.050**
ALBUMIN	0.278				<0.001	0.89	0.84–0.95	**0.001**	<0.001	1.06	0.95–1.18	0.318	<0.001	0.93	0.83–1.05	0.222

ASA American Society of Anesthesiologists; *CCI* Comprehensive Complication Index. *DD-LPS* dedifferentiated liposarcoma; *WD-LPS* well-differentiated liposarcoma *LMS* leiomyosarcoma;; *NOS* undifferentiated sarcoma (not otherwise specified); *N.A.* not applicable; *MVR* multivisceral resection. Missing values due to stepwise variable selection in cases of low number of events

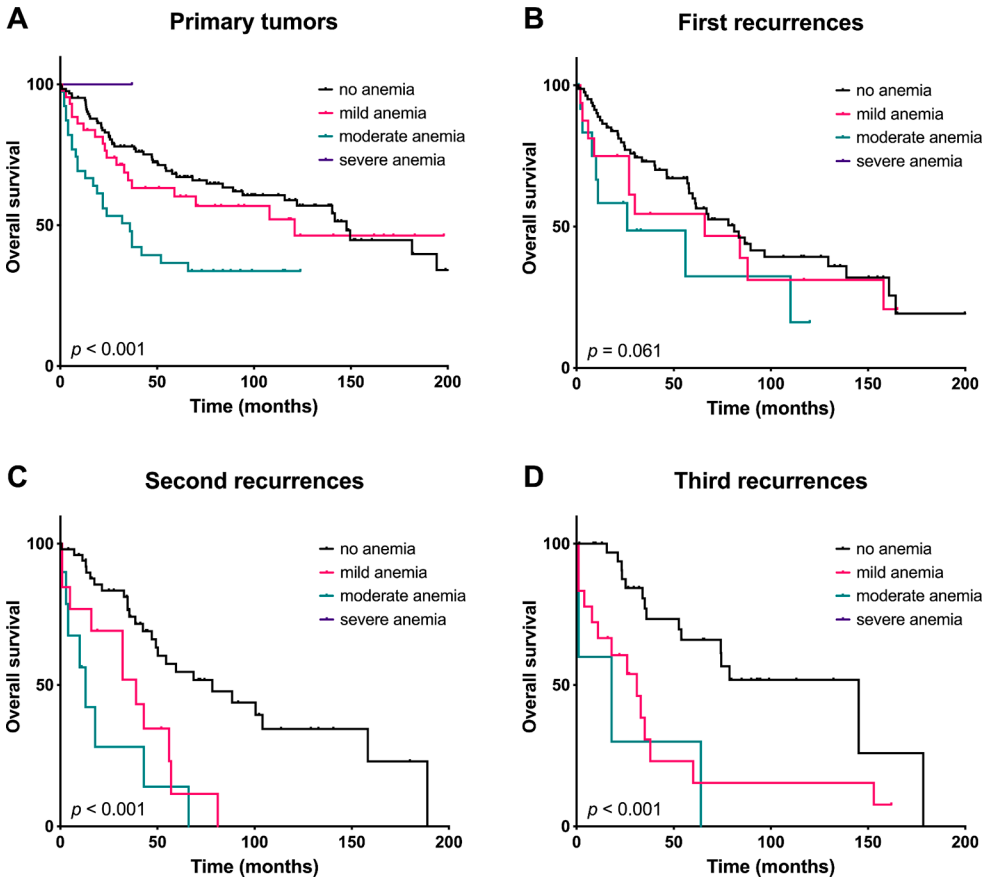

Fig. 3 Kaplan-Meier curves with log-rank test, indicating overall survival after resection of primary tumors (**A**) as well as after resection of first (**B**), second (**C**) and third tumor recurrences (**D**), depending on preoperative hemoglobin levels. Classification of anemia according to WHO: mild: Hb 11.0–11.9 g/dl in women; Hb 11.0–12.9 g/dl in men, moderate: Hb 8.0–10.9 g/dl, severe: Hb < 8.0 g/dl

These factors could confound associations between nutritional parameters and outcomes. Despite these limitations, the study has several strengths. To our knowledge, this study represents the largest cohort to date investigating nutritional status in RPS patients. Furthermore, it is the first to explore changes in nutritional status over the course of the disease - a critical consideration given the frequent need for multiple tumor resections in this patient population. Notably, our study likewise is the first to investigate the role of preoperative anemia in RPS patients. In this regard, we observed a considerable prevalence of preoperative anemia, and identified low preoperative Hb values as an independent factor associated with impaired overall survival. Recently it has been demonstrated that nutritional screening and prehabilitation with oral high-protein nutritional support can mitigate malnutrition, leading to improved outcomes [13]. A similar prehabilitational approach should be considered for monitoring and managing Hb levels in RPS patients, with the aim of optimizing patient outcomes and enhancing survival rates.

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Data availability Research data can be assessed upon request for specific scientific projects.Please contact Franziska.willis@chiru.med.uni-giessen.de.

Declarations

Competing interests The authors declare no competing interests.

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Long-term quality of life after resection of retroperitoneal soft tissue sarcoma

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ABSTRACT

Introduction: Retroperitoneal soft tissue sarcoma (RPS) is characterized by high recurrence rates. Since complete tumor resection, often necessitating multivisceral resection, enables long-term survival in both primary and recurrent disease, health related quality of life (QoL) after RPS resection has attracted increasing interest. However, data regarding this topic is limited. Here, we multidimensionally assessed long-term QoL after RPS resection.

Methods: Five previously validated (1. EORTC QLQ-C30, 2. WEMWBS, 3. FoP-Q-SF, 4. PC-PTSD, 5. Pro-CTCAE) were sent to patients having undergone resection of primary, recurrent and metastasized RPS at Heidelberg University Hospital between 10/2001 and 12/2020. Multivariable linear regression models were used to test associations between clinical/demographic variables and patient reported outcomes (PROs).

Results: Questionnaires were answered by 127 patients (71% response rate). The median interval between RPS diagnosis and assessment of PROs was 80 months. The overall Global Health score was 64.1 and comparable to the general German population. RPS patients reported deficits regarding emotional and social functioning, whereas physical limitations were less pronounced. Besides diarrhea, abdominal symptoms were comparable to the overall population. Tumor recurrences, the number of surgeries, multivisceral resections or postoperative complications did not significantly affect long-term QoL ratings.

Conclusion: RPS patients rate their QoL relatively high, even after multiple and multivisceral resections. Psychosocial well-being should be monitored in follow-up sessions to offer tailored support if necessary, thus improving postoperative care.

1. Introduction

Retroperitoneal soft tissue sarcomas (RPS) are rare and heterogenous tumors that account for about 1% of adult malignancies [1]. With an average 5-year overall survival of 67% and a 10-year overall survival of 46% significant long-term survival can be achieved, however, recurrence rates remain high (40–60%) and do not plateau after five years [2–4]. Complete macroscopic tumor resection is the mainstay of therapy for both primary and recurrent tumors [5–8]. To minimize the probability of tumor-infiltrated resection margins, thus reducing local recurrence rates, compartmental resection has become a standard surgical approach for RPS [5]. This approach includes resection of all organs and structures adjacent to the tumor, frequently necessitating multivisceral resection (MVR) [5,9,10]. RPS patients consequently undergo

