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Liposarkome des Bewegungsapparates

Therapie und Prognose in Abhängigkeit zur Entität

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Mitberichterstatter:	Prof. Dr. med. Matthias Siebeck
Dekan:	Prof. Dr. med. dent. Reinhard Hickel
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Einleitende Zusammenfassung

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Eidesstattliche Versicherung

Ich, Jessica Rauh, versichere hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema *„Liposarkome des Bewegungsapparates. Therapie und Prognose in Abhängigkeit zur Entität"* selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

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München, den 15.07.2019 Jessica Rauh

Inhaltsverzeichnis

1. Abkürzungsverzeichnis

ALT	Atypical lipomatous tumour, atypisches Lipom
CDK4	Cyclin-dependent kinase 4
LR	Lokalrezidiv
MDM2	murine double minute 2
OS	overall survival, Gesamtüberleben
WDLS	well differentiated liposarcoma

2. Publikationsliste

2.1. Veröffentlichung I

The role of surgical margins in atypical Lipomatous Tumours of the extremities

2.2. Veröffentlichung II

Myxoid liposarcoma: local relapse and metastatic pattern in 43 patients

3. Einleitung und Grundlagen

Etwa 1% aller neudiagnostizierten Tumoren bei Erwachsenen sind Sarkome. Die Inzidenz beträgt drei bis sechs Fälle pro 100.000 Einwohner pro Jahr. Dabei stellen Liposarkome mit einer Häufigkeit von 15-20% nach dem malignen fibrösen Histiozytom die zweithäufigste Tumorentität unter den Sarkomen dar [1,2]. Innerhalb der Liposarkome unterscheidet man atypische Lipome (atypical lipomatous tumour, ALT), myxoide bzw. myxoid/rundzellige, pleomorphe sowie dedifferenzierte Liposarkome. Atypische Lipome bzw. myxoid/rundzellige Liposarkome, welche Inhalt der im Rahmen dieser Arbeit verfassten Veröffentlichungen sind, sind mit einer Häufigkeit von 40-45% bzw. 30-50% die häufigsten lipomatösen Tumoren [3,4,5,6,7].

Sowohl atypische Lipome als auch myxoide Liposarkome treten vor allem in den tiefen Weichteilen der Extremitäten, und hier insbesondere im Bereich des Oberschenkels, auf. Beide Subtypen betreffen Männer und Frauen gleich häufig. Hinsichtlich des Erkrankungsalters lassen sich epidemiologische Unterschiede feststellen: Atypische Lipome betreffen bevorzugt Erwachsene mittleren Alters, myxoide dagegen vor allem junge Erwachsene. Die Spitzeninzidenz der ALT liegt in der sechsten, die der myxoiden in der vierten und fünften Lebensdekade [5,6]. Während atypische Lipome durch ihr lokal aggressives Wachstum, jedoch typischerweise nicht-metastasierendes Verhalten charakterisiert sind, neigen myxoide Liposarkome zur Metastasierung in nicht-pulmonale Weichgewebe. Hierzu zählen beispielsweise das Retroperitoneum, der Knochen oder die kontralaterale Extremität [8]. Myxoide Liposarkome erweisen sich als besonders strahlensensibel, und zeigen somit eine gute Wirksamkeit einer neoadjuvanten Radiatio [9,10,11]. Aus genetischer Sicht stellt das myxoide Liposarkom eine durch die Translokation t(12;16) gekennzeichnete Variante des Liposarkoms dar. Charakteristischerweise ist der Anteil an runden Zellen variabel und kann als negativer prognostischer Faktor angesehen werden [5,12].

Aufgrund des oben beschriebenen speziellen Verhaltens der atypischen Lipome wurde der bis in die 1970er Jahre verwendete Begriff des „well differentiated liposarcoma“ zugunsten der Bezeichnung „atypical lipomatous tumour“ weitestgehend verlassen. Dies gilt insbesondere für Tumoren im Bereich der Extremitäten oder des Rumpfes, wo eine vollständige chirurgische Exzision leichter zu erzielen ist als bei retroperitoneal wachsenden Raumforderungen [13,14]. Bei diesen operativ schwer zugänglichen Prozessen ist selbst bei atypischen Lipomen trotz der guten Differenzierung sowie des Fehlens von Metastasen potentiell ein tödlicher Verlauf möglich. In diesen Fällen, und insbesondere dann, wenn der Tumor zu Lokalrezidiven neigt, erscheint die Bezeichnung “well differentiated liposarcoma“ (WDLS) weiterhin passender [6,15]. Diese Uneinheitlichkeit hinsichtlich der Terminologie birgt allerdings die Gefahr von Missverständnissen im Rahmen der Diagnostik. ALT und WDLS sind jedoch synonym und beschreiben sowohl morphologisch und biologisch als auch karyotypisch identische Läsionen. Die Entscheidung bezüglich der Terminologie sollte deshalb interdisziplinär zwischen Chirurgie und Pathologie getroffen werden [6].

In bis zu zehn Prozent der Fälle kommt es, insbesondere bei tiefsitzenden retroperitoneal gelegenen atypischen Lipomen zur Dedifferenzierung. Es handelt sich dabei um die Entwicklung einer nicht-lipomatösen Sarkomkomponente mit variablem histologischen Grad. Das Risiko hierfür scheint allerdings bei in den Extremitäten lokalisierten Läsionen signifikant geringer zu sein. Etwa 90% der dedifferenzierten Liposarkome entstehen *de novo*. Hinsichtlich des Manifestationsalters ergeben sich keine wesentlichen Unterschiede verglichen mit den atypischen Lipomen. Beide Geschlechter erkranken gleich häufig. Fernmetastasen werden nach fünf Jahren in 15-20% der Fälle mit einer Gesamtmortalität zwischen 28-30% beobachtet [16].

ALT/WDLS und dedifferenzierte Liposarkome lassen sich unter Umständen nur schwer gegenüber gutartigen Lipomen und anderen gering differenzierten Weichteilsarkomen abgrenzen. Molekularpathologische Untersuchungen zeigen jedoch, dass ALT/WDLS und dedifferenzierte Liposarkome durch bestimmte Genamplifikationen (MDM2 und CDK4) auf Chromosom 12q13-15 charakterisiert sind. Dies führt zu einer Überexpression der entsprechenden Gene, welche typischerweise bei gutartigen Lipomen oder anderen Weichteilsarkomen fehlt [17,18].

Der seltenste Subtyp (5%) unter den Liposarkomen ist das pleomorphe Liposarkom. Es tritt bei beiden Geschlechtern gleich häufig und meist bei älteren Patienten (über 50 Jahre) auf. Wie alle Liposarkome manifestiert es sich bevorzugt an den Extremitäten, während Stamm und Retroperitoneum seltener betroffen sind. Generell gilt das pleomorphe Liposarkom als aggressiver Tumor, der häufig (30-50%) metastasiert und dabei vorwiegend die Lunge befällt. Die tumorassoziierte Gesamtmortalität liegt bei 40-50% [19].

4. Zielsetzung der Untersuchungen

Aufgrund der Heterogenität der genannten Tumorsubtypen, insbesondere hinsichtlich der Neigung zur Metastasierung, wird deutlich, dass sich sowohl therapeutische als auch prognostische Unterschiede ergeben. Eine differenzierte Betrachtung der Tumorentitäten erscheint somit trotz bestehender Gemeinsamkeiten unerlässlich und erfolgte in den im Rahmen dieser Arbeit veröffentlichten Manuskripten insbesondere für die atypischen und myxoiden Liposarkome. Eine weite Resektion kann bei den ALT aufgrund ihrer Tumorgröße und der typischerweise tiefen Lokalisation zu schwerwiegenden funktionellen Defiziten führen. Folglich muss geklärt werden, ob und wann eine marginale Resektion zugunsten des höheren postoperativ erzielten Funktionsniveaus angestrebt werden sollte. Dieser Frage wird im Folgenden in der Publikation „The role of surgical margins in atypical Lipomatous Tumours of the extremities“ nachgegangen. Das Ziel des zweiten Fachartikels „Myxoid liposarcoma: local relapse and metastatic pattern in 43 patients“ ist die Analyse der lokalen Kontrollraten, des Metastasierungsmusters und des Überlebens von Patienten mit myxoidem Liposarkom in Abhängigkeit von der durchgeführten Therapie in Verbindung mit dem individuellen Risikoprofil. Die übergeordnete Fragestellung dieser Arbeit lautet, welche tumor-

und stadiengerechten Therapieoptionen bei den jeweiligen Tumorsubtypen zur Verfügung stehen und wie sich diese auf die Prognose auswirken.

5. Zusammenfassung

5.1. Methoden

Zwischen 1983 und 2015 erfolgte bei 104 Patienten mit Liposarkom der Extremitäten und des Körperstamms eine chirurgische Resektion. Die präoperative Erfassung der Tumorgröße und der genauen Tumorlokalisation erfolgte in der Mehrzahl der Fälle mittels Magnetresonanztomographie (MRT), oder alternativ durch Computertomographie (CT). Die Resektionsränder wurden als R0 (weite Resektion) definiert, wenn sie von gesundem Gewebe umgeben waren, bzw. als R1 (marginale Resektion), wenn bei geschlossener Tumorkapsel histopathologisch Tumorgewebe im Resektionsrand nachweisbar war. Bei den atypischen Lipomen wurde meist eine R1-Resektion, in einem Fall eine R2-Resektion, angestrebt, wobei makroskopisch sichtbar Tumorgewebe belassen wurde. Im Verlauf wurden alle Patienten hinsichtlich des Auftretens von Lokalrezidiven (LR) oder Fernmetastasen untersucht. Außerdem wurde das Gesamt-, sowie das Rezidiv-freie Überleben mithilfe des Kaplan-Meier-Verfahrens berechnet.

