Aus der Klinik für Orthopädie, Physikalische Medizin und Rehabilitation
Klinik der Ludwig-Maximillians-Universität München

Direktor: Prof. Dr. Dipl.-Ing. Volkmar Jansson

Einfluß von Grading und Resektionsabstand auf das progressionsfreie Gesamtüberleben bei Chondrosarkompatienten

Dissertation

zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

Vorgelegt von
Dr. med. univ. Julian Dominik Fromm
aus
Stuttgart

2020

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Berichterstatter:	Prof. Dr. med. Hans Roland Dürr
Mitberichterstatter:	PD Dr. med. Wenko Smolka Prof. Dr. med. Christian Graeb
Dekan:	Prof. Dr. med. dent. Reinhard Hickel
Tag der mündlichen Prüfung:	30.07.2020

Inhaltsverzeichnis

Eidesstattliche Versicherung

Eidesstattliche Versicherung

Fromm, Julian Dominik

Name, Vorname

Ich erkläre hiermit an Eides statt,

dass ich die vorliegende Dissertation mit dem Titel

„Einfluß von Grading und Resektionsabstand auf das progressionsfreie Gesamtüberleben bei Chondrosarkompatienten“

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen wurden, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Julian Fromm

München, den 04.08.2020

Für meine Familie
Babsi, Hannah und Claus

Abkürzungsverzeichnis

CS – Chondrosarkom / chondrosarcoma
WE – wide excision
EB – en bloc resection
A – Amputation / amputation
CT – Computertomografie / computed tomographie scan
MRT – Magnetresonanztomografie
ACT – atypical cartilaginous tumor
LR – Lokalrezidiv / local recurrence
OS – overall survival
LRFS – local recurrence free survival
ACT – atypical cartilaginous tumor
MRI – magnetic resonance Imaging

Publikationen

Originalarbeiten

Fromm J, Klein A, Baur-Melnyk A, Knösel T, Linder L, Birkenmaier C, Roeder F, Jansson V, Dürr HR. *Survival and prognostic factors in conventional central chondrosarcoma.*

BMC Cancer (2018) 18:849

Fromm J, Klein A, Baur-Melnyk A, Knösel T, Linder L, Birkenmaier C, Roeder F, Jansson V, Dürr HR. *Survival and prognostic factors in conventional G1 chondrosarcoma.*

World Journal of Surgical Oncology (2019) 17:155

Kongressbeiträge

Fromm J, Klein A, Baur-Melnyk A, Knösel T, Linder L, Birkenmaier C, Roeder F, Jansson V, Dürr HR. *Therapie und Prognose der Chondrosarkome*

6. Nationale Sarkomkonferenz, Berlin 2016

Fromm J, Klein A, Baur-Melnyk A, Knösel T, Linder L, Birkenmaier C, Roeder F, Jansson V, Dürr HR. *Prognose und Therapie von Chondrosarkomen*

DKOU, Berlin 2016

Fromm J, Klein A, Baur-Melnyk A, Knösel T, Jansson V, Dürr HR *Therapy and prognosis in chondrosarcoma*

EMSOS 2016, 27./28.05.2016, La Baule, Frankreich

Klein A, **Fromm J,** Baur-Melnyk A, Knösel T, Jansson V, Dürr HR *Therapy and prognosis in chondrosarcoma*

International Society of Limb Salvage (ISOLS), 12.05.2017, Kanazawa, Japan.

Einleitung

Chondrosarkome sind, nach den Osteosarkomen, die zweithäufigsten primär malignen Sarkome und machen mit rund 20% einen großen Teil aller Knochensarkome aus [1]. Ausgangsgewebe ist immer der Knorpel [2]. Obwohl sich die Inzidenz der CS in den letzten 30 Jahren nahezu vervierfacht hat (z.T. sicher auch aufgrund der Änderung der Klassifikation), sind große Patientenpopulationen oder prospektive Studien weiterhin selten[3].

Primär vs Sekundär

Von den primären Chondrosarkomen, welche spontan auftreten, werden die sekundären Chondrosarkome unterschieden, welche sich auf der Grundlage von benignen kartilaginären Veränderungen wie zum Beispiel solitären Enchondromen, kartilaginären Exostosen oder im Rahmen von Grunderkrankungen wie dem Morbus Ollier oder dem Maffiucci Syndrom bilden[4]. Gemäß ihrer Lage im Knochen werden sie in zentrale, periphere oder juxtakortikale Chondrosarkome unterteilt [5].

Diagnostik

Das Chondrosarkom ist eine Erkrankung des fortgeschrittenen Erwachsenenalters. Die meisten Chondrosarkome treten um das 5. Lebensjahrzehnt auf, gerade mesenchymale oder klarzellige CS kommen auch bei jüngeren Patienten vor. Die Patienten werden meistens aufgrund von subakuter Schwellung und Schmerzen beim Arzt vorstellig [6]. Die Diagnostik erfolgt dann radiologisch mittels konventionellem Röntgen, CT und (kontrastmittelgestützter) Magnetresonanztomografie. Die Unterscheidung zwischen benignen und niedrig-malignen Knorpeltumoren ist radiologisch schwierig. Besonders die Differenzierung zwischen Enchondromen und G1 zentralen Chondrosarkomen ist klinisch/radiologisch nicht eindeutig. Auch die Biopsie zur histologischen Sicherung der Entität trägt zu dieser Differenzierung meist nicht bei, kann aber höhergradige Malignität ausschließen [7-10].

Histologische Einteilung

Histologisch sind Chondrosarkome eine heterogene Gruppe mit sechs Unterformen und sehr unterschiedlichem biologischen Verhalten. (s. Tbl. 1). Die histologische Diagnose ist maßgeblich für die Therapie und die Prognose der Patienten. Bei entsprechender Therapie liegt das 10-Jahres-Überleben zwischen <1% beim dedifferenzierten CS und rund 90% beim klarzelligen oder juxtacorticalen CS (Tbl. 1). Metastasierung oder das Auftreten eines Lokalrezidivs verschlechtern die Prognose der Patienten signifikant. Diese ist sehr vom histologischen Subtyp abhängig. Während klarzellige CS relativ niedrig maligne sind, neigen zum Beispiel mesenchymale CS trotz aggressiver chirurgischer Therapie zu Lokalrezidiven und Metastasierung[3]. Basis der ist die Resektion der Läsion. In Abhängigkeit vom histologischen Grading reicht die chirurgische Therapie von einer intraläsionalen Kürettage (ACT) bis hin zur ausgedehnten En-bloc Resektion oder Amputation [11-13]. Aufgrund der geringen Mitoserate und niedrigen Vaskularität ist eine Chemotherapie beim CS meist nicht effektiv. Auch die Radiotherapie zeigt wenig Erfolg, ist jedoch bei höhergradigen Tumoren und inkompletter Resektion gerade an schwierigen Lokalisation, wie der Wirbelsäule hilfreich.

	Konventionelle CS	Myxoide CS	Periostale CS	Klarzellige CS	Dedifferenzierte CS	Mesenchymale CS
% Anteil aller CS	~ 80%	~ 10%	< 2%	< 2%	~ 2 – 10%	< 2%
Erkrankungsalter (Dekade)	~ 5.	~5.	2. – 4.	Jedes Alter (peak 3. – 5.)	Jedes Alter (peak 5.)	Jedes Alter (peak 2.)
Lokalisation	Becken, prox. Femur / Humerus	Prox. Femur / Humerus	Metaphyse Femur / Humerus	Prox. Extremitäten	Becken Femur	variabel
Grading	G1 – 3	Low grade	Low grade	Low grade	High grade	Low grade
10-Jahres Überleben	G1 > 90% G2~53-90% G3~29-55%	70-90%	~ 90%	> 90%	<1%	~ 40%
Therapie	Nach Grading	WE	WE	EB	WE/ CTx	WE/ CTx

Tbl. 1 Übersicht über die Prävalenz, Therapie und die Prognose der histologischen Subtypen der Chondrosakome[2, 5, 14-36]

In diesen Fällen sind meist hohe Dosen (>60 GY) und unter Umständen eine Partikeltherapie sinnvoll [5].