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Abbreviations

CCI	comprehensive complication index
DD-LPS	dedifferentiated liposarcoma
DM	distant metastases
EBRT	external beam radiation therapy
IORT	intraoperative radiation therapy
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer - Core Quality of Life Questionnaire,
FoP	fear of progression
FoP-Q-SF	Fear of Progression Questionnaire (short form)
IQR	interquartile range
LMS	leiomyosarcoma
LPS	liposarcoma
LR	local recurrence
MVR	multivisceral resection
MWB	mental well-being
PC-PTSD	Primary Care - Posttraumatic stress disorder Screening
Pro-CTCAE®	Patient Reported Outcomes – Common Terminology Criteria for Adverse Events
PROs	patient reported outcomes
PTSD	posttraumatic stress disorder
QoL	quality of life,
RPS	retroperitoneal soft tissue sarcoma
RT	radiation therapy
ST	systemic therapy
WD-LPS	well-differentiated liposarcoma
WEMWBS	Warwick-Edinburgh Mental Well-Being Scale

extensive surgeries and have to indefinitely attend regular follow-up evaluations to monitor recurrence [5,7]. Albeit these factors pose particular physical and psychological challenges, data concerning the impact of RPS surgery on patients' quality of life (QoL) are scarce. The PROSa study as well as the SURVSARC study investigated health-related QoL in patients suffering from bone and soft tissue sarcomas, and reported significant differences in health-related QoL depending on sarcoma type and location [11,12]. For RPS, however, only few data from relatively small patients' cohorts are available so far [12–16]. Analyses based on an Italian cohort revealed reasonable and improving QoL after MVR during the first year after surgery [13]. Alternative analyses from retrospective cohorts suggest that postsurgical QoL might be unstable initially, and that a follow-up for at least 2 years is necessary to evaluate long-term postoperative QoL [12,14,15]. Neither the impact of multiple operations on QoL, nor mental well-being (MWB) and fear of progression (FoP) as addressed by specific questionnaires have been investigated in RPS patients yet. We therefore aimed to analyze patient reported outcomes (PROs) after resection and re-resection of RPS regarding physical as well as emotional and social components.

2. Patients and methods

2.1. Patients

Following approval by the ethics board of the University of Heidelberg (S-593/2020), in May 2021 we contacted all patients who underwent resection of primary, recurrent or metastasized RPS between 10/2001 and 12/2020 at Heidelberg University Hospital, and who were still alive according to a prospectively maintained RPS database. Patients with gastrointestinal stromal tumors and those with embryonal, pediatric or gynecological RPS were excluded from the analysis. The study was registered at the *German Clinical Trials Register* (DRKS00023223).

All patients were treated to achieve macroscopically complete tumor resections with en-bloc resection of contiguous organs [17,18]. Indications for reresection of a recurrent tumor as well as additive chemo- and radiation therapy were determined on a case-by-case basis according to multidisciplinary tumor board review. Post-operative complications were graded according to Clavien-Dindo and the Comprehensive Complication Index (CCI) [19]. To represent the burden of postoperative complications during the entire course of the disease, CCI scores from each hospital stay were added, resulting in a cumulative CCI score with a minimum of 0 and no fixed maximum.

2.2. Assessment of quality of life

To multimodally assess different aspects of QoL, we sent 5 already validated questionnaires (1. EORTC-QLQ-C30, 2. WEMWBS, 3. FoP-Q-SF, 4. PC-PTSD, 5. Pro-CTCAE) to all patients. All questionnaires were also validated in German language [20–24].

The *European Organisation for Research and Treatment of Cancer - Core Quality of Life Questionnaire* (EORTC QLQ-C30) assesses general health-related QoL and has been widely used and validated for cancer patients as well as for general populations [25]. It contains 30 questions and assesses QoL multidimensionally via 5 multi-item functional subscales (physical, role, emotional, cognitive and social functioning), one global health status/Qol scale, three multi-item symptom subscales (pain, fatigue, nausea/vomiting) as well as six stand-alone items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). All subscales and the individual items have a score range from 0 to 100. For functional scales a higher score represents better function and a higher QoL, whereas for symptom scales a higher score indicates more severe complaints [25].

To assess MWB we used the *Warwick-Edinburgh Mental Well-Being Scale* (WEMWBS), which has been validated in psychiatric settings as well as the general population [21,26,27]. This instrument covers subjective well-being and psychological functioning using 14 questions, which are answered on a five-point Likert scale and then added up for the final score. The minimum score is thus 14 and the maximum score is 70, with a higher score indicating a higher level of MWB [26].

The short form of the Fear of Progression Questionnaire (FoP-Q-SF) assesses different aspects of FoP (affective reactions, partnership/family, occupation, and loss of autonomy) and consists of 12 questions, answered on a five-point Likert scale, which are added up to a final score with high scores indicating a high level of FoP. In this study a score of 4 or 5 in at least 50% of items was defined as a cut-off for moderate FoP, and a score of 4 or 5 in at least 75% of all items was defined as a cut-off for high FoP [28].

The *Primary Care - Posttraumatic stress disorder Screening* (PC-PTSD) provides an initial orientation concerning the prevalence of PTSD. It captures the important PTSD symptom clusters of re-experiencing, avoidance, overexcitement, and emotional numbing with four items [29]. Questions are dichotomous and to be answered with “yes” or “no”. To screen for PTSD with a sensitivity of about 80% at cost of a specificity of only 60–70%, the cut-off is set at “yes” at least twice [30].

The *Patient Reported Outcomes – Common Terminology Criteria for Adverse Events* (PRO-CTCAE) is a patient-oriented questionnaire

developed and validated to assess therapy-associated symptoms in cancer patients [31]. It consists of 124 items that measure 78 different symptoms. Most items consist of a five-point Likert scale and are rated from 0 to 4. In addition, there are some dichotomous items that are assigned the values 0 or 1. For this study, 18 symptom complexes with particular relevance to patients who underwent RPS resection were selected, such as changes in bowel habits, sexual or urogenital symptoms, pain and paresthesia [11,13].

Additionally, patients were asked to rate their current QoL on a scale from 1 to 10.

2.3. Statistics

Data were analyzed applying descriptive statistics. Multivariable linear regression models were used to test associations between clinical/demographic variables and PROs. To correct for non-normal/heteroskedastic residuals, wild bootstrapping with 2000 replications was performed [32]. Regression models were only calculated when the ANOVA indicated a good fit for the data ($p \leq 0.05$). In case of dichotomous dependent variables (PTSD screening) a logistic regression analysis was performed. See **Supplements** for details on included variables. Spearman's rank correlations were performed between current QoL ratings and scores from other above-mentioned questionnaires. Comparisons of EORTC QLQ-C30 scores between the RPS cohort and the general German population (GP) stratified by sex and age as well as comparisons between patients with liposarcoma and other RPS entities and comparisons depending on the time elapsed since the last resection were presented graphically using histograms. Differences greater than 10 score points are considered clinically relevant.

SPSS (Version 28.0.0.0) was used for all statistical analyses. The level of statistical significance was set to $p \leq 0.05$ (two-tailed).

3. Results

3.1. Clinicopathological features and quality of life

Questionnaires were returned by 127 out of 180 contacted patients (71%). 97 patients (77%) initially presented with primary disease, 27 (21%) with local recurrence and 3 (2%) with distant metastases after prior treatment elsewhere. Demographic, clinicopathological, and treatment details are shown in Table 1 and Supplementary Table 1.

The median interval between first diagnosis and completion of questionnaires was 80 months (IQR: 33–140 months) and the median interval between last operation and completion of questionnaires was 31 months (IQR: 12–73 months). The average EORTC-QLQ-C30 score for global health/QoL was 64.1. Fig. 1 reveals EORTC values from the study population as compared to normative data from the general German population [20].

According to the WEMWBS questionnaire average or high MWB (score ≥45) was attributed to a majority of patients (109; 86%). Ratings indicating possible depression (score 41-44) were found in 10 patients (8%), and ratings indicating probable depression (score ≤41) were present in 8 patients (6%). 21 patients (17%) suffered from moderate FoP, whereas only 3 patients (2%) showed signs of a high FoP. 28 patients (22%) fulfilled cut-off criteria for PTSD. Most frequent symptoms after RPS resection included bloating and experience of abdominal as well as general pain.