5.2. Ergebnisse

Allgemein: Histologisch zeigte sich bei 40 Patienten ein atypisches Lipom, bei 43 Patienten ein myxoides, bei 8 Patienten ein pleomorphes und bei 13 Patienten ein dedifferenziertes Liposarkom. Hinsichtlich des Gradings wurden, unter Vernachlässigung der 40 atypischen Lipome, 23% als G1, 47% als G2 und 30% als G3 klassifiziert. In 69 Fällen war der Oberschenkel, in 12 der Unterschenkel, in je 6 der Oberarm, der Stamm oder die Kniekehle, in 3 Fällen die Axilla und in den weiteren Fällen sonstige Regionen betroffen. 22 Patienten (21%) verstarben zwischenzeitlich. Das Follow-Up der lebenden Patienten betrug im Durchschnitt 54,7 (3-332) Monate.

Atypische Lipome/myxoide Liposarkome: Das Durchschnittsalter zum Zeitpunkt der Operation war bei den ALT mit 61,9 Jahren höher als bei den myxoiden Liposarkomen mit 48,6 Jahren. Auch der mittlere Tumordurchmesser der ALT war mit 17 cm größer als der der myxoiden Liposarkome, wo er 12 cm betrug. Beide Tumortypen fanden sich mehrheitlich im Bereich der unteren Extremität: In 33 von 40 Fällen bei den ALT und in 40 von 43 Fällen bei den myxoiden Liposarkomen. Die atypischen Lipome wurden vorwiegend (in 31 Fällen) R1-, in acht Fällen R0- und einmal R2-reseziert. Demgegenüber erfolgte bei den myxoiden Liposarkomen bei 31 Patienten eine weite und in zwölf Fällen eine marginale (R1) Resektion. Die myxoiden Liposarkome wurden im Rahmen des Gradings weiterhin unterteilt. Dabei wurden 14 Fälle als G1, 25 Fälle als G2 und 4 Fälle als G3 eingestuft. Das mittlere Follow-Up lag bei 46 (myxoide) bzw. 40 Monaten (ALT). Während der Nachbeobachtungszeit starben 4 der ALT-Patienten durch nicht tumorassoziierte Ursachen; eine Dedifferenzierung oder das Auftreten von Metastasen wurde nicht beobachtet. Jedoch entwickelten 3 (7,5%) der R1-resezierten Patienten Lokalrezidive. Zwei der drei

Rezidive traten bei bereits vorbekannten Rezidiv-Patienten auf. Bei den myxoiden Liposarkomen zeigten sich bei 4 Patienten Metastasen (alle nicht-pulmonal), 3 davon bereits zum Zeitpunkt der Tumorresektion. Es gab 9 Todesfälle, darunter alle 4 Patienten mit Metastasen. Vier (9,3%) Patienten entwickelten ein LR; auch hier gingen allen R1-Resektionen voraus. Das 5-Jahres-LR-freie Überleben betrug 82%, das Gesamtüberleben (OS) 81% nach 5 Jahren und 72% nach 10 Jahren. In multivariaten Analysen zeigten Alter und Grading einen signifikanten Einfluss auf das Gesamtüberleben, in univariaten Analysen konnte dies für die Parameter „Alter > 48 Jahre", sowie „Fernmetastasen" dokumentiert werden.

Bei den **pleomorphen und dedifferenzierten Sarkomen** spielten die Resektionsränder in Hinblick auf das Gesamtüberleben nicht-signifikant, aber im Trend nur für die R2-Resektionen verglichen mit allen nicht-R2-Resektionen eine Rolle (p=0,074). Hinsichtlich des Lokalrezidivrisikos war dies ebenfalls orientierend (aber nicht signifikant) zu sehen (R0: 0% vs. R1: 14% vs. R2: 50%, p=0,069). 26% dieser Gruppe zeigten bereits initial, weitere 10% im Verlauf, Metastasen. Insgesamt entwickelte sich bei beiden Entitäten unabhängig von der Weite des erzielten Resektionsrandes, auch bei unter 1 mm, lediglich bei einem Patienten ein Lokalrezidiv. Auch bezüglich der Überlebenszeit ergab sich innerhalb der R0-Resektionen kein Unterschied in Abhängigkeit der Weite des Resektionsrandes. 49 Patienten mit nicht-atypischen Liposarkomen wurden bestrahlt. Dies wirkte sich nicht signifikant auf das Überleben oder die Lokalrezidivrate aus.

5.3. Schlussfolgerungen

Zusammenfassend lässt sich feststellen, dass sich sowohl ALT als auch myxoide Liposarkome im Allgemeinen durch eine gute Prognose auszeichnen. Während ALT in der Regel nicht metastasieren und das Risiko für eine Dedifferenzierung auch laut einer Metaanalyse der englischen Literatur der vergangenen 30 Jahre nur etwa 1% beträgt, sind myxoide Liposarkome durch die Neigung zur nicht-pulmonalen Metastasierung gekennzeichnet. Daraus ergibt sich hinsichtlich Planung und Durchführung der jeweiligen Therapie ein unterschiedliches Vorgehen. So erweist sich die marginale Resektion unter Erhalt der Tumorkapsel bei ALT als ausreichend und zeigt eine vertretbare LR-Rate. Im Falle eines Rezidivs kann dieses selbst bei großer Nähe zu wichtigen Leitungsbahnen ohne erhebliche Morbidität durch eine Re-Resektion behandelt werden [20]. Im Gegensatz dazu ist bei Patienten mit myxoiden Liposarkomen in Abhängigkeit des jeweiligen Risikoprofils neben der chirurgischen Resektion des Tumors häufig zusätzlich eine prä- oder postoperative Strahlentherapie indiziert. Des Weiteren ist, insbesondere bei Hochrisikopatienten, im Rahmen des Stagings und der Verlaufskontrolle eine bildgebende Diagnostik des Thorax, des Abdomens, der Wirbelsäule und des Beckens zur Erkennung von Metastasen notwendig. Dies geschieht vorzugsweise aufgrund des besonderen Metastasierungsmusters mittels Ganzkörper-MRT oder CT-Scan und MRT der Wirbelsäule und des Beckens.

Bei Patienten mit dedifferenzierten und pleomorphen Sarkomen zeigte sich zwischen den nicht-R2-resezierten (R0- bzw. R1-) und den R2-resezierten Tumoren hinsichtlich des Gesamtüberlebens zwar im Trend ein Unterschied, dieser war aber nicht signifikant. Hinsichtlich des Auftretens von Lokalrezidiven in

Abhängigkeit der Resektionsränder konnte sich ebenfalls lediglich ein Trend, jedoch ohne Signifikanz, abzeichnen. Auch die Weite des erzielten Resektionsrandes innerhalb der R0-Resektionen hatte weder Einfluss auf die Lokalrezidivrate noch auf die Überlebenszeit.

6. Summary

6.1. Methods

From 1983 to 2015 surgical resection was performed in 104 patients with liposarcoma of the extremities and body trunk. In terms of preoperative imaging, predominantly magnetic resonance imaging (MRI) and in some cases computed tomography (CT) was used to define size and location of the tumour. Resection margins were defined as R0 (wide resection) if a rim of healthy tissue around the lesion was present, or R1 (marginal resection) if the margins were contaminated but the tumour capsule remained closed. In atypical lipomas, R2 resection was attempted in few selected patients leaving tumour tissue macroscopically present at the resection margin. All patients were followed up for evidence of local recurrence (LR) or distant metastasis. In addition, overall and recurrence-free survival were calculated using the Kaplan-Meier method.

6.2. Results

Generally: Histological examination showed atypical lipoma in 40 patients, myxoid liposarcoma in 43 patients, pleomorphic liposarcoma in 8 patients and dedifferentiated liposarcoma in 13 patients. Neglecting the 40 atypical lipomas, 23% of tumours were classified as G1, 47% as G2 and 30% as G3. In 69 cases the thigh was affected, in 12 the lower leg, in 6 each the upper arm, the trunk or the popliteal fossa, in 3 cases the axilla and in all other cases other regions. 22 patients (21%) died during follow-up, which was 54.7 (3-332) months in average.

ALT and myxoid liposarcoma: For ALT the mean age at surgery was higher (61.9 years) than for myxoid liposarcomas (48.6 years). The mean tumour size of ALT was 17 cm, that of myxoid liposarcomas only 12 cm. Both types of tumours were found predominantly in the lower limb: 33 cases out of 40 in ALT and 40 cases out of 43 in myxoid liposarcomas. For atypical lipoma a wide (R0-) resection was performed in 8 cases, a marginal (R1-) in 31 cases and an R2-resection in one patient. In contrast, the myxoid liposarcomas showed a wide resection in 31 patients and a marginal resection in 12 cases. Furthermore, as part of the grading the myxoid liposarcomas were subdivided: 14 cases were classified as G1, 25 cases as G2 and 4 cases as G3. The mean follow-up was 46 months (myxoid liposarcoma) and 40 months (ALT). During follow-up, 4 ALT patients died due to causes that were not tumour-related; dedifferentiation of tumours or the appearance of metastastatic disease were not observed. However, 3 (7.5%) patients (all R1) developed local recurrences. Two of our 3 recurrences occurred in already relapsed cases. In myxoid liposarcomas, 4 patients showed metastatic disease (all non-pulmonary), 3 of them already at the time of surgery. Nine patients died, including the 4 metastatic patients. Four (9.3%) patients developed LR (all R1). 5-year LR-free survival was 82%, overall survival (OS) was 81% at 5 years and 72% at 10 years. In multivariate analysis

age and grading proved to have a significant impact on overall survival; in univariate analysis, this could be documented for age over 48 years and distant metastasis.