Konventionelle Chondrosarkome

Die primären, konventionellen, zentralen Chondrosarkome machen mit rund 80 - 85% aller CS den größten Anteil aus. Sie betreffen bevorzugt Männer und sind am häufigsten zentral, am Becken, der Skapula, am proximalen Femur oder Humerus lokalisiert. Das Erkrankungsalter liegt meist um die 5. Dekade. Das histologische Grading ist entscheidend für Therapie und Prognose. Wie bereits beschrieben, ist nach der radiologischen Diagnostik in der Regel eine Biopsie zur histologischen Sicherung der Entität nötig [7-10]. Histologisch werden die Tumoren entsprechend ihrer Mitoserate, Zellularität, Größe und Variabilität des Zellkerns und der Hyperchromasie in drei Grade eingeteilt. Allerdings ist die histopathologische Einteilung oft schwierig und unterliegt einer erheblichen Interobserver-Variabilität [6].

Prognose und Therapie der konventionellen Chondrosarkome

Es sind in der Literatur verschiedene prognostische Faktoren für Patienten mit konventionellen CS beschrieben. Es hat sich gezeigt, dass ein großes Tumorvolumen, die Tumorlokalisation am Becken und ein Lokalrezidiv eine schlechtere Prognose bedeuten [36-39]. Auch Metastasen oder ein höheres Erkrankungsalter verschlechtern die Prognose signifikant [39]. Der wichtigste Prognosefaktor bleibt allerdings das histologische Grading [36, 39].

G1 Chondrosarkome sind hoch differenziert und haben mit einem 10-Jahres-Überleben von über 90% generell eine gute Prognose. Nach der aktuellen Nomenklatur der WHO wird das G1 CS deshalb als „atypical cartilaginous tumor“ bezeichnet. Die WHO klassifiziert das G1 CS / ACT als „locally aggressive lesion“, welches nur in Ausnahmefällen metastasiert. Lokalrezidive sind möglich, haben jedoch bei G1 CS /ACT keinen Einfluss auf das Überleben [40]. G2 und G3 Tumore haben eine deutlich schlechtere Prognose mit einem kombinierten 5-Jahres-Überleben von 53% [6]. Einige Studien differenzieren und beschreiben bei G2 CS, bessere Überlebensraten [5]. Die Metastasierungstendenz und das Risiko eines Lokalrezidivs nehmen mit zunehmender

Dedifferenzierung und steigendem Grading zu, so dass bei G2 und G3 Tumoren die weite Resektion beziehungsweise en-bloc Resektion notwendig sind. Aufgrund seiner Klassifikation als „locally aggressive lesion“ und dem weniger malignen Verhalten hat sich beim G1 CS / ACT die intraläsionale Kürettage und lokale neoadjuvante Therapie durchgesetzt [41-43]. Verschiedene Studien haben keinen Überlebensvorteil bei ausgedehnter Resektion gegenüber der intraläsionalen Kürettage bei G1 CS / ACT gezeigt [36, 43]. Trotzdem besteht bezüglich der Therapie kein eindeutiger Konsens und es sind verschiedene Einschränkungen der Indikation zur intraläsionalen Kürettage beschrieben [2, 42]. Obwohl Lokalrezidive bei G1 CS /ACT mit 0-18% generell niedrig sind, sind sie in mehreren Studien dennoch häufiger als bei einer ausgedehnten Resektion [2, 13, 41, 44, 45]. Rund 10% der Lokalrezidive der G1 CS / ACT sind schlechter differenziert als der Primätumor. Diese haben dann eine erhöhte Metastasierungstendenz und machen eine erneute, ausgedehntere, chirurgische Intervention nötig [6, 13, 46].

Ziel

Wie in der Einleitung beschrieben, ist bei G2 und G3 CS die ausgedehnte Resektion die Therapie der Wahl. Gerade beim CS, welches gehäuft am Becken auftritt, ist es aber oft schwierig, ausreichend weite Resektionsränder zu erreichen. In einer Studie von 2015 mit 1.114 Patienten zeigte sich die Resektionsweite zudem nicht als unabhängiger Prognosefaktor für das Gesamtüberleben[36]. Ziel der hier beschriebenen ersten Studie „*Survival and prognostic factors in conventional central chondrosarcoma“* war es deshalb zu klären, wie weit im Gesunden reseziert werden sollte und ob die Lokalisation am Becken unabhängig von der Resektionsweite als alleiniger Risikofaktor für eine schlechtere Prognose steht.

In der zweiten Studie „*Survival and prognostic factors in conventional G1 chondrosarcoma“* war es das Ziel, die Neubewertung der G1 CS als ACT und damit als „locally aggressive lesion“ durch die WHO zu hinterfragen und anhand unserer großen, homogenen Patientenpopulation zu überprüfen, ob Lokalrezidive tatsächlich keinen Einfluss auf das Überleben haben und ob der ACT tatsächlich nur lokal aggressiv ist, oder doch zur Metastasierung neigt.

Übergreifend hatten beide Studien, neben einer internen Qualitätskontrolle gegenüber den auswärts publizierten Daten, die Überprüfung und Festlegung von etablierten Prognosefaktoren für das Gesamtüberleben von Patienten mit Chondrosarkomen zum Ziel.

Zusammenfassung

Material und Methoden

Zwischen 1982 und 2014 wurden insgesamt 87 Patienten mit konventionellen Chondrosarkomen chirurgisch an unserer Klinik behandelt. Die Diagnosen wurden nach klinischer und radiologischer Diagnostik mittels histologischer und immunhistochemischer Untersuchung bestätigt. Die Tumorgröße und –lokalisation wurde präoperativ mittels CT und MRT bestimmt. Präoperativ erfolgte typischerweise ein Thorax-CT zur Metastasensuche.

Alle Tumoren wurden reseziert. Die Resektionsränder wurden als R0 definiert, wenn der Tumor allseits durch tumorfreies Gewebe umgeben war (weite Resektion). Als R1-Resektionen wurden Präparate definiert, bei denen histopathologisch der Tumor an den Resektionsrand heranreichte, die Tumorkapsel aber intakt war (marginale Resektion). Patienten, die mittels intraläsionaler Kürettage behandelt wurden, wurden als R1-Resektionen gewertet. In ausgewählten Fällen wurden die Tumoren aus verschiedenen Gründen geplant nur teilreseziert. Diese Resektionen wurden als R2- Resektionen gewertet.

Von den 87 Patienten wurden 37 histopathologisch als G1 CS / ACT klassifiziert. Diese Patienten wurden daraufhin, unabhängig von einer bereits bestehender Metastasierung, in die gesonderte Auswertung und Publikation der G1 CS eingeschlossen.

Das Auftreten von Lokalrezidiven (LR) und Metastasierung wurde mittels MRT und Röntgenaufnahme des Thorax überprüft.

Ein positives Votum der Ethikkommission der Medizinischen Fakultät der LMU für diese Studie liegt vor.

Statistische Analyse

Zur statistischen Auswertung des Gesamt- und LR-freien-Überlebens wurde das Kaplan-Meier-Modell verwendet. Die Signifikanz wurde mittels Log-Rank, Chi-Quadrat oder Cox-Regression berechnet. Ein $p < 0.05$ wurde als statistisch signifikant gewertet. Die Auswertung erfolgte mittels MedCalc Software bzw. SPSS 24.

Ergebnisse – konventionelle zentrale Chondrosarkome

Von 87 Patienten, die aufgrund eines konventionellen Chondrosarkoms chirurgisch behandelt wurden, waren 54 männlich und 33 weiblich. Das Durchschnittsalter betrug 51.7 Jahre (15- 83 Jahre). In 44 Fällen war die untere Extremität betroffen, in 10 Fällen die obere Extremität, das Becken in 21 Fälle und der Körperstamm in 12 Fällen. In 57,5% (N = 50) der Fälle zeigte sich ein extraossäres Tumorwachstum. Die Vorstellung erfolgte in über 50% (52%, N = 44) der Fälle aufgrund von Schmerzen, durchschnittlich 9 Monate (0 – 358 Monate) nach Symptombeginn. 11 Patienten (13%) wurden aufgrund einer Schwellung, 6 (7%) aufgrund einer pathologischen Fraktur vorstellig. Bei den übrigen Patienten zeigten sich weitere Symptome wie eine Bewegungseinschränkung oder neurologische Auffälligkeiten. In 70 Fällen (81%) erfolgte präoperativ eine Biopsie. 4 Patienten waren zum Vorstellungszeitpunkt bereits auswärts mittels intramedullärem Nagel oder Endoprothese voroperiert worden. In 4 Fällen war der Tumor bereits initial metastasiert.