Median current QoL rated on a scale ranging from 1 to 10 was 7 (IQR: 6-8). According to Spearman's rank correlations, patients' current QoL ratings correlated well with the EORTC-QLQ-C30 score for global health/QoL ($r_s = 0.75$). Indeed, high ratings concerning physical ($r_s = 0.74$), role ($r_s = 0.67$), emotional ($r_s = 0.51$), social functioning ($r_s = 0.57$) and MWB ($r_s = 0.64$) were associated with high ratings of current QoL. Possible presence of PTSD ($r_s = -0.32$) or FoP ($r_s = -0.39$) correlated only weakly with current QoL ratings. Regarding clinical symptoms, we observed a strong correlation between the presence of fatigue ($r_s = -0.65$), and a moderate correlation between insomnia ($r_s = -0.41$) and current QoL. Presence of pain correlated moderately ($r_s = -0.48$) with current QoL. Interestingly, abdominal symptoms showed no or only weak correlation with current QoL (diarrhea: $r_s = -0.26$; constipation: $r_s = -0.29$; bloating: $r_s = -0.37$; abdominal pain: $r_s = -0.38$). The cumulative complication burden was not correlated with current QoL ($r_s = -0.10$). An overview of assessed QoL data is provided in Table 2. Further details regarding clinical symptoms and their correlation to QoL are provided in Supplementary Table 2 and in Fig. 2a.

Table 1
Demographic, clinical ans pathological characteristics.

	VALUE	%/SD/IQR
N	127	
CURRENT AGE	62	12.4
AGE AT INITIAL PRESENTATION	56	12.7
SEX		
MALE	65	51.2
FEMALE	62	48.8
INITIAL PRESENTATION		
PRIMARY TUMOR	97	76.4
LOCAL RECURRENCE	27	21.3
DISTANT METASTASES	3	2.4
HISTOLOGY		
DD LPS	55	43.3
WD LPS	30	23.6
LMS	12	9.4
NOS	5	3.9
OTHER	9	7.1
INTERMED. MALIGNANCY	16	12.6
INITIAL TUMOR GRADE		
G1	27	21.3
G2	38	29.9
G3	17	13.4
DOES NOT APPLY	45	35.4
RESECTION STATUS OF PRIMARY OPERATION AT OUR CENTER		
R0/R1	122	96.1
R2	5	3.9
TUMORSIZE (CM). MEDIAN	15	8.4–23.0
MULTIFOCALITY		
NO	119	93.7
YES	8	6.3
MVR		
NO	68	53.5
YES	59	46.5
RADIATION THERAPY		
NO	78	61.4
YES	49	38.6
PREOPERATIVE	9	7.1
POSTOPERATIVE	22	17.3
EBRT ALONE	12	9.4
IORT ALONE	18	14.2
EBRT + IORT	19	15.0
SYSTEMIC THERAPY		
NO	119	93.7
YES	8	6.3
RELAPSE		
DEVELOPMENT OF (FURTHER) LR	29	22.8
DEVELOPMENT OF DM	6	4.7
DEVELOPMENT OF DM AND LR	14	11.0
FOLLOW UP		
FROM OP (MONTHS)	63	27.6–106.5
FROM FIRST DIAGNOSIS (MONTHS)	80	33.2–139.9
INTERVAL BTW. LAST OP AND FOLLOW-UP (MONTHS)	31	12.0–73.0

DD-LPS dedifferentiated liposarcoma, *WD-LPS* well-differentiated liposarcoma, *LMS* leiomyosarcoma, *NOS* undifferentiated sarcoma (not otherwise specified), *EBRT* external beam radiation therapy, *IORT* intraoperative radiation therapy, *LR* local recurrence, *DM* distant metastases, *OP* operation.

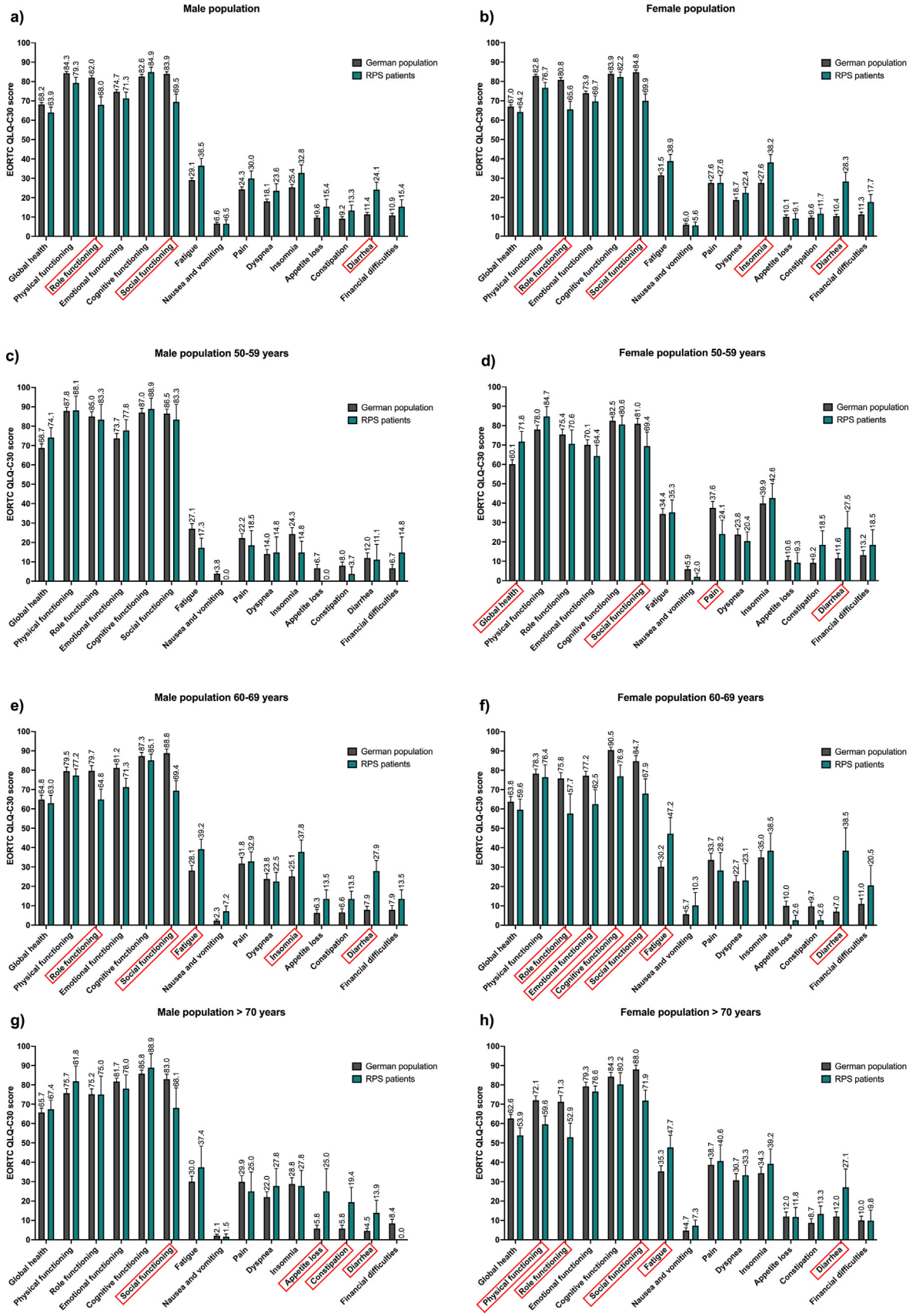


Fig. 1. Comparison of EORTC QLQ-C30 scores between the RPS cohort and the general German population (GP) by sex and age. Differences greater than 10 are considered clinically relevant (red rectangles).
a) Male population: GP (n = 505) versus RPS (n = 65)

Table 2
Overview of QoL ratings in 127 RPS patients.