Concerning **pleomorphic and dedifferentiated sarcomas**, overall survival was hardly influenced by the margins of resection, except for a not statistically significant difference between the R2-resection group and the combined results of R0 and R1 group ($p = 0.074$). Regarding the risk of local recurrence this was also a trend (but not significant) (R0: 0% vs. R1: 14% vs R2: 50%, $p = 0.069$). 26% of this group already showed metastatic disease initially, another 10% during follow-up. Both subtypes developed only one local recurrence which was independent of the expanse of the tumour-free margin, even at less than 1 mm. Regarding the survival time, there was also no difference within the R0-resections depending on the expanse of the tumor-free margin. Radiotherapy was performed in 49 patients with non-atypical liposarcomas. This did not significantly affect survival or local recurrence rates.

6.3. Conclusions

In summary both ALT and myxoid liposarcomas generally have a good prognosis. ALT usually do not metastasize and the risk of dedifferentiation is as low as about 1% according to our meta-analysis of the English literature of the last 30 years. Myxoid liposarcomas are characterized by the propensity for non-pulmonary metastasis. This results in a different staging procedure in planning and implementing the respective therapy. Thus, marginal resection of the tumour while trying to maintain the tumour capsule around the lesion proves to be sufficient in ALT with an acceptable rate of LR. In case of recurrence re-resection is possible without substantial morbidity even in cases with proximity to major nerves or blood vessels [20]. In contrast, in patients with myxoid liposarcoma, in addition to surgery, risk-adapted pre- or postoperative radiotherapy is often indicated. Furthermore, especially in high-risk patients, staging and follow-up requires imaging studies of the chest, abdomen, spine and pelvis for detection of suspected metastatic disease. This is preferably done by whole-body MRI, or CT scans and MRI of the spine and pelvic region.

In patients with dedifferentiated and pleomorphic sarcomas, a difference in overall survival between the R2- and the combined results of R0- and R1-resected tumours was indicative, but not significant. Regarding the appearance of local recurrences between the different types of resection margins, there was also only a trend without significance. The expanse of the resection margin within the R0-resections had no effect on the local recurrence rate or on the survival time.

7. Veröffentlichung I

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BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

The role of surgical margins in atypical Lipomatous Tumours of the extremities

Jessica Rauh[1], Alexander Klein[1], Andrea Baur-Melnyk[2], Thomas Knösel[3], Lars Lindner[4], Falk Roeder[5,6], Volkmar Jansson[1] and Hans Roland Dürr[1*]

Abstract

Background: Atypical lipomatous tumours (ALT) are common adipocytic tumours. Due to their large size and deep-seated location, wide resection might result in severe functional deficits. The question which margins should be aimed is hence discussed controversially.

Methods: Forty consecutive patients underwent limb-sparing resections. Margins were defined as R0 (wide resection), R1 (marginal resection) or R2 if tumour was left. All patients were followed for evidence of local recurrence or remote metastases. Overall and recurrence-free survival was calculated.

Results: The mean age at the time of surgery was 61.9 years. The mean tumour diameter was 17 cm with no patient having metastatic disease. In 8 cases a wide (R0) resection, in 31 cases a marginal (R1) and in one patient a R2-resection was performed. The median follow-up time was 40 months. Four patients died due to causes that were not tumour-related. 3 (7.5%) patients (all R1) developed local recurrences. Two of our 3 recurrences in this series occurred in 6 already recurring cases. We observed no dedifferentiation of tumours and no metastatic disease.

Conclusions: ALT represents a comparatively common diagnosis in large deep-seated lesions of the extremities, especially in patients over 60 years. Marginal resection shows an acceptable rate of local recurrence. The risk of dedifferentiation as proven also in a metaanalysis of the English literature of the last 30 years is close to 1%, metastatic disease is exceedingly rare.

Keywords: Atypical lipoma, Surgery, Recurrence, Dedifferentiation, Prognostic factors

Background

Well into the 1970s, the term "well-differentiated liposarcomas" was used to describe a class of adipocytic soft tissue tumours with local aggressive behavior but typically without metastatic spread. Based on this particular behavior, they have been renamed as "atypical lipomatous tumours (ALT)" or "atypical lipomas" if seen in the extremities or at the trunk where complete surgical excision is easier achievable than in a retroperitoneal location [1, 2]. In body regions that are more difficult to access surgically and where local recurrence is common and where a lethal outcome is possible without dedifferentiation of the tumour or metastatic disease, the term "well-differentiated liposarcoma (WDLS)" is still more appropriate [3, 4]. ALTs are with a frequency of 40–45% the most common adipocytic tumours, often seen after the fifth decade of life with a slight male predominance [3, 5]. Growing slowly this may result in comparatively large tumours.

On the benign side of the spectrum, large deep-seated lipomas do not show an overexpression of MDM2 and CDK4, thus allowing for a clear histopathological distinction from more aggressive lesions.

So the decision whether to classify a histolopathologically well-differentiated liposarcoma as an ALT or as a WDLS is mainly based on tumour location and surgical resectability and reflects the course of the disease with respect to the incidence of dedifferentiation and distant metastases [6].

Based on their typically large size and deep-seated location, a wide resection might result in severe functional deficits. So a controversial discussion about what type of margins (marginal vs wide resection) should be aimed

* Correspondence: hans_roland.duerr@med.uni-muenchen.de
[1]Musculoskeletal Oncology, Department of Orthopaedic Surgery, Physical Medicine and Rehabilitation, University Hospital, Ludwig-Maximilians-University, Campus Grosshadern, Marchioninistr. 15, D-81377 Munich, Germany
Full list of author information is available at the end of the article

for and whether adjuvant radiotherapy might reduce the risk of local recurrence is still ongoing [7]. This study reflects the experience of treating these lesions at a referral sarcoma center.

Methods

From 1988 through 2015, 40 consecutive patients with ALT of the extremities and the trunk were treated at our institution, 39 of them after 2002. All tumours were located deep to the fascia and had a diagnosis of ALT based on histopathological features and immunohistochemistry.

In terms of preoperative imaging, predominantly magnetic resonance imaging (MRI) and in some cases computed tomography (CT) was used to define size and precise location of the tumour. A CT scan of the chest was the standard study to exclude metastatic disease.

All patients underwent limb-sparing surgical resection. The margin was defined as R0 if a rim of sound tissue around the lesion was present (wide resection) or R1 if the margins were contaminated but the tumour capsule with the latter remaining closed (marginal resection). In few selected patients, part of the tumour was left as part of the surgical strategy and these were classified as a R2 resection.

In all cases, we performed an MDM2 and CDK4 immunostaining as surrogate marker for MDM2 gene amplification. In ambivalent cases MDM2 fluorescent in situ hybridization (FISH) analysis was performed (Fig. 1).

All patients were followed for evidence of local recurrence or distant metastases in general by MRI scans and chest x-rays.

For statistical analysis, overall and recurrence-free survival were calculated according to the Kaplan-Meier method. Significance analysis was performed using the Log-Rank Test or the Chi-Square Test. The data analysis software used was MedCalc®.

Results

This series

The mean age of the 21 male and 19 female patients was 61.9 years (range: 9–86). The lower extremity was involved in 33 cases (29 thigh, 4 lower calf), the upper and lower arm in 1 each, the axilla in 2 and the trunk in 3 patients. The mean tumour size was 17 cm (range: 4–65).

The mean duration of symptoms prior to surgery was 26 months (range, 1–323): 38 (95%) patients complained of swelling, 11 (28%) of pain. Neurological impairment (sensory) or restriction of movement was seen occasionally. Two patients were diagnosed as a consequence of ruling out a suspected deep vein thrombosis. Thirty-one patients had a biopsy taken at our institution or existing histopathology studies from previous surgeries. Local recurrence after surgery at other institutions was seen in 6 cases and occurred at a mean of 15 months after the preceeding surgery. No patient had evidence of metastatic disease.

In 8 cases a wide (R0) resection, in 31 a marginal (R1, Figs. 2 and 3) and in one patient with recurrent disease after 5 previous surgeries (71 years old, involvement of the sciatic nerve) a R2-resection was performed. Surgical complications included transient motor deficits in 3 patients, prolonged wound healing in 3, hematoma in 3, one infection and lymphedema in one patient. In 4 patients an adjuvant radiotherapy was performed. Two of these patients suffered from recurrent lesions and two from primary disease with infiltration of critical structures and marginal resections.