In 42 Fällen (48%) erfolgte die ausschließliche Tumorresektion. Eine Resektion und Tumorprothesenimplantation erfolgte in 24 Fällen (28%). In 11 Fällen (13%) wurde eine Amputation notwendig und in 10 Fällen (11%) erfolgte eine Kürettage.

Von den 87 Patienten konnten 54 (62%) R0-reseziert werden, in 31 Fällen (36%) wurde der Tumor R1-reseziert und in 2 Fällen (2%) R2. Am Becken wurden 48% der CS R1- oder R2-reseziert, an der unteren Extremität waren es 41%, an der oberen Extremität 20% und stammnah 25% (n.s.). Histologisch zeigten sich 37 (43%) G1 CS, 41 (47%) G2 CS und 9 (10%) G3 CS. In 20 Fällen (23%) erfolgte aus verschiedensten Gründen (unter anderem aufgrund einer Materiallockerung und –dislokation, Infektionen, Hämatomen oder zur Nachresektion) eine chirurgische Revision.

Die durchschnittliche Nachbeobachtungszeit betrug 68 Monate (0 – 379 Monate) in insgesamt 68 überlebenden Patienten. Bei einem Patienten war die Nachbeobachtungszeit unter 12 Monaten, 8 Patienten konnten nur für 12 - 24 Monate nachverfolgt werden. 24 Patienten verstarben während der Nachbeobachtung.

Das lokalrezidivfreie Überleben unserer Patienten betrug 75% nach 5 Jahren. Von den insgesamt 21 Lokalrezidiven in unserer Patientenpopulation traten 52% in den ersten 12 Monaten und 81% in den ersten 24 Monaten nach der Operation auf. Das späteste LR trat bei unseren Patienten nach 10 Jahren auf. Es zeigte sich eine statistisch signifikante Korrelation zwischen der Lokalisation des Tumors und der Resektionsweite zum lokalrezedivfreien Überleben. Dies bestätigte sich auch in der multivariaten Analyse.

Initial waren bei 4 Patienten (4,6%) Metastasen nachweisbar. Einer dieser Patienten blieb nach der Resektion derselben tumorfrei, 19 Patienten entwickelten im Verlauf eine Metastasierung. Zum Studienende zeigten 22 Patienten (23%) Metastasen, ein Großteil davon (13 Patienten) in der Lunge. Nur 5 dieser Patienten waren zum Studienende noch am Leben. Von den 22 Patienten mit Metastasen hatten 8 (36%) ein Lokalrezidiv, während 20% der nicht-metastasierten Patienten ein Lokalrezidiv entwickelten (n.s.).

Das Gesamtüberleben der Patientenpopulation betrug 79% nach 5 und 75% nach 10 Jahren. Das Grading erwies sich als statistisch signifikant für das Gesamtüberleben ($p = 0.0099$). Auch eine Metastasierung ($p < 0.0001$) und das Auftreten eines Lokalrezidivs ($p = 0.0219$) zeigten sich statistisch signifikant auf die Prognose. Während die Resektionsweite keinen signifikanten Einfluss auf das Gesamtüberleben hatte, zeigte sich die Lokalisation des Tumors als wichtiger Prädiktor für das Gesamtüberleben ($p = 0.0008$). Die multivariate Analyse zeigte, dass ein schlechteres Tumorgrading, Metastasierung, höheres Alter und die Tumorlokalisation am Becken prognostisch ungünstig für das Gesamtüberleben sind. Die Resektionsränder und das Auftreten von Lokalrezidiven hatten keinen Einfluss auf das Überleben.

Schlussfolgerungen konventionelle zentrale Chondrosarkome

Es konnte gezeigt werden, dass Riskofaktoren wie das Grading, die Metastasierung, das Alter und die Tumorlokalisation das Gesamtüberleben signifikant beeinflussen. Die Resektionsweite beeinflusste das lokalrezidivfreie Überleben, aber nicht das Gesamtüberleben. Dies ist, gerade bei schlechter differenzierten Läsionen, erstaunlich, deckt sich aber mit den wenigen Studien, welche die Resektionsweite als Risikofaktor mittels multivariater Analyse überprüft haben.

Ergebnisse – konventionelle G1 Chondrosarkome

Von den 37 Patienten mit konventionellen G1 CS waren 12 weiblich und 25 männlich. Das Durchschnittsalter betrug 47.1 Jahre (17 - 84 Jahre). In 4 Fällen war die obere Extremität betroffen, in 23 Fällen die untere Extremität. Bei jeweils fünf Patienten betraf der Tumor das Becken oder trat stammnah auf. In 16 Fällen zeigte sich ein extraossäres Wachstum.

Die Patienten litten zum Vorstellungszeitpunkt seit durchschnittlich 19.8 Monaten (0 – 153 Monate) an Symptomen durch den Tumor. 19 Patienten (51%) beklagten Schmerzen, 3 (8%) an einer Schwellung, in 5 Fällen (11%) zeigte sich eine pathologische Fraktur und in 6 Fällen (16%) war das Chondrosarkom ein Zufallsbefund. Die übrigen Patienten hatten weitere Beschwerden wie eine Bewegungseinschränkung oder neurologische Auffälligkeiten. In 31 Fällen (84%) wurde präoperativ eine Biopsie durchgeführt. 6 Patienten wurden auswärts mittels intramedullärer Nagelung oder Endoprothesen voroperiert. Ein Patient zeigte initial bereits Metastasen.

In 28 Fällen (76%) wurde der Tumor primär reseziert oder kürettiert. Eine Tumorendoprothese wurde in 8 Fällen (22%) implantiert. In einem Fall (2%) wurde eine Amputation notwendig. Bei 23 Patienten (64%) erfolgte eine R0-Resektion und in 14 Fällen (38%) eine R1-Resektion. In der Studienpopulation gab es keine R2 Resektionen. Am Becken warn 66% der Resektion R1-Resektionen, an der unteren Extremität waren es 92% und an der oberen Extremität 33%. Stammnah erfolgte keine R1-Resektion.

Bei 5 Patienten (14%) wurde aufgrund verschiedenster Komplikationen eine Revision notwendig.

Das durchschnittliche Follow-up in unserer Studie betrug 127.9 Monate (0 – 344 Monate). Nur 3 Patienten hatten ein Follow-up von unter 24 Monaten, und 13 Patienten (35%) unter 5 Jahren. Insgesamt 5 Patienten verstarben während des Beobachtungszeitraumes, einer während der ersten 12 Monate, einer nach 7 und 3 weitere nach über 15 Jahren.

Das Gesamtüberleben betrug 97% nach 5 Jahren, 92% nach 10 Jahren und 67% nach 20 Jahren. Das lokalrezidivfreie Überleben betrug 96% nach 5 Jahren und 83% nach 10 Jahren. Insgesamt entwickelten 5 Patienten (14%) Lokalrezidive, einer davon während der ersten 5 Jahre und 4 während der ersten 10 Jahre. In unserer Patientenpopulation zeigte sich die Resektionsweite als statistisch signifikanter Prädiktor für das Auftreten eines Lokalrezidivs ($p = 0.035$). Es zeigte sich jedoch keine Korrelation zwischen dem Patientenalter oder der Tumorlokalisation. Dies bestätigte sich in der multivariaten Analyse.

Keiner der Patienten mit Lokalrezidiv verstarb bis zum Studienende. Ein Patient entwickelte allerdings ein Lokalrezidiv und eine Metastasierung.

6 Patienten (16%) der Studienpopulation entwickelten während der Studie Metastasen. Ein Patient war initial metastasiert, blieb aber nach der Resektion metastasenfrei. Das durchschnittliche metastasenfreie Überleben betrug 86% nach 5 und 75% nach 20 Jahren. In der multivariaten Analyse zeigten sich keine statische Korrelation zwischen der Resektionsweite, der Tumorlokalisation und einer Metastasierung.

Eine Metastasierung zeigte sich als statisch signifikanter Prädiktor für das Gesamtüberleben ($p<0.0001$). Ein Alter über 50 Jahre zeigte einen Trend zum schlechterem Gesamtüberleben, war aber nicht statisch signifikant. Auch das Auftreten eines Lokalrezidivs und die Tumorlokalisation zeigten keine statistische Signifikanz in Bezug auf das Gesamtüberleben.