	VALUE	%/SD/IQR
N	127	
EORTC (MEAN SCORE)		
GLOBAL HEALTH STATUS	64.1	21.5
PHYSICAL FUNCTIONING	78.0	22.8
ROLE FUNCTIONING	66.8	32.3
EMOTIONAL FUNCTIONING	70.5	23.6
COGNITIVE FUNCTIONING	83.6	20.2
SOCIAL FUNCTIONING	69.7	30.1
PAIN	28.8	30.4
FATIGUE	37.7	28.9
NAUSEA AND VOMITING	6.1	15.5
DYSPNOEA	23.0	26.5
INSOMNIA	35.4	32.5
APPETITE LOSS	12.3	26.8
CONSTIPATION	12.5	22.3
DIARRHEA	26.1	34.0
FINACIAL DIFFICULTIES	16.5	29.4
WEMWBS		
PROPABLE DEPRESSION ($\leq$40)	8	6.3
POSSIBLE DEPRESSION (41-44)	10	7.9
AVERAGE MENTAL WELL BEING (45-59)	64	50.4
HIGH MENTAL WELL BEING ($\geq$60)	45	35.4
FOP-Q-SF		
NO FEAR OF PROGRESSION	103	81.1
MODERATE FEAR OF PROGRESSION (4 OR 5 IN $\geq$ 50% OF ITEMS)	21	16.5
HIGH FEAR OF PROGRESSION (4 OR 5 IN $\geq$ 75% OF ITEMS)	3	2.4
PTSD SCREENING		
NEGATIVE	99	88.0
POSITIVE	28	22.0

Overview of QoL ratings in a cohort of 127 retroperitoneal sarcomas as assessed with 5 questionnaires: *EORTC QLQ-C30*: range 0–100; functional scales and global health score: higher score indicates higher QoL; symptom scores: higher score indicates more severe complaints. *WEMWBS*: range 14–70. *FOP-Q-SF*: 12 questions with 5-point Likert scale. *PC-PTSD*: 4 dichotomous questions; cut-off for PTSD is set at "yes" twice.
EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer - Core Quality of Life Questionnaire, *FoP-Q-SF* Fear of Progression Questionnaire (short form), *IQR* interquartile range, *PTSD* posttraumatic stress disorder, *QoL* quality of life, *SD* standard deviation, *WEMWBS* Warwick-Edinburgh Mental Well-Being Scale.

3.2. Impact of local recurrence, distant metastasis and multiple surgeries

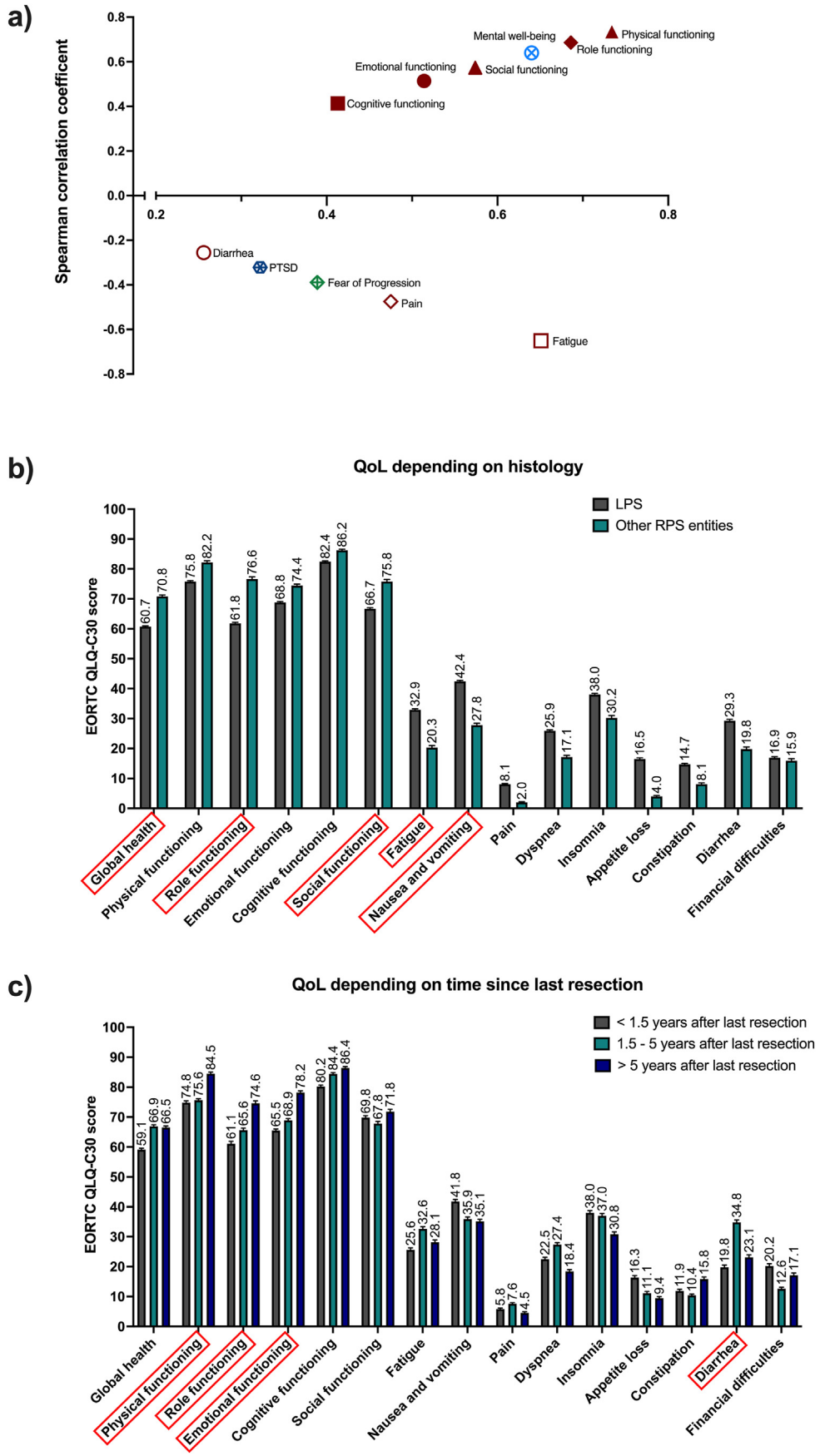
After initial surgery at our department 43 patients (34%) developed at least one local recurrence (LR) and 20 patients (16%) developed distant metastases (DM). 58 (46%) underwent a single operation, 27 (21%) had two operations, 12 (10%) three operations, 9 (7%) four operations, and 20 patients (16%) underwent surgery five or more times. Neither the development of LR nor DM was significantly associated with decreased global health status/QoL, or affect physical functioning as assessed by EORTC QLQ-C30 (Table 3 and Fig. 3a). However, patients undergoing more than two surgeries were significantly more likely to suffer from diarrhea (yes vs. no: β: 37.45 $\pm$ 8.50; $p < 0.001$) or edema (yes vs. no: β: 0.86 $\pm$ 0.29; $p = 0.006$). In multivariable analysis, neither the development of tumor recurrence, nor the number of surgeries had a significant impact on fear of progression or mental well-being (Fig. 3b). Repeated tumor recurrence is common among patients with liposarcoma (LPS), which make up the majority of patients in this cohort (67%). LPS patients exhibit higher rates of LR compared to other types of RPS, necessitating lifelong regular follow-up. Still, FoP was not more pronounced in LPS patients compared to other entities, nor did results of the PTSD screening differ between the two groups. Nonetheless, scores for fatigue were higher in LPS patients and EORTC-QLQ-C30 ratings for role functioning, social functioning and of global health/QoL were reduced compared to other RPS entities (Fig. 2b and Supplementary Table 3).