The median follow-up time was 40 months (range, 2–151). Nine patients had a follow-up of less than

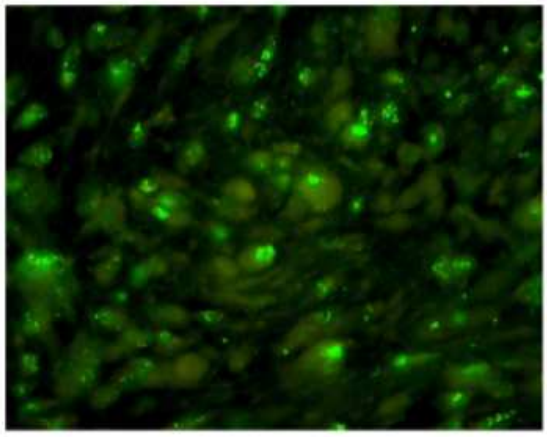

Fig. 1 Fluorescent in situ hybridization (FISH) analysis with MDM2 amplification with clusters of green signals. Centromer is red

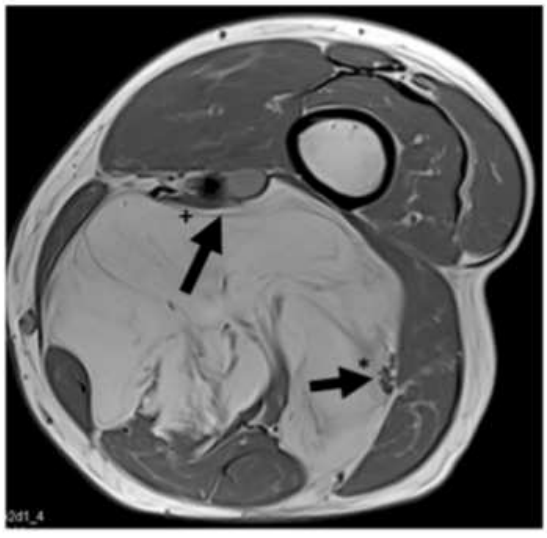

Fig. 2 A T2-weighted MRI scan shows an atypical lipoma in the dorsal aspect of the thigh in an 81-year old patient. The sciatic nerve (*) and the major vessels (+) are close to the tumour

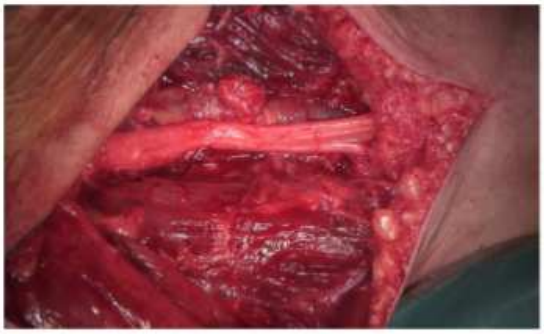

Fig. 3 Same patient as Fig. 2. The tumour has been marginal resected keeping the sciatic nerve and the major vessels

9 months whereas 13 had a follow-up of more than 60 months. Four patients died due to non-tumour-related causes.

The 5-year local recurrence free survival in this cohort was 95%. In total, 3 (7.5%) patients developed local recurrences at 7, 44 and 62 months after surgery, respectively (Fig. 4). All three patients had a marginal (R1) resection (n.s.). One of the patients had re-resection and is currently tumour-free 9 years after the second resection. Another patient has a small recurrence (after his 4th surgery) without any symptoms and is under "watchful waiting" 6 years after surgery. The third, an 89-year old patient with 14 prior surgeries and with severe heart disease has mild symptoms and has elected not to undergo further surgery (Fig. 5). We observed no case of dedifferentiation and no metastatic disease during their follow-up. In comparison to the rest of the cohort, these three patients had larger tumours (mean 26 compared to 16 cm, n.s.). Two of the 3 recurrences occurred in 6 already recurrent cases and only one after the 34 primary resections (Fig. 6, $p = 0{,}0285$). Out of the 4 irradiated cases none developed local recurrence (n.s.).

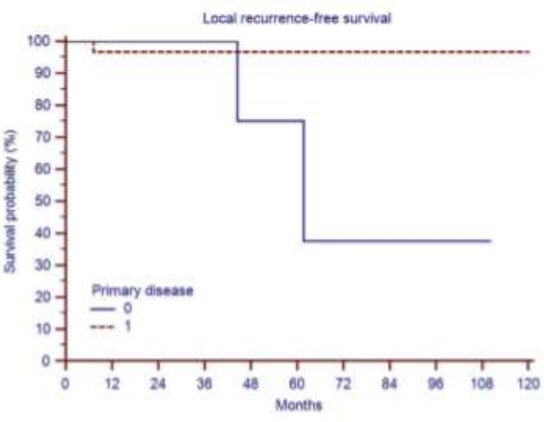

Fig. 4 Local recurrence-free survival in 40 patients with ALS

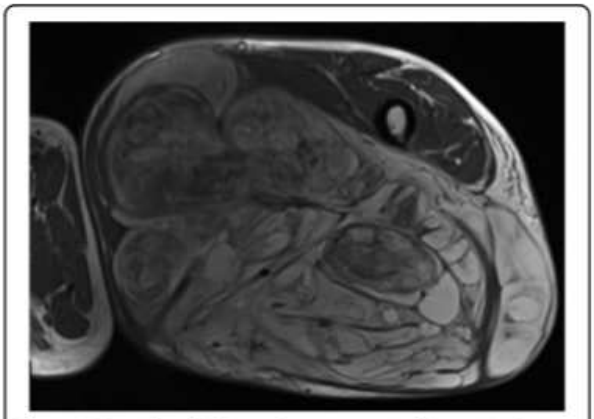

Fig. 5 A T2-weighted MRI scan shows an atypical lipoma in the dorsal aspect of the thigh in an 85-year old patient. This was the 13th local recurrence of the tumour classified always as "lipoma"

Literature

In addition, the English literature of the last 30 years including series with more than 10 cases was reviewed in detail. The results are summarized in Table 1. In total, 1143 patients are described in the papers reviewed. In 1043 of these patients, the margin status was mentioned. 59% of these cases had a marginal and 41% had a wide resection. Regarding local recurrence, information could be extracted in 701 of the patients with defined margins. Local recurrence developed in 17% of the marginally resected and in 7% of the wide resected patients ($p < 0.05$). In the whole group of 1143 patients, local recurrence was seen in 174 (15%) cases. Of these patients 14 (8%) developed a dedifferentiation in the context of local recurrence. No patient in the whole group was shown to have developed metastatic disease. The mean time until recurrence was 5.5 years and in 6 of 10 studies the mean time until local relapse was greater than 5 years.

Discussion

The classification of well-differentiated lipomatous tumours of the extremity and the trunk wall was clarified in the last edition of the WHO manual in 2013 [3]. The term "Atypical Lipoma" is well defined and accepted. Still, controversy exists regarding the rate of local recurrence, dedifferentiation, metastatic disease, surgical margins and adequate follow-up time as well as treatment regimen. Well-differentiated liposarcomas account for approximately 50% of all liposarcomas and are hence seen relatively often [8]. The long duration of symptoms (in this study: mean > 2 years, up to more than 20 years) indicates the low aggressiveness of the tumour. The raised average age of 62 years and the fact that nearly 75% of the patients developed the tumour in the thigh underlines the slow growth potential in large soft-tissue compartments where clinical symptoms are less

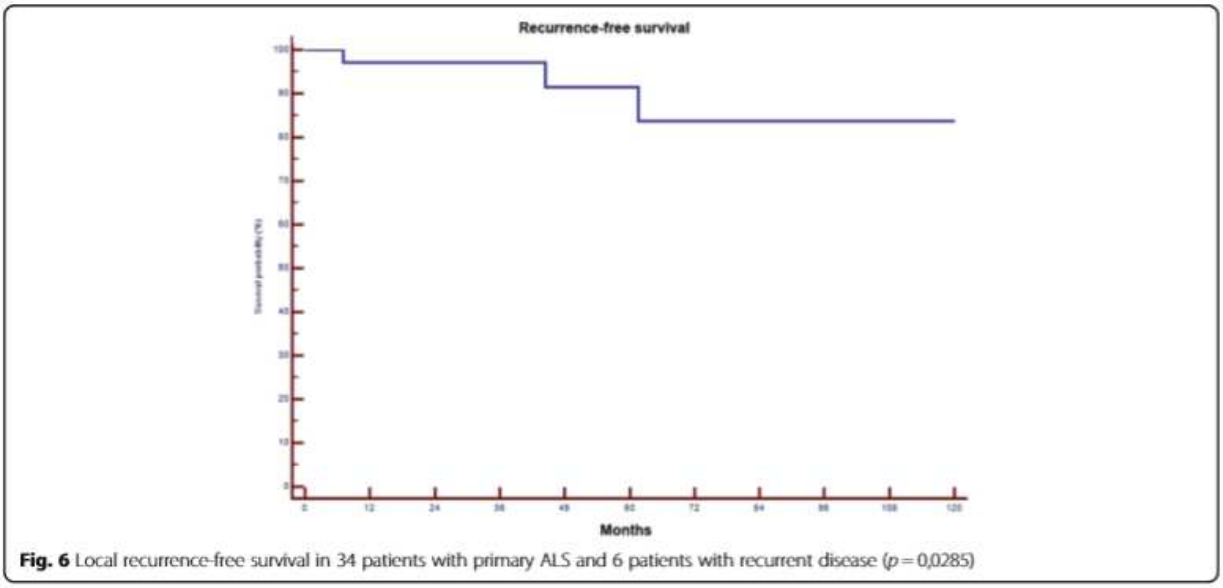

Fig. 6 Local recurrence-free survival in 34 patients with primary ALS and 6 patients with recurrent disease ($p = 0{,}0285$)

noticeable. In many of our cases, MRI proved the lesion either to be an atypical lipoma or a lipoma. Thickened or nodular septa (> 2 mm), non-adipose masses within the tumour, foci of T2-weighted signal lesions, prominent contrast enhancement and size greater than 5 cm have been described as useful to differentiate both lesions from each other [9–12]. Core needle biopsy with subsequent murine double-minute 2 (MDM2) and cyclin-dependent kinase 4 (CDK4) [13–15] analysis might provide more diagnostic accuracy before surgery

Table 1 Summary of oncologic outcome in published series of ALT of extremities and trunk wall.