Nur einer der fünf verstorbenen Patienten zeigte kein extraossäres Tumorwachstum, das extraossäre Wachstums blieb aber bezüglich des OS ohne statische Signifikanz ($p = 0.07$)

Schlussfolgerung konventionelle G1 Chondrosarkome

Zusammenfassend lässt sich sagen, dass die Resektionsweite in unserer Studienpopulation keinen Einfluss auf das Gesamtüberleben der Patienten mit G1 CS hatte. Patienten mit R1-Resektion hatte zwar ein erhöhtes Risiko für ein Lokalrezidiv, dies hatte aber keine Auswirkung auf das Gesamtüberleben. Dies steht damit im Einklang mit der Definition der WHO als „locally agressive lesion".

Im Gegensatz dazu war die Metastasierungsrate in unserer Studienpopulation höher als erwartet (16%) und Patienten mit Metastasen hatten auch beim low-grade CS eine schlechtere Prognose. In unserer Studie konnte aber, im Einklang mit der Literatur, kein Zusammenhang zwischen Lokalrezidiven und Metastasierung gefunden werden.

Es zeigte sich auch, dass die Lokalisation des Tumors beim G1 CS / ACT im Gegensatz zu den höhergradigen Läsionen keinen Einfluss auf das Gesamtüberleben hatte.

Obgleich ohne statistische Signifikanz, deutet die zweistellige Rate an Metastasierung und die hohe Sterblichkeit bei extraossärem Tumorwachstum auf die Notwendigkeit einer differenzierteren Betrachtung der G1 CS hin.

Summary

Material and methods

Between 1982 and 2014, a total of 87 patients with conventional chondrosarcoma were treated at our institution. After clinical and radiologic diagnostics, the diagnosis was confirmed based on histological features and immunohistochemistry. The size and localization of the lesion were pre-operatively defined via MRI and CT scan. Metastatic disease was ruled out before surgery via initial CT of the thorax.

All patients were treated surgically. Resection margins were defined as R0 (wide resection) when the resected lesion was surrounded by healthy tissue, and R1 (marginal resection) when the tumor infiltrated the margins but the capsule was intact. In certain cases, part of the tumor was intentionally left in situ, these resection were classified as R2.

37 out of 87 patients were classified as GI / ACT. These patients were included in a seperate study on low-grade CS regardless of initial metastatic disease.

All patients were regularly checked for local recurrence and metastatic disease via MRI and chest radiographs.

Ethical approval was obtained for this study.

Statistical analysis

The Kaplan-Meier method was used for calculating overall survival (OS) and local recurrence-free survival (LRFS) was calculated according to the Kaplan-Meier method. The Log-Rank, the Chi-square test or the Cox proportional-hazard regression model were used for performing statistic analysis. A $p < 0.05$ was considered statistically significant. MedCalc Software and SPSS 24 were used for data analysis.

Results – conventional central chondrosarcoma

Out of 87 patients treated for conventional central chondrosarcoma, 54 were male and 33 were female. The average age was 51.7 years (15 – 83 years). In 44 cases, the lesion was located in the lower extremity, in 10 cases in the upper extremity, and in 21 cases the lesion was located in the pelvis. The trunk was affected in 12 cases. 57.5% (N = 50) of the cases showed extra-osseus growth. Patients had symptoms for an average of 9 months (range 0 – 358 months) before diagnosis. More than 50% of the patients (52%, N = 44) complained about pain, 11 patients (13%) about swelling. 6 patients (7%) were seen because of a pathologic fracture. The rest showed symptoms, such as loss of function or restriction of movement.

In 70 cases (81%) a biopsy was taken pre-operatively. 4 patients were initially treated with intramedullary nailing or endoprotheses at another institution. In 4 cases the tumor was initally metastasized.

In 42 Cases (48%) the tumor was primarily resected. Resection and megaendoprothesis was performed in 24 cases (28%). In 11 cases (13%) an amputation was necessary and in 10 cases (11%) a curettage was performed.

In 54 of our 87 cases (62%) a wide resection (R0) was performed, in 31 cases (36%) the resection was marginal (R1) and in 2 cases R2. 48% of the pelvic lesions were either R1 or R2 resections. The same was true for 41% of the lower extremity lesions, 20% of the upper extremity lesions and 25% of the lesions located at the trunk (n.s.). Histologically, 37 (43%) G1 CS, 41 (47%) G2 CS and 9 (10%) G3 CS were seen. In 20 cases (23%) surgical revision became necessary for different reasons (e.g. loosening of implants, infections, hematoma, or more aggressive tumor resections).

Follow-up time was 68 months in average (range 0 – 379 months) for the 68 patients that survived. For one patient the follow-up time was less than 12 months, for 8 patients the follow-up was limited to 12 – 24 months. 24 patients died during follow-up.

The 5- year local recurrence free survival was 75%. Out of a total of 21 local recurrences, 52% were seen within the first 12, and 81% within the first 24 months after surgery. The latest LR was seen after 10 years. Statistical analysis showed a significant correlation between localization of the tumor and margin status with the local-recurrence free survival. This was confirmed by multivariate analysis.

Initially metastatic disease (MD) was seen in 4 patients (4,6%). One of these patients was without metastasis after resection. 19 patients developed metastatic disease during follow-up. At the end of the follow-up period, 22 patients (23%) showed metastatic disease. The majority of the tumors metastasized into the lung (13 cases), only 5 of these patients were alive at the end of the follow-up period. Out of 22 patients with MD, 8 (36%) showed local recurrence (LR) as well. In patients without MD,LR was found in 20% (n.s.).

The OS after 5 and 10 years was 79% and 75% respectively. Grading was a statistically significant predictor for OS ($p = 0.0099$) as well as MD ($p < 0.0001$) and LR ($p = 0.0219$). Margin status had no significant impact on OS, whereas the localization of the tumor did show significant impact on OS ($p = 0.0008$). In a multivariate analysis, grading, MD, higher age and pelvic tumor localization proofed to be a significant predictor for a decreased OS. The margin status and LR showed no impact on overall survival.

Conclusions - conventional central chondrosarcoma

Grading, MD, age and localization of the tumor proved to be significant prognostic factors for OS. The resection margin was no risk factor for OS but for LR-free-survival. This is remarkable, especially for the G2 and G3 lesions, but appears to be in concordance with the few other studies published, which investigated the effect of margin status on OS in multivariate analysis.

Results – conventional G1 chondrosarcoma

Out of the 37 patients with conventional G1 CS, 12 were female and 25 were male. The average age was 47.1 years (17 – 84 years). The upper extremity was involved in 4 cases, the lower extremity in 23 cases. The pelvis and the trunk were involved in 5 cases each. In 16 cases there was extra-osseus growth.

The average duration of symptoms before clinical diagnosis was 19.8 months (range 0 – 153 months). 19 patients (51%) initially presented with pain, 3 (8%) with swelling, and in 5 cases (11%) there was a pathological fracture. In 6 cases (16%) the tumor was a coincidental find. The remaining patients showed other symptoms, such as loss of

function or restriction of movement. In 31 cases (84%) a biopsy was taken before surgery. 6 patients were initially treated at a different institution via intramedullary nailing or endoprothesis. One patient presented with MD.

In 28 cases the tumor was treated with resection or curettage. Megaendoprothesis was implanted in 8 cases (22%). In one case (2%) an amputation was necessary. In 23 cases (64%) the tumor was resected with a wide margin (R0), in 14 cases (38%) the resection was conducted marginally (R1). There was no R2 resection. 66% of the pelvic lesions were marginally resected. The same was true for 92% of the lower extremity lesions and 33% of the upper extremity lesions. There was no marginal resection (R1) within the cases where the lesion was located at the trunk.

In 5 cases a surgical revision became necessary due to different reasons.

Mean follow-up time was 127.9 months (range 0 – 344 months). 3 patients had a follow-up period of less than 24 months and 13 (35%) less than 5 years. 5 patients died during follow-up, one within the first 12 months, one after 7 years and 3 after 15 years.

OS was 97% after 5 years, 92% and 67% after 10 and 20 years, respectively. LRFS was 96% after 5 years and 83% after 10 years. 5 patients (14%) developed LR, one within 5 years and 4 within 10 years after initial resection. In our population, resection margin proofed to be a significant predictor for LR ($p = 0.035$). However, there was no correlation between LR and patient age or tumor location. These findings were confirmed by multivariate analysis.

None of the patients with LR died during follow-up. However, one patient developed LR and MD.