An increased time interval between the last operation and completion of questionnaires did not affect global health/QoL ratings as assessed by EORTC-QLQ-C30, or MWB as assessed by WEMWBS (Fig. 3c), but was associated with a reduced likelihood of PTSD (>2 years vs. $\leq$ 2 years: OR: 0.16; $p = 0.003$) according to regression models. Yet, functioning scales as assessed with the EORTC-QLQ-C30 tended to improve over time, whereas most symptoms were stable (Fig. 2c and Supplementary Table 4). Complete results from the regression analysis are provided in Table 3 and Supplementary Table 5.

3.3. Impact of multivisceral resection

Multivisceral resection (MVR, resection of at least three organs) was performed in 68 (54%) of all patients, and 15 patients (12%)

b) Female population: GP (n = 501) versus RPS (n = 62)
c) Male population 50–59 years: GP (n = 100) RPS (n = 9)
d) Female population 50–59 years: GP (n = 101) versus RPS (n = 18)
e) Male population 60–69 years: GP (n = 101) versus RPS (n = 37)
f) Female population 60–69 years: GP (n = 100) versus RPS (n = 13)
g) Male population >70 years: GP (n = 103) versus RPS (n = 12)
h) Female population >70 years: GP (n = 100) versus RPS (n = 17)
EORTC European Organisation for Research and Treatment of Cancer, GP general German population, RPS retroperitoneal soft tissue sarcoma.


a)
Spearman correlation coefficent
Mental well-being
Physical functioning
Role functioning
Emotional functioning
Social functioning
Cognitive functioning
Diarrhea
PTSD
Fear of Progression
Pain
Fatigue
b)
QoL depending on histology
LPS
Other RPS entities
EORTC QLQ-C30 score
Global health
Physical functioning
Role functioning
Emotional functioning
Cognitive functioning
Social functioning
Fatigue
Nausea and vomiting
Pain
Dyspnea
Insomnia
Appetite loss
Constipation
Diarrhea
Financial difficulties
c)
QoL depending on time since last resection
< 1.5 years after last resection
1.5 - 5 years after last resection
> 5 years after last resection
EORTC QLQ-C30 score

underwent more than one MVR. One-sided nephrectomy was performed in 67 patients (53%). Parts of the colon were resected in 33 patients (26%), segmental resection of the small intestine was performed in 24 patients (19%), and partial resection of the psoas muscle was performed in 20 (16%) patients, however resection of lumbal nerves was only necessary in 1 patient. 18 patients (14%) underwent partial pancreatectomy. MVR did not have a significant effect on any of the EORTC-QLQ-C30 scores, neither on MWB, FoP nor the likelihood to develop PTSD (Table 3 and Fig. 3d). Besides dyspnea (β: 21.04 ± 5.84; $p = 0.003$), patients treated with MVR were not at increased likelihood to suffer from specific symptoms caused by MVR. Only in patients with (partial) resection of the pancreas the occurrence of diarrhea was significantly more frequent (β: 27.54 ± 8.42; $p = 0.002$; Table 3).

3.4. Impact of postoperative complications

31 patients (24%) suffered from major surgical complications (Clavien Dindo 3 or higher) during the course of the disease. Intraabdominal abscess (12%), lymphatic fistula (10%) and wound complications (10%) were the most frequent complications. 18 patients (14%) underwent reoperations, and 20 patients (16%) needed radiological or endoscopic interventions due to postoperative complications. Long-term complications such as incisional hernia and bowel obstruction caused by postoperative adhesions occurred in 8 patients (6%) each. The median cumulative CCI was 26.2 (IQR: 20.9–38.7). 59 patients (47%) had no complications at all. Further details are provided in Supplementary Table 1. The occurrence of a major complication was not significantly correlated with the performance of MVR ($r_s = 0.10$) nor with the resection of specific organs or major blood vessels (all $r_s < 0.3$).

Importantly, occurrence of postoperative complications was not associated with impaired QoL scores. Moreover, a complicative postoperative course did not seem to influence psychological well-being or fear of progression, nor was it associated with an increased likelihood to develop PTSD (Table 3 and Fig. 3e).

3.5. Impact of systemic or radiation therapy

Additional radiation therapy was applied in 49 cases (39%). External beam radiation therapy (EBRT; with or without intraoperative radiation therapy (IORT)) was applied in 31 patients, 18 patients (14%) received IORT only. In 9 cases EBRT was applied preoperatively, 22 patients underwent postoperative EBRT. Systemic therapy was applied in only 8 cases (6%). Application of radiation therapy affected the EORTC-QLQ-C30 rating of global health/QoL (yes vs. no: β: 12.17 ± 3.94; $p = 0.003$) and was associated with reduced physical functioning (yes vs. no: β: 11.66 ± 4.65; $p = 0.018$) (Fig. 3f and Table 3).

4. Discussion

This study provides a comprehensive analysis of how various clinicopathological and surgery-associated factors affect long-term QoL in a large cohort of RPS patients. During the course of disease a majority of RPS patients experience local or distant tumor relapse, often necessitating (sometimes repeated) extensive abdominal surgery including MVR, with morbidity rates of 15–20% [33].

Interestingly, in our analysis, neither the necessity of MVR, nor the occurrence of postoperative complications during the course of disease had a significant impact on patients' long-term QoL. Comparable findings were observed by Fiore et al. upon analysis of QoL in 58 Italian patients during the first year after resection of primary RPS [13]. Likewise, the multicenter PATRONUS study, which investigated QoL after major abdominal cancer surgery, revealed no correlation between postoperative complications and patients' QoL ratings [34]. Furthermore, neither undergoing MVR, nor resection of specific organs nor the number of operations performed had a significant impact on physical functioning, global health, mental well-being or fear of progression in our analysis. Recent studies showed that OS of RPS patients is significantly prolonged by resection of local or distant recurrences [6,7,35–37]. Our present findings endorse this surgical approach, demonstrating that important aspects defining QoL are apparently unaffected by multiple resections.

However, patients undergoing more than two operations or partial resection of the pancreas suffered from diarrhea more frequently. Overall, when compared to normative data on QoL from the general German population, diarrhea was more frequent among RPS patients independent of sex and age. Of note, other physical symptoms frequently related to abdominal surgery such as constipation, (abdominal) pain and appetite loss were not more pronounced in RPS patients compared to the general population. Interestingly as well, presence of diarrhea was not correlated with decreased current QoL ratings. Fatigue and insomnia, which were both associated with reduced current QoL, appeared to be more present in RPS patients, especially in women. Chronic fatigue syndromes have been described following nephrectomy [38], in our cohort however, we did not find a correlation between nephrectomy and fatigue. High levels of fatigue strongly correlated with reduced emotional and social functioning. In line with these findings, results for role and social functioning were distinctly worse in RPS patients, whereas differences in physical functioning scores between RPS patients and the general population were minimal. Reduced scores for EORTC QLQ-C30 global health/QoL in LPS patients coincided with higher ratings for fatigue and lower ratings for role and social functioning compared to other RPS entities, altogether corroborating the notion that rather psychosocial and psychological than purely physical aspects affect postresectional QoL. Hence, our results suggest that postoperative patient care should not solely focus on physical symptoms, but likewise on handling of everyday demands and social coping. Regular assessment of PROs in patient follow-up may help to discover areas of complaint earlier, facilitate the discussion of sensitive topics and thereby enable tailored, holistic care [39]. This could be especially true in surgical follow-ups, where focus tends to lie on oncological status and mainly physical limitations. In this context the utilization of a questionnaire to evaluate QoL specifically in sarcoma

Fig. 2. Quality of life in patients undergoing surgical resection of RPS.
a) Correlation of specific symptoms/ratings with current QoL ratings as assessed by Spearman's rank correlations. Symptoms/ratings depicted in red were assessed with the EORTC QLQ-C30. Mental well-being (light blue) was assessed with the WEMWBS. PTSD (dark blue) was assessed with the PC-PTSD. Fear of progression (light green) was assessed with the FoP-Q-SF questionnaire.
b) Comparison of EORTC QLQ-C30 scores between patients with liposarcoma (LPS, n = 85) and patients with other RPS entities (n = 42). Differences greater than 10 are considered clinically relevant (red rectangles).
c) Comparison of EORTC QLQ-C30 scores in relation to the time elapsed since last tumor resection (<1.5 years: n = 43, 1.5–5 years: n = 45, >5 years: n = 39) Differences greater than 10 are considered clinically relevant (red rectangles).
EORTC European Organisation for Research and Treatment of Cancer, *FoP-Q-SF* Fear of Progression Questionnaire (short form), *IQR* interquartile range, *LPS* liposarcoma, OP operation, *PC-PTSD* Primary Care - Posttraumatic stress disorder Screening, *WEMWBS* Warwick-Edinburgh Mental Well-Being Scale.