			Local Recurrence			Dedifferentiation of recurrences	Metastatic disease	Mean time to recurrence (years)
Author	Year	Patients (n)	Wide Resection	Marginal Resection	Total			
Azumi et al. [20]	1987	24			7/24 29%	0/7 0%	0	
Weiss et al. [6]	1992	46			20/46 43%	3/20 15%	0	
Lucas et al. [25]	1993	32	1/9 11%	14/23 61%	15/32 47%	1/15 7%	0	7
Rozental et al. [28]	2002	31	1/9 11%	15/22 68%	16/31 52%	4/16 25%	0	4,7
Kooby et al. [24]	2003	91	0/28 0%	5/63 8%	5/91 5%	3/5 60%	0	6,8
Bassett et al. [23]	2004	51	0/0	14/51 27%	14/51 27%	1/14 7%	0	4
Sommerville et al. [22]	2005	61	0/0	5/61 8%	5/61 8%	0/5 0%	0	3,2
Evans et al. [21]	2007	11			1/11 9%	0/1 0%	0	
Zagars et al. [31]	2007	15			8/15 53%	0/8 0%	0	
Billing et al. [5]	2008	51		4/51 8%	4/51 8%	0/4 0%	0	6,8
Mavrogenis et al. [17]	2011	47	0/8 0%	5/39 13%	5/47 11%	1/5 25%	0	6,1
Yamamoto et al. [8]	2012	40	0/34 0%	0/6 0%	0/40 0%	0/0 0%	0	
Fisher et al. [32]	2013	63	59	4	14/63 22%	0/14 0%	0	
Mussi et al. [33]	2014	171	5/95 5%	11/76 14%	16/171 9%	0/16 0%	0	
Cassier et al. [26]	2014	283[a]	158	121	26/283 9%	0/26 0%	0	
Kito et al. [29]	2015	41	7/11 64%	0/30 0%	7/41 17%	1/7 14%	0	7,9
Chang et al. [7]	2016	45	1/11 9%	7/34 21%	8/45 18%	0/8 0%	0	5,3
Current study		*40*	*0/8 0%*	*3/32 9%*	3/40 8%	0/3 0%	*0*	3,1
Total		1143	15/213 7% 430	83/488 17% 613	174/1143 15%	14/174 8%	0	5,5

[a]Including patients with unknown margin status

[16]. However, due to the fact, that both lesions require the same marginal resection in our assessment, we decided for surgery without biopsy in the radiologically typical cases. Therefore, biopsy was only occasionally performed and especially in those patients at the beginning of this series.

We report an incidence of local recurrence that is half of what has been shown in several other studies with marginal resections. The most probable explanation for this difference in our view is the median follow-up time of 40 months. Only 13 out of 40 patients had a follow-up of more than 60 months. Taking into account that local recurrence developed in most of the other studies in patients more than 60 months after surgery, it is likely that our local recurrence rate will increase over time and this represents a limitation of our study. There is data indicating that the risk of local recurrence is correlated with the time of follow-up [17].

Our data also significantly supports the observation that local recurrence is more often seen in patients who already have recurrent disease [17]. In addition, a statistically significant correlation between local recurrence and marginal or wide resection is evidenced in the literature (Tab. 1). Due to the fact, that most patients have large tumours in close proximity to major vessels or nerves, a wide resection carries a considerable risk of major functional problems and / or complications. Taking into account that dedifferentiation developed only in 14 out of 1143 patients (1.2%) and metastatic disease was not seen in any of the described series, a more aggressive management including wide resections or re-excisions after primary marginal resections seems unreasonable [16]. Also in recurrent cases with close proximity to major nerves or blood vessels, re-resection is possible without substantial morbidity [18]. There are some case reports or small series of patients indicating that dedifferentiation in local recurrence might increases the risk of metastatic disease [5, 17, 19–24].

Dedifferentiation most probably occur only in a small subregion of the tumour surrounded by well-differentiated tumour which supports the concept of surgical removal and entails a much better prognosis than with other dedifferentiated sarcomas [25]. Even recurring dedifferentiated tumours might again exhibit better differentiation [6]. Dedifferentiation is much more common in retroperitoneal (17%) or groin (28%) lesions [6]. This should be taken into account in large extremity tumours extending into the pelvis or the retroperitoneum. Weiss et al., as stated before, mentioned that dedifferentiation which is more often seen in central locations might be not site-dependent, but rather time-dependent. In those locations, the tumour might grow undetected for longer times. In contrast, the experience with large and slowly growing extremity tumours as in our and many other series might in fact prove a true site-dependency.

Radiation therapy did not affect the outcome in this small series of patients with only 4 irradiated cases (no recurrence). In general, radiation therapy is effective in reducing local recurrence in R1-resections (74%) [26, 27] but the question remains, whether adjuvant radiation is necessary if the relapse could be marginally re-resected. Radiation therapy does not affect overall survival [26]. So Cassier et al. conclude that a wait-and-see policy could be adopted for R1- and R2-resected patients provided that a potential reoperation is both feasible and reasonable [26]. However, radiotherapy should be considered especially in recurrent cases where even marginal resections might produce severe functional deficits.

Follow-up time is crucial in this entity. Some authors propose a minimum of 5 years [22, 28], which in the light of the published data with a mean time to relapse of 5.5 years appears too short. As follow-up is increased in most studies, more and more recurrences are detected. The recommended observation period is hence suggested as being 8 years by some authors [29]. There are studies which show a mean time to local relapse of 16 years [8] in later re-resected patients. Regular long-term follow-up is therefore required especially in recurrent cases and should clearly exceed 5 years. We would propose 10 years in total. Whether this is done in a biannually fashion in the first 6 years and annually later as proposed [28] or in a different scheme is controversial. Due to the very low risk of dedifferentiation, clinical observation only is also regarded as being sufficient by some authors [5]. The patient may be advised to examine him- or herself. This is underlined by data showing that in most local recurrences of soft-tissue sarcomas of the extremities, the patient notices them earlier than the investigators in routine follow-up [30].

Conclusions

ALT represents a typical diagnosis in large deep-seated lesions of the extremities, especially in patients over 60 years of age. There are several characteristics in MRI as thickened septa (> 2 mm), non-adipose masses, foci of T2-weighted lesions and contrast enhancement differentiating them from lipomas. Marginal resection of the tumour while trying to maintain the thin capsule around the lesion and only opening the tumour if necessary for the preparation of major vital structures shows an acceptable rate of local recurrence. The risk of dedifferentiation is close to 1% and metastatic disease is exceedingly rare.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
JR Student doing here thesis on liposarcomas. She contacted the patients and collected the data. AK Surgeon on many of the cases, reviewer of the manuscript. AB-M Radiologist reviewing the radiologic investigations. TK Pathologist reviewing the pathologic investigations. LL Oncologist. None of the patients in the study received chemotherapy. But every patient was discussed in the interdisciplinary panel and the decision not to treat was based on this. FR Reviewing the radiotherapy and deciding which patient to treat or not to treat. VJ Surgeon on many of the cases, reviewer of the manuscript. HRD Corresponding author. Developed the study concept, did the final data analysis and provided the major clinical input in writing of the manuscript. Each author has contributed significantly to, and is willing to take public responsibility for this study: its design, data acquisition, and analysis and interpretation of data. All authors have been actively involved in the drafting and critical revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study was approved by the ethics committee of the Medical Faculty, University of Munich. Written consent was obtained from the patients included in this study.

Competing interests
The authors declare that they have no competing interests.

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Author details
[1]Musculoskeletal Oncology, Department of Orthopaedic Surgery, Physical Medicine and Rehabilitation, University Hospital, Ludwig-Maximilians-University, Campus Grosshadern, Marchioninistr. 15, D-81377 Munich, Germany. [2]Institute of Radiology, University Hospital, LMU, Munich, Germany. [3]Institute of Pathology, University Hospital, LMU, Munich, Germany. [4]Department of Medicine III, University Hospital, LMU, Munich, Germany. [5]Department of Radiotherapy, University Hospital, LMU, Munich, Germany. [6]CCU Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany.

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RESEARCH ARTICLE Open Access

Myxoid liposarcoma: local relapse and metastatic pattern in 43 patients

Hans Roland Dürr[1*], Jessica Rauh[1], Andrea Baur-Melnyk[2], Thomas Knösel[3], Lars Lindner[4], Falk Roeder[5,6], Volkmar Jansson[1] and Alexander Klein[1]

Abstract

Background: Liposarcomas are the second most common type of soft tissue sarcomas, 30–50% of these are of myxoid subtype. The aim of this retrospective study was to analyze the local control rate, the metastatic pattern and survival of patients in a consecutive single-institution series.

Methods: From 1983 to 2015, 43 patients with myxoid liposarcoma of the extremities and trunk wall underwent resections. The margin was defined as R0 (wide) or R1 (marginal). Patients were followed for evidence of local recurrence or distant metastasis. Overall and recurrence-free survival was calculated.

Results: The mean age was 48.6 years. The lower extremity was involved in 40 cases, the mean tumour size was 12 cm. In 31 cases a wide and in 12 cases a marginal resection was performed. Grading was G1 in 14, G2 in 25 and G3 in 4 cases.
Nine patient died in follow-up, 4 of them with metastatic disease, all nonpulmonary. 5-year local recurrence (LR) free survival was 82%. 4 (9.3%) patients developed LR (all R1). Overall survival (OS) was 81% after 5 and 72% after 10 years. In multivariate analysis age and Grading proved to be significant on OS. According to univariate analysis, only age over 48 years and distant metastasis had a significant impact on overall survival.

Conclusions: Patients with myxoid liposarcomas have a good prognosis. Myxoid liposarcoma has a distinct pattern of nonpulmonary metastatic disease. Therefore, patients with high-risk extremity myxoid liposarcoma should undergo imaging studies of the chest, abdomen, spine and pelvis as part of their staging and follow-up examinations preferably with whole body MRI, or CT scans and MRI of the spine and pelvic region for detection of suspected metastatic disease.