MD was seen in 6 cases (16%). One patient presented with MD but remained metastasis-free after surgical treatment. 5 patients (14%) developed MD during follow-up. Mean MD-free survival was 86% after 5 and 75% after 20 years, respectively.

Multivariate analysis showed no correlation between resection margins and MD.

MD proofed to be a significant predictor for OS ($p<0.0001$). Age over 50 appears to be a negative prognostic predictor concerning the OS but there was no statistical significance. LR and localization of the lesion showed no statistical correlation to OS.

Only one of the 5 patients that died during the follow-up period showed no extra-osseus tumor growth, however there was no statistical significance (p = 0.07).

Conclusions - conventional G1 chondrosarcoma

In conclusion, there was no correlation between the resection margins and OS in patients with G1 CS. Patients with marginal resection (R1) did show a higher risk for LR, however this did not influence OS. This appears to be in concordance with the WHO's definition of the G1 CS as locally aggressive lesion.

In contrast to that definition as a locally aggressive lesion, the rate of MD (16%) was higher than expected in our population and MD proofed to be a significant predictor for decreased OS even in low grade lesions. However, in our population there was no correlation between LR and MD, which is in concordance with previous studies.

While tumor localization is an important risk factor in high grade lesions there was no correlation between tumor localization and OS in patients with G1 CS / ACT.

Although not statistically significant, the high rate of MD and the high mortality of patients with extra-osseus tumor growth could suggest extra-osseus CS to behave different in this group of G1 lesions.

Veröffentlichung I

Fromm *et al. BMC Cancer* (2018) 18:849
https://doi.org/10.1186/s12885-018-4741-7

BMC Cancer

RESEARCH ARTICLE Open Access

Survival and prognostic factors in conventional central chondrosarcoma

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

Abstract

Background: Chondrosarcoma is the second most frequent primary malignant bone tumor. Treatment is mainly based on surgery. In general, wide resection is advocated at least in G2 and G3 tumors. But which margins should be achieved? Does localization as for example in the pelvis have a higher impact on survival than surgical margins themselves?

Methods: From 1982 to 2014, 87 consecutive patients were treated by resection. The margin was defined as R0 (wide resection), R1 (marginal resection) or, R2 if the tumor was left intentionally. All patients were followed for evidence of local recurrence or distant metastasis. Overall and recurrence-free survival were calculated, significance analysis was performed.

Results: In 54 (62%) cases a R0 resection, in 31 (36%) a R1 and in 2 (2%) patients a R2-resection was achieved. Histology proved to be G1 in 37 patients (43%), G2 in 41 (47%) and G3 in 9 cases (10%). 5-year local recurrence-free survival (LRFS) was 75%. Local recurrence-free survival showed a significant association with the margin status and the localization of the tumor with pelvic lesions doing worst. Metastatic disease was initially seen in 4 patients (4. 6%), 19 others developed metastatic disease during follow-up. Overall survival of the entire group at 5 and 10 years were 79 and 75%, respectively. The quality of surgical margins and the presence of local recurrence did not influence overall survival in a multivariate analysis. Pelvic lesions had a worse prognosis as did higher grades of the tumor, metastatic disease and age.

Conclusions: The mainstay of therapy in Chondrosarcoma remains surgery. Risk factors as grading, metastatic disease, age and location significantly influence overall survival. Margin status (R0 vs. R1) did influence local recurrence-free survival but not overall survival. Chondrosarcomas of the pelvis have a higher risk of local recurrence and should be treated more aggressively.

Keywords: Chondrosarcoma, Surgery, Margin status, Recurrence, Prognostic factors

Background

Following Osteosarcoma, chondrosarcoma (CS) is the second most frequent primary malignant bone tumor accounting for approximately 20% of all bone sarcomas [1]. It constitutes a heterogeneous group of tumors characterized by the production of cartilaginous matrix [2]. Central (conventional) CS represents about 75% of the group. With the introduction of the current WHO classification in 2013 Chondrosarcoma grade I (now officially termed atypical cartilaginous tumor) was reclassified as an intermediate (locally aggressive) tumor, better reflecting its clinical behavior [2]. In these difficult cases, the differential diagnosis towards benign enchondromas is based on a combination of pathology, radiology and clinical features and hence requires a close multidisciplinary assessment [3].

Treatment is mainly based on surgery and chemotherapy is less effective because of a low mitotic index and poor vascularity [4, 5]. Radiotherapy is effective but requires substantial dosage [6].

* Correspondence: hans_roland.duerr@med.uni-muenchen.de
[1]Musculoskeletal Oncology, Department of Orthopedics, 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

In general, wide resection is advocated at least in G2 and G3 tumors. It is assumed that patients with CS have an excellent prognosis after adequate surgery [4] but reviewing the literature and our own results, such assumptions should be looked at in a more detailed fashion. Even the G1 lesions have a risk of metastasis of 6% [7]. There is no clear consensus on what exactly constitutes "adequate surgery". Which margins should be achieved? Does localization as for example in the pelvis have a higher impact on survival than surgical margins taken for themselves? In a metaanalysis on 1114 patients published in 2015, the surgical margin were not identified as an independent predictor of overall survival [8]. In consequence, the traditional dogma of adequate margins, as stated by some authors [9, 10] had to be called into question.

The main aim of this retrospective study was to analyze a homogenous group of patients with primary central CS of bone, treated at a single tumor center. We sought to determine prognostic factors for overall and local recurrence-free survival. Secondary aim was to asses our own results on the background of the published data.

Methods

From 1982 to 2014, 87 consecutive patients with chondrosarcoma of the extremities, pelvis and trunk wall were treated at our institution. All tumors had a diagnosis of chondrosarcoma based on histological features and immunohistochemistry.

Prior to surgical resection, predominantly magnetic resonance imaging (MRI) and in some cases computed tomography (CT) was used to define size and localization of the tumor. A CT scan of the chest was performed to determine the presence or absence of metastatic disease.

All patients underwent surgical resection. The margin was defined as R0 if a rim of healthy tissue around the lesion was present (wide resection) or R1 if the margins were contaminated but the tumor capsule remained closed (marginal resection). In select patients, a planned partial resection was performed in order to avoid severely mutilating surgery. This was classified as a R2 resection.

Statistical analysis

All patients were followed for evidence of local recurrence (LR) or distant metastasis in general by regional MRI scans and chest radiographs. Clinical outcomes of local recurrence (LR), local recurrence-free survival (LRFS) and overall survival (OS) were used for assessment. LRFS and OS were defined either as the time from surgery to the first occurrence of local recurrence or to death from any cause. For statistical analysis, overall and local recurrence-free survival were calculated according to the Kaplan-Meier method. Significance analysis was performed using the Log-Rank, the Chi-Square test or the Cox proportional-hazards regression model. A P value of less than 0.05 was considered statistically significant. The data analysis software used was MedCalc® (MedCalc Software, Ostend, Belgium).

Results

The median age of the 54 male and 33 female patients was 51.7 years (mean 50.3, range 15–83). The lower extremity was involved in 44 cases (29 femur, 18 of them proximal; 11 tibia, 10 of them proximal; fibula and feet 2 each), the upper extremity in 10 (7 humerus, 5 of them proximal; radius, ulna and hand 1 each), the pelvis in 21 and the trunk in 12 (8 scapula, 2 ribs, clavicle and thoracic spine 1 each) patients. Fifty patients (57.5%) showed extraosseous tumor growth.

The median duration of symptoms prior to diagnosis was 9 months (range, 0–358) and the majority of patients (44 = 52%) complained of pain, 11 (13%) of swelling. A pathologic fracture led to the diagnosis in 6 (7%) patients. Neurological impairment or restriction of movement was seen occasionally. 70 (81%) patients had a biopsy or histology before surgery. In 2 cases, the biopsy was interpreted as a cartilaginous exostosis and in 3 cases as an enchondroma. Four patients had already undergone surgery at other institutions by means of intramedullary nailing or by resection and endoprosthetic reconstruction. In these cases, the tumor had either gone unidentified or it had been underestimated. Only 4 patients had metastatic disease initially.

Resections of the tumor alone were performed in 42 cases (48%), resections and reconstructions with megaendoprostheses in 24 cases (28%), amputations in 11 patients (13%) and curettages in 10 instances (11%). A wide (R0) resection was performed in 54 (62%) cases, a marginal (R1) resection in 31 cases (36%) and an R2-resection in 2 (2%) patients. With pelvic lesions, 48% of surgical margins were either R1 or R2, at the lower extremity 41%, at the upper extremity 20% and at the trunk 25% (n.s.). Histology proved to be G1 in 37 patients (43%), G2 in 41 (47%) and G3 in 9 cases (10%).