Table 3
Association between patient reported outcomes and clinical/demographic variables.

EORTC	GLOBAL HEALTH				
ANOVA	R^2	*df*	F	f^2	*p*-VALUE
	0.211	16; 109	1.82	0.267	0.037
REGRESSION		PARAMETER ESTIMATE (MEAN ± SE)	95% CI		*p*-VALUE
SEX	FEMALE VS. MALE	3.21 ± 3.95	−4.11 − 11.28		0.462
NUMBER OF OPERATIONS	>2 VS. ≤ 2	−7.39 ± 5.74	−18.45 - 3.69		0.230
INTERVAL SINCE LAST OPERATION	>2 YEARS VS. ≤ 2 YEARS	8.05 ± 4.29	0.38 - 17.22		0.083
AGE		−0.29 ± 0.14	−0.57 − −0.03		0.053
CUMULATIVE COMPLICATION BURDEN	MODERATE VS. NONE	−8.06 ± 4.43	−16.07 - 1.38		0.092
	SEVERE VS. NONE	−10.66 ± 6.16	−22.16 - 1.5		0.104
CLAVIEN-DINDO >3	YES VS. NO	18.36 ± 7.06	4.78 - 31.85		**0.010**
DISTANT METASTASES	YES VS. NO	−0.97 ± 5.31	−11.13 - 9.6		0.860
LOCAL RECURRENCE	YES VS. NO	0.87 ± 4.96	−8.72 - 10.5		0.871
SYSTEMIC THERAPY	YES VS. NO	−1.83 ± 8.33	−17.41 - 14.23		0.838
RADIATION THERAPY	YES VS. NO	−12.17 ± 3.94	−19.83 − −4.12		**0.003**
MVR	YES VS. NO	−1.82 ± 4.63	−9.93 - 7.85		0.726
KIDNEY RESECTION	YES VS. NO	6.17 ± 5.25	−5.06 − 15.53		0.268
COLON RESECTION	YES VS. NO	4.16 ± 4.67	−4.67 - 13.67		0.410
SMALL BOWEL RESECTION	YES VS. NO	5.65 ± 6.13	−6.24 - 17.4		0.391
PANCREAS RESECTION	YES VS. NO	−9.16 ± 4.7	−18.46 - 0.06		0.071
EORTC	PHYSICAL FUNCTIONING				
ANOVA	R^2	*df*	F	f^2	*p*-VALUE
	0.27	16; 106	2.451	0.37	0.003
REGRESSION		PARAMETER ESTIMATE (MEAN ± SE)	95% CI		*p*-VALUE
SEX	FEMALE VS. MALE	0.85 ± 4.1	−6.93 - 9.07		0.848
NUMBER OF OPERATIONS	>2 VS. ≤ 2	−6.67 ± 5.75	−17.41 - 5.18		0.294
INTERVAL SINCE LAST OPERATION	>2 YEARS VS. ≤ 2 YEARS	5.15 ± 3.96	−1.6 − 13.84		0.245
AGE		−0.53 ± 0.14	−0.81 − −0.24		**0.001**
CUMULATIVE COMPLICATION BURDEN	MODERATE VS. NONE	−4.79 ± 4.6	−13.68 - 4.61		0.347
	SEVERE VS. NONE	−8.48 ± 9.35	−26.03 − 8.37		0.440
CLAVIEN-DINDO >3	YES VS. NO	12.23 ± 10.22	−6.73 - 31.02		0.321
DISTANT METASTASES	YES VS. NO	−8.26 ± 6.72	−21.64 - 4.68		0.270
LOCAL RECURRENCE	YES VS. NO	−0.85 ± 5.02	−10.43 - 8.85		0.877
SYSTEMIC THERAPY	YES VS. NO	4.03 ± 9.95	−15.49 - 23.14		0.709
RADIATION THERAPY	YES VS. NO	−11.66 ± 4.65	−20.78 − −2.47		**0.018**
MVR	YES VS. NO	−9.4 ± 5.23	−19.65 - 0.86		0.098
KIDNEY RESECTION	YES VS. NO	6.15 ± 5.43	−4.88 - 16.01		0.310
COLON RESECTION	YES VS. NO	10.11 ± 3.78	2.96 - 18.23		0.015
SMALL BOWEL RESECTION	YES VS. NO	−2.41 ± 6.3	−15.07 − 9.76		0.702
PANCREAS RESECTION	YES VS. NO	0.59 ± 6.36	−11.55 - 12.74		0.928
EORTC	DYSPNEA				
ANOVA	R^2	*df*	F	f^2	*p*-VALUE
	0.217	16; 109	1.889	0.277	0.029
REGRESSION		PARAMETER ESTIMATE (MEAN ± SE)	95% CI		*p*-VALUE
SEX	FEMALE VS. MALE	−5.62 ± 4.69	−15.1 − 3.16		0.277
NUMBER OF OPERATIONS	>2 VS. ≤ 2	9.97 ± 6.29	−2.51 - 21.93		0.149
INTERVAL SINCE LAST OPERATION	>2 YEARS VS. ≤ 2 YEARS	−5.25 ± 4.77	−14.83 - 3.53		0.322
AGE		0.32 ± 0.18	−0.05 - 0.68		0.109
CUMULATIVE COMPLICATION BURDEN	MODERATE VS. NONE	−0.66 ± 6.14	−12.96 - 10.6		0.928
	SEVERE VS. NONE	0.35 ± 8.78	−17.73 - 17.05		0.975
CLAVIEN-DINDO >3	YES VS. NO	−12.28 ± 9.15	−30.69 - 5.38		0.223
DISTANT METASTASES	YES VS. NO	4.08 ± 6.58	−8.84 - 17.41		0.583
LOCAL RECURRENCE	YES VS. NO	−6.42 ± 5.97	−18.68 - 5.13		0.325
SYSTEMIC THERAPY	YES VS. NO	−14.03 ± 11.58	−37.03 − 8.33		0.274
RADIATION THERAPY	YES VS. NO	14.67 ± 6.02	3.45 - 27.03		**0.026**
MVR	YES VS. NO	21.04 ± 5.84	9.78 - 32.5		**0.003**
KIDNEY RESECTION	YES VS. NO	−16.54 ± 5	−26.43 − −6.68		**0.002**
COLON RESECTION	YES VS. NO	−2.38 ± 5.27	−12.66 - 7.66		0.694
SMALL BOWEL RESECTION	YES VS. NO	−2.28 ± 6.46	−14.64 - 10.21		0.751
PANCREAS RESECTION	YES VS. NO	−3.7 ± 7.37	−18.03 − 10.41		0.660
EORTC	DIARRHEA				
ANOVA	R^2	*df*	F	f^2	*p*-VALUE
	0.26	16; 108	2.37	0.351	0.005
REGRESSION		PARAMETER ESTIMATE (MEAN ± SE)	95% CI		*p*-VALUE
SEX	FEMALE VS. MALE	1.98 ± 5.63	−9.42 - 13.27		0.739
NUMBER OF OPERATIONS	>2 VS. ≤ 2	37.45 ± 8.5	20.35 − 53.99		**<0.001**