Keywords: Sarcoma, Myxoid liposarcoma, Surgery, Recurrence, Prognosis, Survival

Background

Sarcomas in adult patients comprise approximately 1% of all newly diagnosed cancers with an incidence of 3–6 cases per 100,000 population [1, 2]. Liposarcomas are the second most common type of soft tissue sarcomas (15–20%), 30–50% of these are of myxoid or myxoid round cell subtype [3–5]. Myxoid liposarcoma is a genetically distinct variant of liposarcoma, characterized by a t(12:16) translocation. A variable content of round cells is characteristic and known as a poor prognostic factor (> 5%) [5, 6].

From a clinical point of view an important factor of this usually slow-growing, deep seated tumour mainly located in the lower extremities is the propensity to metastasize to nonpulmonary soft-tissues as the retroperitoneum, the bone or the contralateral limb [7]. Furthermore, myxoid liposarcoma is particular radiosensitive thus neoadjuvant radiation protocols may be very effective [8–10].

The aim of this retrospective study was to analyze the local control rates, the metastatic pattern and survival of patients in a consecutive single-institution series.

* Correspondence: hans_roland.duerr@med.uni-muenchen.de
[1]Musculoskeletal Oncology, Department of Orthopaedic Surgery, Physical Medicine and Rehabilitation, Campus Grosshadern, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany
Full list of author information is available at the end of the article

Methods

From 1983 to 2015, 43 consecutive patients with myxoid liposarcoma of the extremities and trunk wall had been treated in our institution, 37 of them since 2005. All tumours were located deep to the fascia and had a diagnosis of myxoid liposarcoma based on histological features and immunohistochemistry. Thirty-seven patients had primary, 6 recurrent disease.

Preoperative staging included at least MRI (predominantly) or CT of the primary tumour region and CT chest. All patients underwent limb-sparing surgical resection. The margin was defined as R0 if a rim of sound tissue around the lesion was present (wide resection) or R1 if the margins were contaminated but the tumour capsule closed (marginal resection). The French Federation of Cancer Centers grading system was used to assign tumour grade [11]. All patients were followed routinely for evidence of local recurrence or distant metastasis.

For statistical analysis, overall and recurrence-free survival were calculated by the Kaplan-Meier method. Univariate subgroup analysis were done using the log-rank test (time-to-event data) or the chi-square test. For multivariate analysis a Cox proportional-hazard regression model was used. Significance analysis was performed using the log-rank test, the Chi-Square test or the Cox proportional-hazards regression. The data analysis software used was MedCalc®.

Results

The mean age of the 21 male and 22 female patients was 48.6 years (range, 18–83). The lower extremity was involved in 40 cases (25 thigh, 9 lower calf, 5 popliteal region, 1 ft), the upper arm in 1 and the trunk in 2 patients. The mean tumour size was 12 cm (range, 1–33).

The mean duration of symptoms was 15 months (range, 0–71), 35 (81%) patients complained of swelling, 5 (12%) of pain. Neurological impairment (sensory) or restriction of movement was seen occasionally. Forty patients had a biopsy or histology from previous surgeries, in 3 cases surgery was done as excisional biopsy. In 3 patients metastatic disease was evident at the time of surgery (2 primary, one of them also in local recurrence). The metastatic lesions were found in the retroperitoneal space, the lumbar spine and the lymph nodes of the pelvis.

In 31 cases a wide (R0) resection and in 12 a marginal (R1) resection was achieved. In wide resections the margins were smaller than 1 mm in 9 patients, between 1 and 5 mm in 11 and larger than 5 mm in 11 patients. Grading was G1 in 14, G2 in 25 and G3 in 4 cases.

Surgical complications included transient neurapraxia in 7 patients, prolonged wound healing in 10, hematoma or seroma in 7, lymphedema in 3, infection in 1 and fractures in 3 (all after periostal resection and radiotherapy). In total 14 surgical revisions had to be performed. Twenty-one patients received postoperative and 11 patients preoperative radiation therapy. Indication for radiation therapy was seen generally in patients with G2/G3 lesions or after marginal resection in G1 lesions. Chemotherapy of variable protocols had been applied in 22 patients.

Nine patient died in follow-up, 4 of them had proven metastatic disease disease. The median follow-up of the surviving was 46 months (range, 2–305). Nine patients had a follow-up of less than 24 months, 4 of them less than 12 months.

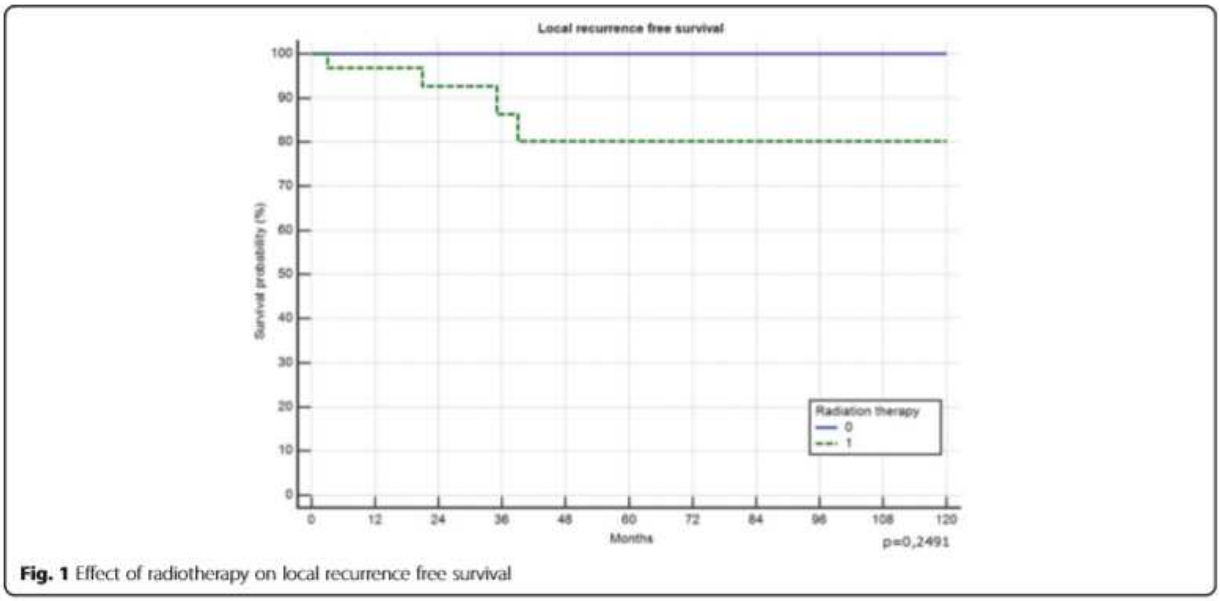

Fig. 1 Effect of radiotherapy on local recurrence free survival

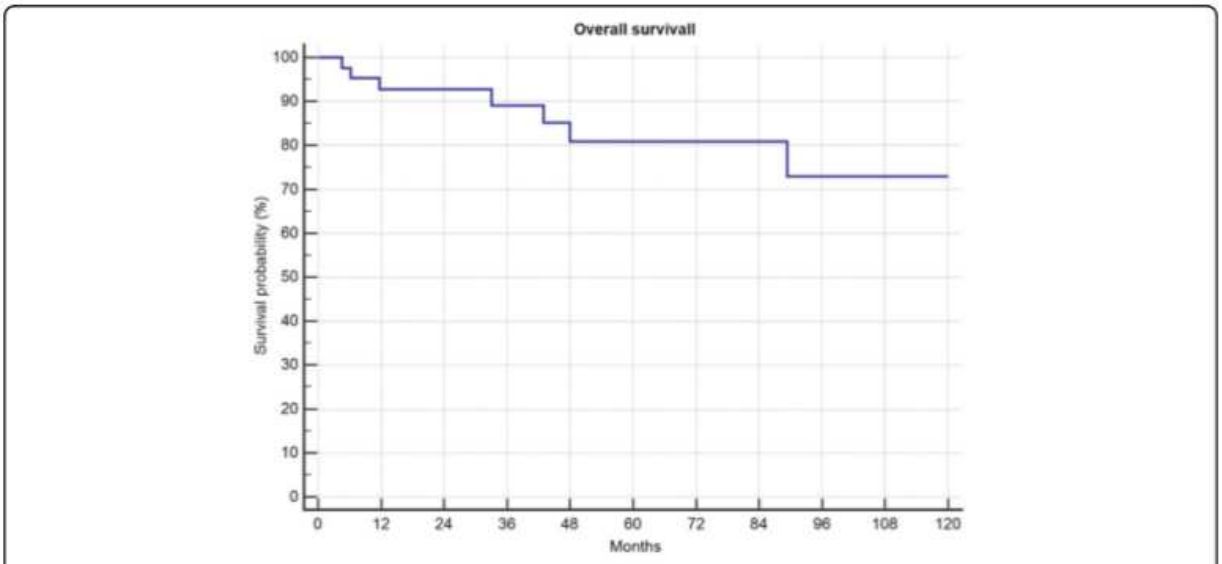

Fig. 2 Overall survival in 43 patients with myxoid liposarcoma

5-year local recurrence free survival was 82%. In total 4 (9.3%) patients developed local recurrences 21, 34, 42 and 49 months after surgery. All of them had a marginal (R1) resection (4/12 R1, 0 of 31 R0; $p = 0.0034$) and suffered from G2 tumours (n.s.). Two of them had primary tumours, 2 had been treated for locally recurrent disease ($p = 0.034$). All 4 received radiation therapy (2 preoperative, 2 postoperative). Only one of those 4 had metastatic disease (initially) and deceased in follow-up. Local recurrence free survival in those patients with risk factors necessitating radiation therapy was not significantly different than the local recurrence free survival in patients without (Fig. 1). In one patient metastatic disease developed 2 months after resection of a primary tumour retro- and intraperitoneal, all 3 patients with preexisting metastatic disease showed progression. Overall survival was 81% after 5 years and 72% after 10 years (Fig. 2), progression free survival was 78% after 5-years (Fig. 3). Patients with primary tumours had a mean overall survival of 196 months in recurrent disease 60 months respectively (n.s.). In multivariate analysis the patient and tumour-dependent factors as age, Grading and size proved to be significant on overall survival. Including recurrent disease, only age and grading remained significant (Table 1).