In 20 patients (23%), surgical revisions due to complications had to be performed. This included:

Nine revisions due to dislocation or loosening of implants or bone grafts, 6 deep infections, 2 hematomas, and more aggressive tumor resection, neurological impairment and vessel injury in 1 case each.

In 63 surviving patients, the median follow-up time from surgery to last information on the patient was 68 months (range, 0–379). One patient was lost to follow-up less than 12 months after surgery, 8 patients had a follow-up of 12–24 months. Twenty-four patients deceased during follow-up.

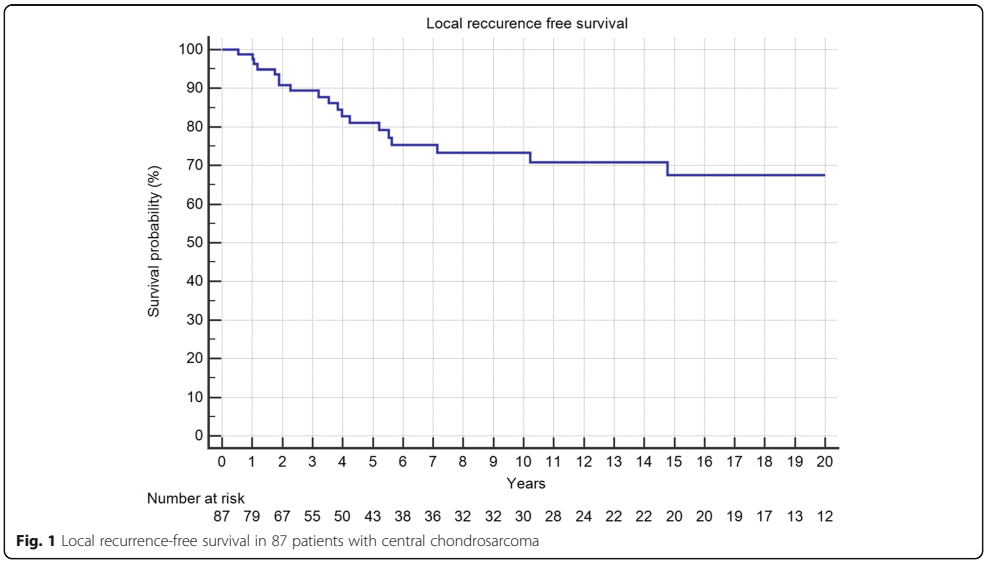

Fig. 1 Local recurrence-free survival in 87 patients with central chondrosarcoma

Five-year local recurrence-free survival was 75%. In total, 21 (24%) patients developed local recurrences, of which 52% occured in the first 12 months and 81% in the first 24 months after surgery (Fig. 1). The latest LR was seen after 10 years. Local recurrence-free survival showed a significant association with the margin status and the localization of the tumor with pelvic lesions doing worst (Table 1, Figs. 2 and 3). In multivariate analysis, both kept significance.

Metastatic disease was initially seen in 4 patients (4.6%). One of those patients stayed free of disease after resection, 19 others developed metastatic disease during follow-up. At final follow-up, 22 (23%) patients had metastatic disease, 13 of which were located in the lung, 3 in the spine, one in the femur, one in visceral organs and 4 in multiple localizations. Only 5 of these patients were alive with disease at final follow-up. Of these 22 patients with metastatic disease, only 8 also had a LR (36%) whereas 20% of non-metastasized patients had LR which was not statistically significant. Grading showed a trend towards metastatic disease in follow-up with 14% in G1, 30% in G2 and 44% in G3 tumors but without statistical significance ($p = 0.0815$).

Overall survival of the entire group at 5 and 10 years was 79 and 75%, respectively. Grading proved to be a significant factor (Fig. 4, $p = 0.0099$) as was metastatic disease (Fig. 5, $p < 0.0001$). Local recurrence also had a strong effect (Fig. 6a, $p = 0.0219$). Regarding margin status (Fig. 6b, n.s.) and localization (Fig. 7) only the latter had an influence on survival ($p = 0.0008$).

Table 1 Factors influencing local recurrence (margin status, location) and local recurrence free survival

Local recurrence	No	Yes	*p*-value	5-year LRFS	10-year LRFS	*p*-value
R0	45 (83%)	9 (17%)	0.1025*	84.7%	81.4%	0.0204+
R1	20 (65%)	11 (35%)		61.9%	61.9%	
R2	1 (50%)	1 (50%)		0%	0%	
Upper Extremity	10 (100%)	0 (0%)	0.0568*	100%	100%	0.053+
Lower Exremity	35 (80%)	9 (20%)		79.0%	79.0%	
Pelvis	12 (57%)	9 (43%)		55.7%	44.7%	
Trunk	9 (75%)	3 (25%)		75.0%	75.0%	

*Chi-squared test;
+Logrank test

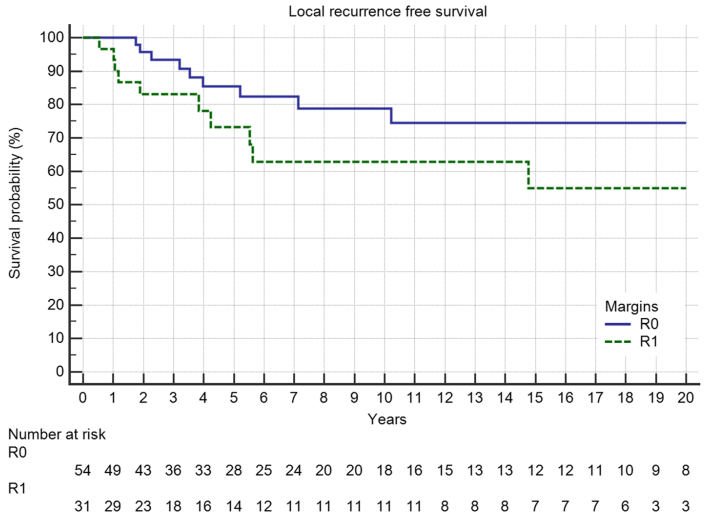

Fig. 2 The impact of surgical margins on local recurrence-free survival in R0 and R1 resected patients ($p = 0.05$)

In general, male and female patients showed no difference whereas age with a cut-off of 50 years was a significant predictor of outcome (Fig. 8, $p = 0.019$).

As shown in Table 2, the quality of surgical margins and the presence of local recurrence did not influence overall survival in a multivariate analysis. Pelvic lesions led to a worse prognosis as did higher tumor grade, presence of metastatic disease and greater age.

Discussion

Age in general is a very strong factor of overall survival as shown in data out of the SEER Database (USA) [11].

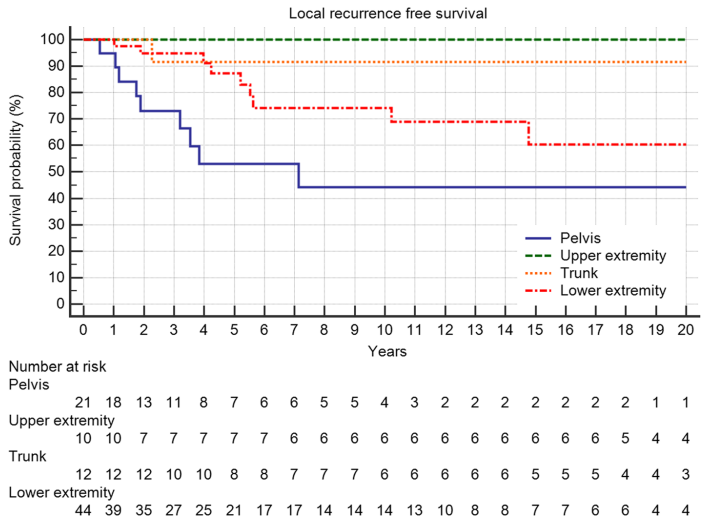

Fig. 3 The impact of tumor localization on local recurrence-free survival ($p = 0.0532$)