Table 3 (*continued*)

EORTC	DIARRHEA				
ANOVA	R^2	*df*	F	f^2	*p*-VALUE
	0.26	16; 108	2.37	0.351	0.005
REGRESSION		PARAMETER ESTIMATE (MEAN ± SE)	95% CI		*p*-VALUE
1INTERVAL SINCE LAST OPERATION	>2 YEARS VS. ≤ 2 YEARS	0.63 ± 6.07	−11.5 − 12.38		0.931
AGE		0.02 ± 0.23	−0.41 - 0.48		0.934
CUMULATIVE COMPLICATION BURDEN	MODERATE VS. NONE	−1.75 ± 6.49	−14.61 - 10.55		0.810
	SEVERE VS. NONE	−8.44 ± 8.66	−25.16 - 8.23		0.381
CLAVIEN-DINDO >3	YES VS. NO	1.53 ± 9.96	−17.67 - 21.04		0.881
DISTANT METASTASES	YES VS. NO	−8.43 ± 10.05	−27.48 - 11.53		0.453
LOCAL RECURRENCE	YES VS. NO	−9.65 ± 7.43	−24.26 - 5.01		0.237
SYSTEMIC THERAPY	YES VS. NO	−13.2 ± 14.07	−39.29 - 13.82		0.420
RADIATION THERAPY	YES VS. NO	11.9 ± 6.79	−1.41 - 25.19		0.114
MVR	YES VS. NO	−5.91 ± 6.04	−17.98 - 5.95		0.376
KIDNEY RESECTION	YES VS. NO	−4.47 ± 7.6	−18.86 - 10.72		0.601
COLON RESECTION	YES VS. NO	8.24 ± 7.16	−5.8 − 22.33		0.294
SMALL BOWEL RESECTION	YES VS. NO	−12.67 ± 10.46	−33.49 - 7.55		0.275
PANCREAS RESECTION	YES VS. NO	27.57 ± 8.42	11.34 − 43.61		**0.002**
PRO-CTCAE®	EDEMA				
ANOVA	R^2	*df*	F	f^2	*p*-VALUE
	0.21	16; 109	1.81	0.173	0.039
REGRESSION		PARAMETER ESTIMATE (MEAN ± SE)	95% CI		*p*-VALUE
SEX	FEMALE VS. MALE	0.05 ± 0.17	−0.28 - 0.37		0.786
NUMBER OF OPERATIONS	>2 VS. ≤ 2	0.86 ± 0.29	0.3 - 1.43		**0.006**
INTERVAL SINCE LAST OPERATION	>2 YEARS VS. ≤ 2 YEARS	−0.27 ± 0.17	−0.63 - 0.07		0.166
AGE		0.01 ± 0.01	0 − 0.03		0.068
CUMULATIVE COMPLICATION BURDEN	MODERATE VS. NONE	0.04 ± 0.23	−0.39 - 0.51		0.882
	SEVERE VS. NONE	−0.28 ± 0.25	−0.79 - 0.17		0.313
CLAVIEN-DINDO >3	YES VS. NO	−0.58 ± 0.26	−1.09 − −0.07		**0.037**
DISTANT METASTASES	YES VS. NO	−0.23 ± 0.23	−0.67 - 0.22		0.349
LOCAL RECURRENCE	YES VS. NO	0.97 ± 0.52	−0.02 - 1.96		0.087
SYSTEMIC THERAPY	YES VS. NO	0.41 ± 0.23	−0.03 - 0.85		0.091
RADIATION THERAPY	YES VS. NO	0.04 ± 0.28	−0.47 - 0.6		0.897
MVR	YES VS. NO	0.11 ± 0.21	−0.31 - 0.51		0.657
KIDNEY RESECTION	YES VS. NO	−0.23 ± 0.19	−0.6 - 0.15		0.265
COLON RESECTION	YES VS. NO	0.19 ± 0.2	−0.22 - 0.58		0.399
SMALL BOWEL RESECTION	YES VS. NO	−0.5 ± 0.25	−0.98 − −0.02		0.061
PANCREAS RESECTION	YES VS. NO	−0.07 ± 0.29	−0.63 - 0.49		0.816
PTSD SCREENING					
REGRESSION		**ODDS RATIO**	**95% CI**		***p*-VALUE**
SEX	FEMALE VS. MALE	0.95	0.33 - 2.75		0.922
NUMBER OF OPERATIONS	>2 VS. ≤ 2	3.12	0.51 - 19.1		0.218
INTERVAL SINCE LAST OPERATION	>2 YEARS VS. ≤ 2 YEARS	0.16	0.05 - 0.54		**0.003**
AGE		0.97	0.93 - 1.01		0.174
CUMULATIVE COMPLICATION BURDEN					0.621
	MODERATE VS. NONE	0.56	0.13 - 2.39		0.437
	SEVERE VS. NONE	1.53	0.18 - 13.35		0.700
CLAVIEN-DINDO >3	YES VS. NO	0.13	0.02 - 0.7		**0.018**
DISTANT METASTASES	YES VS. NO	2.43	0.43 - 13.72		0.313
LOCAL RECURRENCE	YES VS. NO	0.50	0.06 - 4.21		0.526
SYSTEMIC THERAPY	YES VS. NO	1.77	0.48 - 6.44		0.388
RADIATION THERAPY	YES VS. NO	1.41	0.16 - 12.57		0.758
MVR	YES VS. NO	1.10	0.29 - 4.17		0.889
KIDNEY RESECTION	YES VS. NO	0.68	0.19 - 2.35		0.538
COLON RESECTION	YES VS. NO	0.83	0.24 - 2.91		0.768
SMALL BOWEL RESECTION	YES VS. NO	0.26	0.05 - 1.3		0.101
PANCREAS RESECTION	YES VS. NO	0.23	0.04 - 1.45		0.118

Regression models were only calculated when the ANOVA indicated a good fit for the data ($p \leq 0.05$). For dichotomous dependent variables (PTSD screening) a logistic regression was performed. *CI* confidence interval, *EORTC* European Organisation for Research and Treatment of Cancer, *PTSD* posttraumatic stress disorder, *Pro-CTCAE®* Patient Reported Outcomes − Common Terminology Criteria for Adverse Events, *SE* standard deviation.

patients, as currently being developed by the EORTC Quality of Life group, may offer additional assistance in the future.

Since the development of local recurrences does not plateau, lifelong follow-up is recommended. It appears plausible that persistent confrontation with the disease may cause psychological distress. This study is the first to examine the role and prevalence of FoP in a RPS cohort. Interestingly, the majority of patients experiences no FoP (81%), and several different parameters of QoL were not significantly affected by FoP. Nonetheless, FoP was observed in one fifth of patients and thus should not be neglected in postoperative follow-up sessions. Moreover, the fraction of patients with potential PTSD appears surprisingly high in comparison with other cancer cohorts, where the proportion of PTSD is about 10% [40]. However, it has to be considered that the PC-PTSD is