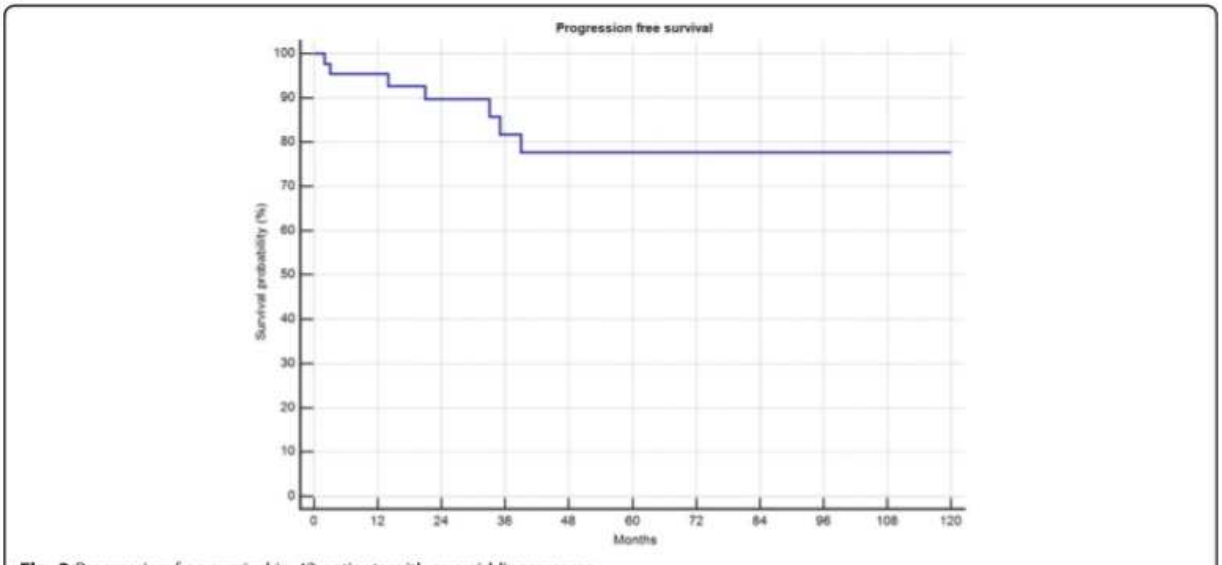

Fig. 3 Progression free survival in 43 patients with myxoid liposarcoma

Table 1 Cox proportional-hazards regression of grading and size of the tumor and age of the patient

Factor	P	HR	95% CI
Age	0,0027	1,16	1,05–1,27
Grading	0,0239	26,30	1,54–448,91
Size	0,1961	1,07	0,97–1,18
Primary/Recurrent	0,9607	0,00	0

HR indicates hazards ratio; CI 95% confidence interval

According to univariate analysis, only age over 48 years and presence or development of distant metastasis had a significant impact on overall survival (Fig. 4).

Discussion

The crude rate of local recurrences (LR) and distant metastasis (DM) was 9% each. Overall survival (OS) was 81% after 5 years and 72% after 10 years. These results seem to compare favourably with published series reporting LR rates of 13–33%, DM rates of 11–38% ad 10-year OS rates of 55–86%, although age distribution and tumour sizes (our mean 12 cm, published 9–14 cm) were similar in our compared to the mentioned studies [12–18]. The in literature described shorter OS in recurrent cases failed significance in this series. We identified tumour size, grading and age with a cut off of 45–60 years as prognostic factors regarding overall survival according to multivariate analysis [13, 15, 18, 19]. In contrast, we could not verify a significant negative impact of recurrent disease with regard to OS as reported by other investigators, probably due to the small number of patients. Obviousely these patients are a selected group as they have already recurred. They are likely to be more biologically aggressive as evidenced by the fact

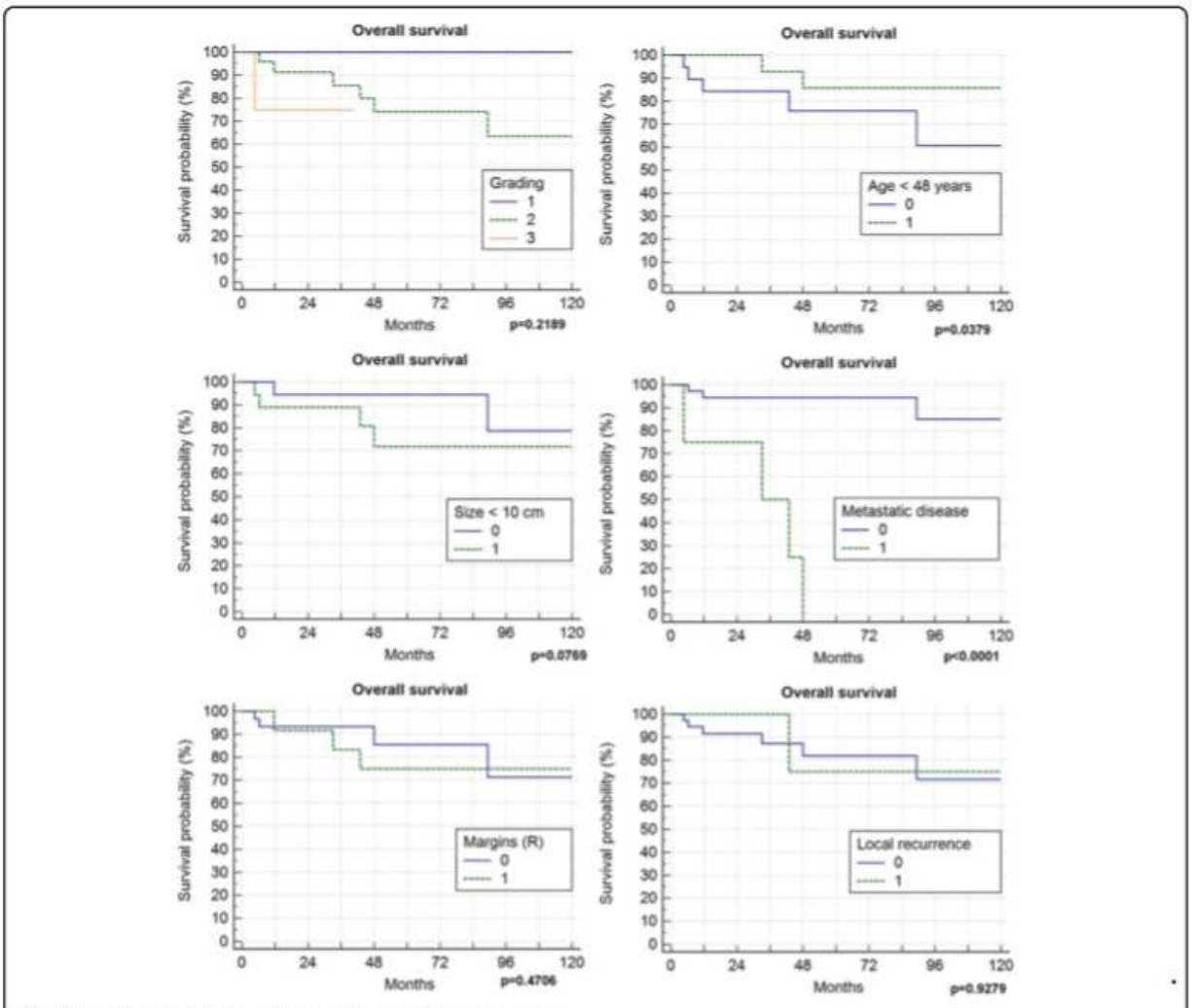

Fig. 4 Overall survival in dependence to different clinical parameters

that out of our 6 patients 3 (50%) developed a relapse (2 local and 1 distant).

As shown in Fig. 4 grading has an impact, mainly between grade 1 and 2, weaker between 2 and 3, as also described by Fiore et al. [17]. We did not compare the amount of the round cell component with a cut-off level of 5% to differentiate pure myxoid liposarcoma (MLPS) from round cell liposarcoma (RCLPS). MLPS tumours always were graded 1, there as RCLPS may reflect the worse survival in in the group of G2 or 3 tumours.

Metastatic disease has a strong impact on survival with a poor outcome. All our 4 patients who had MD at diagnosis or developed MD in the course of the disease died with a median survival of 33 months. This comparatively long survival in MD stands in contrast with other metastasized soft tissue sarcomas but represents the experience of other authors, too [7, 20]. The distinctive pattern of MD is well known in myxoid liposarcoma. Common sites are the retroperitoneum, abdominal wall and abdominal cavity [7]. Schwab et al. reported 17% of patients developing skeletal metastases, more than one-half of metastatic events in their series [21]. Estourgie et al. described 13 of 14 patients with MD had extrapulmonary lesions [20]. Because of MD developing also in soft tissues, multicentric lesions at diagnosis should be seen critically and may represent in fact MD [22–24]. This metastasis in fat-bearing areas is unique and might be contributed by the expression of high levels of adipophilin and chemokine (C-X-C motif) receptor 4 (CXCR4), which are both correlated with adipogenesis and metastasis [25].

Conventional methods of imaging as chest x-rays, CT or even PET-scans well established in other soft tissue sarcomas may fail in detecting metastastic disease in myxoid liposarcoma.