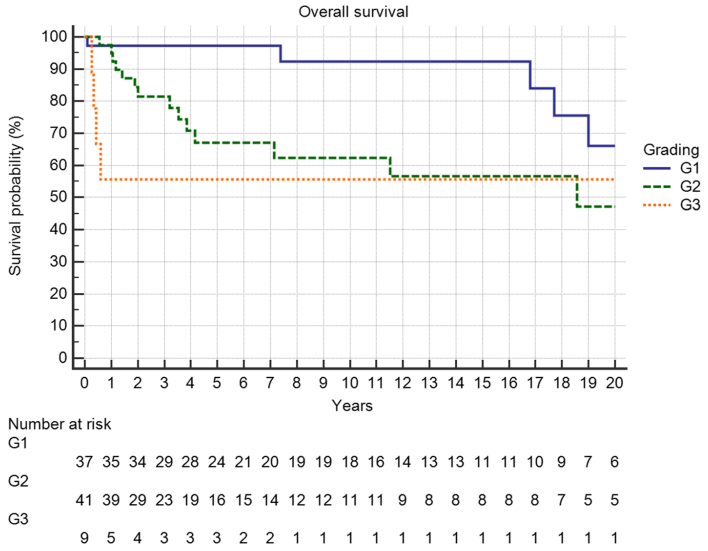

Fig. 4 Overall survival is strongly influenced by tumor grading ($p = 0.0099$)

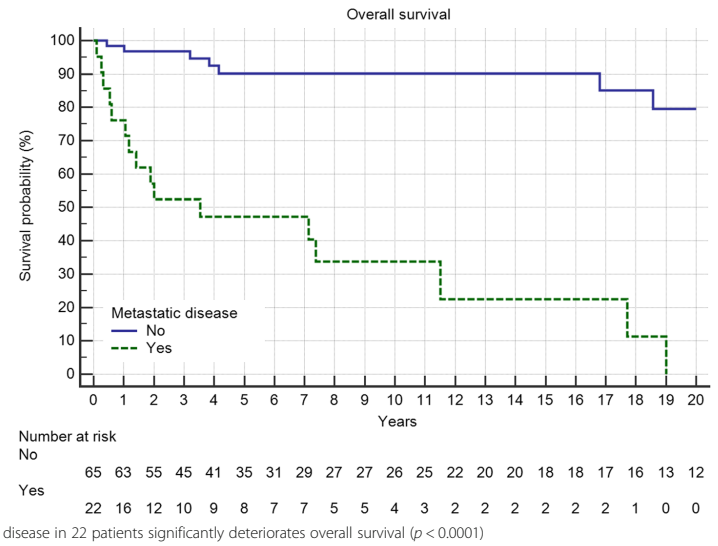

Fig. 5 Metastatic disease in 22 patients significantly deteriorates overall survival ($p < 0.0001$)

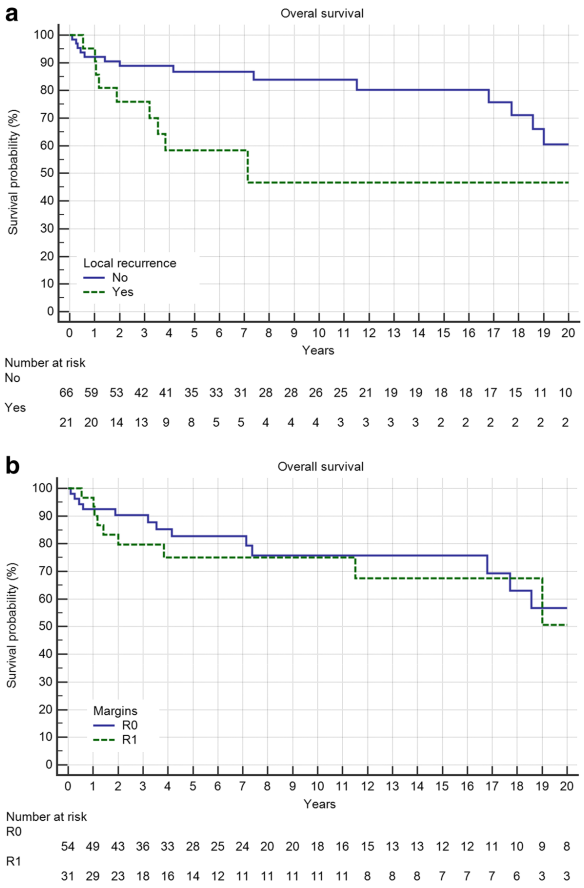

Fig. 6 **a** Local recurrence in 21 patients reduces overall survival ($p = 0.0219$). **b** The surgical margin (R2 only 2 cases) does not influence overall survival (n.s)

Location is undoubtedly also an important aspect. As highly significantly shown in our data, pelvic location of a chondrosarcoma has a worse prognosis. This kept significance also in multivariate analysis. Our 5 and 10-year survival rates in those patients are 50 and 42%, respectively. In central chondrosarcomas, published 10-year survival rates vary between 54 and 88% [12–17]. This variability in survival depends very much on whether peripheral chondrosarcomas were included and how many patients in the study group had a low-grade chondrosarcoma or recurrent disease. Regarding margins, in pelvic lesions these were associated with LR [12, 13, 16, 17] but not OS [12, 15, 17]. In other studies LR did clearly influence OS [12–14]. However, the opposite observation, indications that LR did not influence OS has also been published [16]. Some authors showed that LR influenced metastatic disease and hence secondarily OS [13].

The main conclusion in summarizing the published literature and our own data is, that chondrosarcoma of the pelvis does exhibit a more aggressive behaviour and should not be curetted even in low-grade tumors. Local recurrence might lead to dedifferentiation and metastatic disease.

In general, low-grade central CS showed a good prognosis with a 5- and 10-year OS of 97 and 92%. But 5 of our

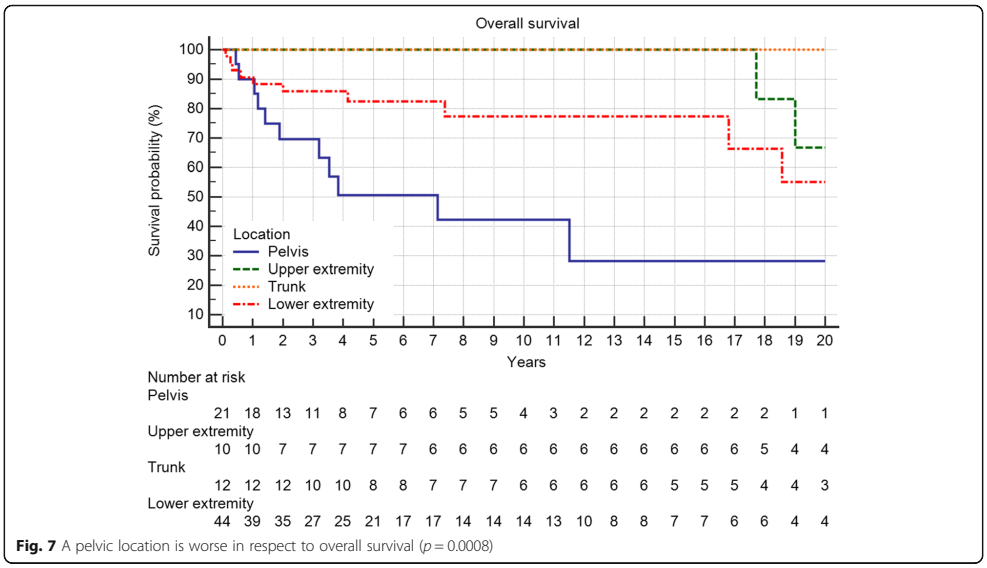

Fig. 7 A pelvic location is worse in respect to overall survival ($p = 0.0008$)

37 patients (14%) developed LR and 6 (16%) developed metastatic disease (MD), 4 of which eventually (11%) died from it. The published data on G1 chondrosarcoma is conflicting. From 0% LR and MD [18, 19], 2% LR and 0% MD [20], 3% LR and 3% MD [21], 4% LR and 0% MD [22], 5% LR and 0% MD [23], 6% LR and 0% MD [24, 25], 9% LR and 0% MD [26], 11% LR and 3% MD [27], 13% LR and 4% MD [28], 13% LR and 5% MD [29] to 18% LR and 6% MD [7] a variety of different results are reported. 5-year survival ranges from 82 to 99% and 10-year survival from 89 to 95% [8]. This reflects the problem of differentiation of benign enchondromas and atypical cartilaginous