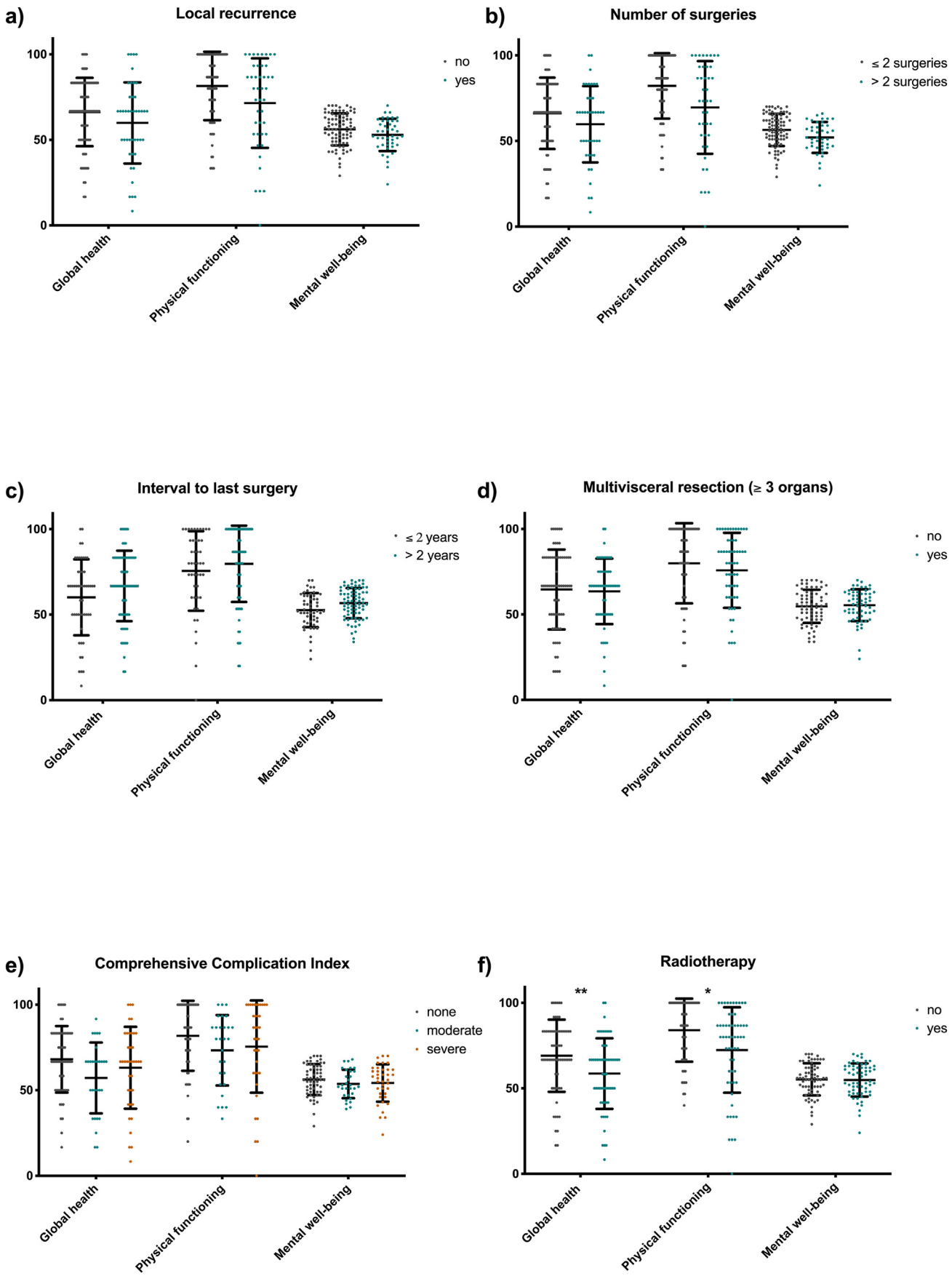

a)
Local recurrence
100
50
0
Global health
Physical functioning
Mental well-being
no
yes
b)
Number of surgeries
≤ 2 surgeries
> 2 surgeries
c)
Interval to last surgery
≤ 2 years
> 2 years
d)
Multivisceral resection (≥ 3 organs)
no
yes
e)
Comprehensive Complication Index
none
moderate
severe
f)
Radiotherapy
**
*
no
yes

Fig. 3. Scores for global health (EORTC QLQ-C30), physical functioning (EORTC QLQ-C30) and mental well-being (WEMWBS) in relation to
a) Development of local recurrence
b) Number of surgeries
c) Interval to last surgery
d) Multivisceral resection (MVR)
e) Cumulative complication burden in the course of the disease (none: Cum. CCI 0, moderate: Cum. CCI 1-25, severe: Cum. CCI >25)
f) Application of radiotherapy.
CCI comprehensive complication index, *EORTC* European Organisation for Research and Treatment of Cancer, *MVR* multivisceral resection, *WEMWBS* Warwick-Edinburgh Mental Well-Being Scale.

merely a screening tool and not used for diagnostics. Moreover, these findings must be interpreted carefully as they were not consistent with generally good MWB and QoL ratings as observed applying other questionnaires.

Results from our present study suggest that application of radiation therapy (RT) is associated with lower scores for physical functioning as well as lower global health scores. These findings differ from previously published data on the topic with no association between RT and QoL [11,13,15]. A secondary analysis of QoL data from the randomized STRASS trial comparing preoperative RT versus surgery alone will shed further light in this issue [41]. QoL scores of patients treated with RT in our cohort may be comparatively low, as in the beginning of the investigated period a majority of patients received RT postoperatively or intraoperatively, which was adapted to purely preoperative application in the meantime due to lower toxicities and better oncological results. The results of the randomized STRASS trial and especially a recent propensity score (PS)-matching analysis of off-trial STREXIT results, provide further support that RT should be restricted to patients with selected indications, namely G1 and G2 liposarcoma [41,42]. Alternative irradiation strategies with putatively milder toxicity, such as irradiation with carbon ions or protons [43] are subject of ongoing investigations [44] and may further improve postoperative QoL.

A major limitation of our study resides in its retrospective nature. The lack of baseline QoL data impedes the interpretation of reduced QoL ratings with regard to the course of disease. Moreover, there is a survivorship bias. Indeed, patients who died shortly after surgery due to aggressive and advanced disease or severe postoperative complications could not be included in this analysis. There might be an additional responder bias, however, by achieving a high response rate of 71%, we were able to minimize this effect. Another limitation is the long inclusion period. Changes and improvement in RPS treatment over the years may also affect QoL and may bias our findings. Encompassing 127 patients, this is so far the largest available cohort of RPS patients with QoL data, nonetheless the interpretation of multivariable regression analysis is limited and validation in larger, ideally multicenter and prospectively assessed cohorts is necessary. Furthermore, single-center data always calls for careful interpretation of significant findings, especially regarding the transferability of results. However, our cohort is consistent to major RPS cohorts regarding tumor as well as patient characteristics, operative strategies, postoperative morbidity, and recurrence rates, altogether indicating that our results are representative [3,4,16,33].

5. Conclusions

Longterm survival rates after resection of RPS survival have significantly improved during the past 15 years [45], and health related QoL has therefore become an important topic. We multidimensionally assessed long-term postoperative QoL in the so far largest cohort of RPS patients. RPS patients rated their overall postresectional QoL as good. Long-term QoL was not significantly influenced by postoperative complications, the number of operations, or MVR. Moreover, with exception of diarrhea, the occurrence of physical symptoms related to abdominal surgery such as abdominal pain, constipation, nausea, and appetite loss was not more pronounced in the RPS patients compared to the general population. However, RPS patients more commonly complained of deficiencies concerning psychological than physical aspects of QoL. These findings suggest that clinical follow-ups should place focus on mental well-being to enable early tailored support if necessary.

CRediT authorship contribution statement

Franziska Willis: Formal analysis, Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft. **Lena Buck:** Conceptualization, Data curation, Investigation, Visualization. **Julian Musa:** Formal analysis, Validation, Writing – review & editing. **Ulf Hinz:** Formal analysis, Writing – review & editing. **Gunhild Mechtersheimer:** Writing – review & editing. **Katharina Seidensaal:** Writing – review & editing. **Stefan Fröhling:** Writing – review & editing. **Markus W. Büchler:** Writing – review & editing. **Martin Schneider:** Supervision, Validation, Writing – original draft.

Declaration of competing interest

Franziska Willis, Lena Buck, Julian Musa, Ulf Hinz, Gunhild Mechtersheimer, Katharina Seidensaal, Stefan Fröhling, Markus W. Büchler and Martin Schneider have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.07.003.

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