In one of our metastatic patients, even FDG-PET-CT was not able to detect the skeletal lesion as shown in Fig. 5 [26–28]. In a 2010 published survey all 8 patients with skeletal MD were positive on MRI, 2 out of 4 were negative in bone scans and 6 out of 8 were negative in CT scans [29]. Therefore WBMRI seems to be the most reliable method at present. For example Seo et al. demonstrated sensitivity and specifity rates of 80%/97% in soft-tissue lesions and 85%/99% in bony lesions respectively in a series of 15 patients [30]. Stevenson et al. reported 28 patients who received whole-body MRI and CT. Of 38 lesions found on MRI, 29 were located inside a corresponding CT field of view but only 5 of 8 soft-tissue lesions and none of 21 bony lesions were detected [31].

Patients with positive surgical margins had a 30% risk of LR compared to 0% in wide resections. But this did not influence OS neither if we correlated it to margins nor to LR itself. Only one out of 4 patients with LR developed DM. In literature this is discussed controversially.

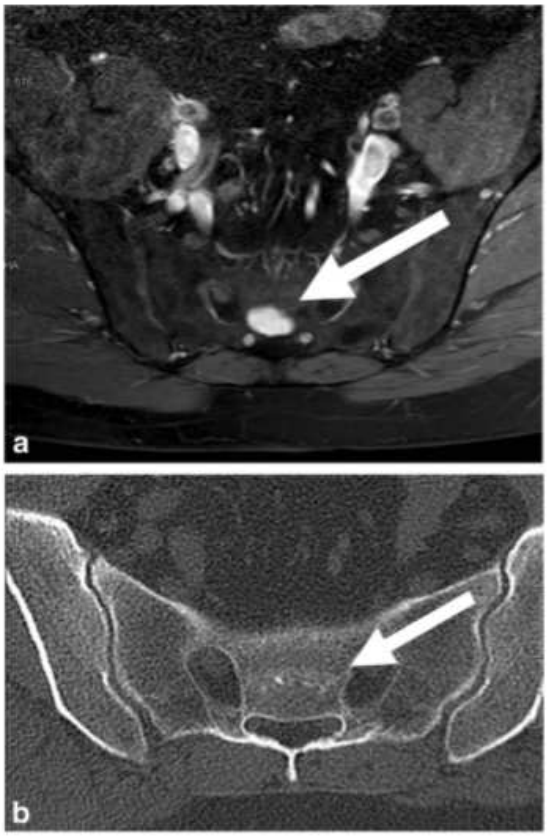

Fig. 5 a-c 41-year old patient with solitary metastatic disease in the sacrum (S3) 6 years after surgery of the primary in the right calf. Lesion clearly detectable on MRI (**a**) but not on CT (**b**) or PET-CT scan (**c**)

Margins seem to influence disease specific survival but not metastasis-free survival [32]. This may be caused by the inclusion of patients with critical locations as retroperitoneum or head and neck in this studies, not included in this series. Further on, we found a clear but insignificant trend between larger tumour size and the presence of contaminated margins.

Interestingly, in this study radiation therapy had a great influence on therapy by decreasing the size of many tumours in a significant proportion, whereas it did not influence LR. This is in contrast to Guadagnolo et al. from the MDACC where in 11 patients with positive surgical margins and radiotherapy (median dose 50 Gy) no one showed LR [8]. Chung et al. from Toronto published a 98% LR-free 5-year survival with only 2 recurrences in 88 patients [9]. Using radiotherapy in marginal or even intralesional resections in 10 patients the addition of radiotherapy resulted in no local relapse at a mean follow-up of 58 months [33]. Even in a hypofractionated protocol (5 × 5 Gy followed by immediate surgery) in 32 patients a 5-year LR of 10% was achieved [34]. In many other

retrospective studies, as in ours, in which radiation is part of therapy in selected cases a strong bias with more relevant risk factors in patients in the radiotherapy group might influence the result. However, the effect of neoadjuvant radiotherapy on tumour size could be seen in many of our cases. This was not part of this study protocol but as described by Pitson et al. in 16 patients 50 Gy of preoperative radiotherapy induced a significant reduction of 59% in the mean MRI tumour volume [10].

Chemotherapy has been applied in many of our cases due to a general regime in soft tissue sarcomas in our sarcoma center. Going back in literature doxorubicin- and dacarbazine-based chemotherapy had been proven to be effective in myxoid liposarcoma [35]. More recently trabectedin had shown beneficial effects both as second-line chemotherapy and in neoadjuvant protocols [36, 37].

Conclusion

In summary patients with myxoid liposarcomas generally have a good prognosis. Overall survival was 72% after 10 years, local recurrence was seen only in 9% of the patients treated with limb-sparing surgery and risk-adapted radiation therapy. Preoperative radiation therapy further provides a substantial effect in decreasing tumour size. This particular subtype of soft tissue sarcomas has specific characteristics as a distinct pattern of nonpulmonary metastatic disease. Therefore, patients with high-risk extremity myxoid liposarcoma should undergo imaging studies of the chest, abdomen, spine and pelvis as part of their staging and follow-up examinations preferably with whole body MRI, or CT scans and MRI of the spine and pelvic region for detection of suspected metastatic disease.

Abbreviations

CI: Confidence interval; cm: Centimeter; CT: Computed tomography; DM: Distant metastasis; FDG-PET: Fluordesoxyglucose-positron emission tomography; G1, G2, G3: Grading according to the French Federation of Cancer Centers grading system; HR: Hazard ratio; LR: Local recurrence; MD: Metastatic disease; MLPS: Pure myxoid liposarcoma; MRI: Magnetic resonance imaging; n.s.: Not significant; OS: Overall survival; R0, R1, R2: Resection margin; RCLPS: Round cell liposarcoma; WBMRI: Whole-body magnetic resonance imaging

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HRD: Corresponding author. Developed the study concept, did the final data analysis and provided the major clinical input in writing of the manuscript. JR: Student doing here thesis on desmoid-type fibromatosis. She contacted the patients and acquiered the data, involved in drafting and revising of the manuscript. AB: Radiologist reviewing the radiologic investigations, involved in drafting and revising of the manuscript. TK: Pathologist reviewing the pathologic investigations, involved in drafting and revising of the manuscript. LL: Oncologist. Every patient was discussed in the interdisciplinary panel and the final decision regarding chemotherapy was based on this; involved in drafting and revising of the manuscript. FR: Reviewing the radiotherapy and deciding which patient to treat or not to treat, involved in drafting and revising of the manuscript. VJ: Surgeon on many of the cases, reviewer of the manuscript, involved in drafting and revising of the manuscript. AK: Surgeon on many of the cases, involved in drafting and revising of the manuscript. Each author has contributed significantly to, and is willing to take public responsibility for this study: its design, data acquisition, and analysis and interpretation of data. All authors have been actively involved in the drafting and critical revision of the manuscript. All authors read and approved the final manuscript.

Authors' information

All authors are part of the SarKUM, the Bone and Soft Tissue Tumor Center of the University Hospital, Ludwig-Maximilians-University Munich.

Ethics approval and consent to participate

This study was approved by the ethics committee of the Medical Faculty, University of Munich. Written consent was obtained from all surviving patients included in this study. In accordance with the ethics committee, the data from non-surviving patients were irreversible anonymized for statistical evaluation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Author details

[1]Musculoskeletal Oncology, Department of Orthopaedic Surgery, Physical Medicine and Rehabilitation, Campus Grosshadern, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany. [2]Institute of Radiology, Campus Grosshadern, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany. [3]Institute of Institute of Pathology, Campus Grosshadern, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany. [4]Department of Medicine III, Campus Grosshadern, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany. [5]Department of Radiation Oncology, Campus Grosshadern, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany. [6]CCU Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany.

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9. Eigenanteil an den vorgelegten Arbeiten

Der Beitrag der Doktorandin, die in dem Fachartikel „The role of surgical margins in atypical lipomatous tumours of the extremities" als Erstautorin und in „Myxoid liposarcoma: local relapse and metastatic pattern in 43 patients" als Ko-Autorin auftritt, umfasst zum einen die Kontaktaufnahme mit den Patienten, sowie die eigenständige Erhebung und Auswertung der Patientendaten. Zum anderen war sie in Zusammenarbeit mit Prof. Dr. H.R. Dürr an der klinischen Interpretation der Daten, sowie an der Verfassung und Überarbeitung beider Veröffentlichungen maßgeblich beteiligt.

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12. Lebenslauf

PERSÖNLICHE DATEN

Name: Jessica Bettina Rauh
Nationalität: deutsch
Alter: 25, geboren am 09. August 1992 in Augsburg

AUSBILDUNG

2013-2018: *Studium der Humanmedizin, Klinik (abgeschlossen am 05.06.2018, Gesamtleistung 2,0)* an der Ludwig-Maximilians-Universität München (LMU)

2011-2013: *Studium der Humanmedizin, Vorklinik (1. Staatsexamen im August 2013, Leistung 80,8%)* an der Ludwig-Maximilians-Universität München (LMU)

2003-2011 *Gymnasium Königsbrunn (Mai 2011 Abitur, Note: 1,2)*

FAMULATUREN

02.2016-03.2016	Praxis für Gynäkologie	München
07.2015-08.2015	Orthopädie	LMU, Campus Großhadern
07.2014-08.2014	Praxis für Pädiatrie	München
03.2014-04.2014	Innere Medizin	Hall in Tirol, Österreich

PRAKTISCHES JAHR

12.2017-03.2018	Kinder- und Jugendpsychiatrie	Bern, UPD
10.2017-12.2017	Unfallchirurgie	Fort-de-France, Martinique
09.2017-10.2017	Kinderchirurgie	Klinikum Augsburg
05.2017-09.2017	Innere Medizin	Bern, Hirslanden-Gruppe