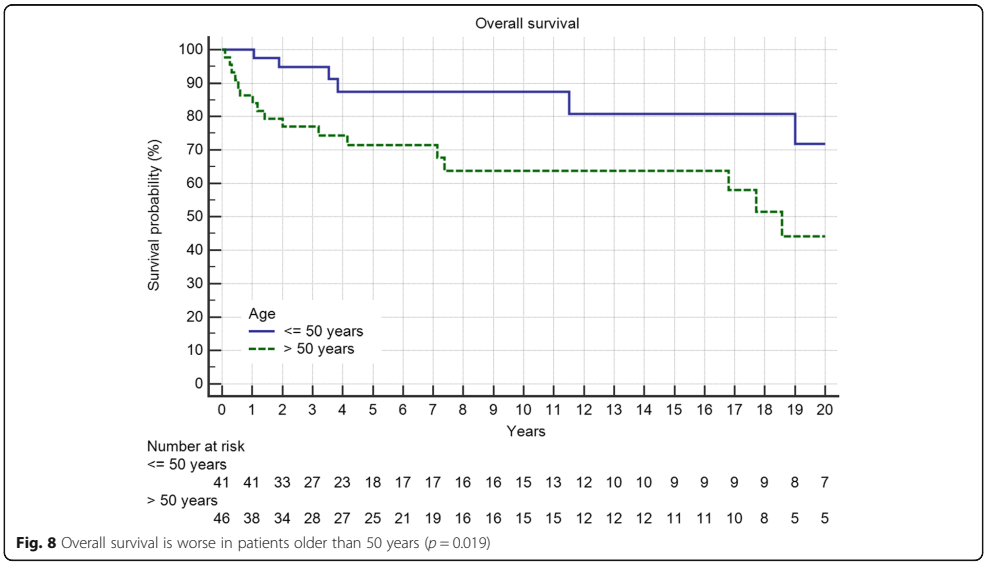

Fig. 8 Overall survival is worse in patients older than 50 years ($p = 0.019$)

Table 2 Cox proportional-hazards regression for overall survival in relation to grading, metastatic disease, age, margin status, location and local recurrence

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Grading	2532 (1360-4715)	**0,0034**	3208 (1380-7457)	**0,0067**
Metastatic disease	11,477 (4,6288-28,4589)	**< 0,0001**	14,763 (4819-45,229)	**< 0,0001**
Age < =50	2906 (1143-7389)	**0,0251**	0,307 (0,115-0,822)	**0,0188**
Margin status	1311 (0,642-2678)	0,4571	1152 (0,4997-2655)	0,7401
Pelvic/Non-pelvic	0,309 (0,165-0,578)	**0,0002**	0,441 (0,231-0,845)	**0,0136**
Local recurrence	2614 (1115-6125)	**0,0270**	1233 (0,448-3394)	0,6847

P-values in bold indicates significance

tumor and the heterogenous distribution of therapy and localization in these studies [3, 30–32]. Bauer et al. treated 40 patients with enchondromas and 40 patients with low-grade CS. His results showed no difference between groups [33]. So intralesional curettage with and without adjuvants is a valid option in most of those patients, but as stated above, central lesions should be resected because of their higher recurrence rates [27].

Metastatic disease was seen in 23%. This is about the same as described by other authors [10, 34–36]. There are series with a lesser [37, 38] or a higher [16, 39] proportion of metastatic disease. This reflects the importance of patient selection. The inclusion of initially non-metastasized patients only, patients with G2/3 lesions only or patients with axial or pelvic localizations only has a strong impact on MD and survival. In general MD is bad news for the patient with a 5-years overall survival of less than 50%. As shown in Table 2, MD is the most significant negative prognostic factor. There are patients, in whom metastatic disease is manageable by resection, local radiation or systemic therapy, leading to survival rates of 10–30% after 10 years, as also in this study. But this is the exception, mainly seen in G1 tumors [9, 34, 40]. Our results show, that MD is more common in G2/3 lesions as described by others [9, 34, 39, 41] but it is independent from surgical margins with the same rate of MD in R0 and R1 resected patients, and also independent from LR. This is in some respect in contrast to the literature [9, 10, 35] but other authors did see the same, confirming grade and location [42] as risk factors or grade as the only significant risk factor [16] for MD in multivariate analyses. In a large survey in Finland [36] the decade of diagnosis was the only significant factor on MD with an increased risk in the 1980s.

One of the most urgent questions is which margin should be obtained and how does margin influence LR and OS. In our study, local recurrence-free survival was significantly associated with margin status and LR influenced OS as in most of the published studies [9, 35, 43]. But in our data as well as in previous publications, LR and margin status showed no effect on overall survival in multivariate analysis [34]. We have to admit, that we only could include 2 cases with a R2 margin. Those seem to have a worse prognosis. There are not many studies including margin status in a multivariate analysis of overall survival [7, 10]. Lee shows a significant impact of margins on overall survival for patients with high-grade CS but the curves for wide and marginal resections did separate only after 120 months with just two events in the marginal group later on [10]. Fiorenza in 2002 reported findings identical to ours, namely a significant influence of LR on OS in univariate analysis and no influence of margin status in multivariate analysis [9]. LR remained significant as did grade and location. So in concordance with other groups, we conclude that LR after adequate resection is more likely to be a marker of the aggressiveness of the tumor than a consequence of failed local therapy [34, 44, 45]. We still maintain the premise of adequate resection, but some authors state that also intracompartmental grade 2 chondrosarcomas with a non-aggressive radiologic pattern can be treated by curettage without negatively affecting prognosis [46]. In patients with local recurrence but without MD, further aggressive surgery appears to constitute a good chance of cure (64% published by Fiorenza et al.) [9].

Conclusions

The mainstay of therapy in chondrosarcoma of bone is surgery. Risk factors such as tumor grading, metastatic disease, age and location significantly influence overall survival. Margin status did influence local recurrence-free survival but not overall survival. Regarding the latter, the literature is inconclusive mainly due to a large heterogeneity of the study populations. Chondrosarcomas of the pelvis have a higher risk of local recurrence and should therefore be treated more aggressively at least to avoid local complications.

Abbreviations

CS: Chondrosarcoma; CT: Computed Tomography; G1, G2, G3: Grading according to the French Federation of Cancer Centers grading system; LR: Local recurrence; LRFS: Local recurrence-free survival; MD: Metastatic

disease; MRI: Magnetic resonance imaging; n.s.: Not significant; OS: Overall survival; R0, R1, R2: Resection margin; WHO: World Health Organization

Funding
This study was not supported by any grants or external funding.

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

Authors' contributions
JF Student doing his thesis on chondrosarcomas. He contacted the patients and acquiered the data. AK. Surgeon on many of the cases. AB. Radiologist reviewing the radiologic investigations. TK. Pathologist reviewing the pathologic investigations. LL. Oncologist. Every patient was discussed in the interdisciplinary panel and the decision not to treat was based on this. CB. Surgeon. FR. Reviewing the radiotherapy and deciding which patient to treat or not to treat. VJ. Surgeon on many of the cases. HRD. Corresponding author. Developed the study concept, did the final data analysis and provided the major clinical input in writing 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.

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. For non-surviving patients data were irreversibly anonymized as recommended by the ethics committee.

Consent for publication
Not applicable.

Competing interests
All authors have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work. This study was not supported by any grants or external funding. The authors declare that they have no competing interests.

Publisher's Note

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

Received: 16 January 2018 Accepted: 10 August 2018
Published online: 24 August 2018

References

1. Rozeman LB, Cleton-Jansen AM, Hogendoorn PC. Pathology of primary malignant bone and cartilage tumours. Int Orthop. 2006;30(6):437–44.
2. Hogendoorn P, Bovee J, Nielsen GP. Chondrosarcoma (grades I-III) including primary and secondary variants and periosteal chondrosarcoma. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, editors. WHO Classification of Tumours of Soft Tissue and Bone, vol. 4. Lyon: International Agency for Research on Cancer (IARC); 2013. p. 264–9.
3. Ferrer-Santacreu EM, Ortiz-Cruz EJ, Diaz-Almiron M, Pozo Kreilinger JJ. Enchondroma versus chondrosarcoma in long bones of appendicular skeleton: clinical and radiological criteria-a follow-up. J Oncol. 2016;2016:8262079.
4. Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, Bovee JV. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320–9.
5. van Maldegem AM, Gelderblom H, Palmerini E, Dijkstra SD, Gambarotti M, Ruggieri P, Nout RA, van de Sande MA, Ferrari C, Ferrari S, et al. Outcome of advanced, unresectable conventional central chondrosarcoma. Cancer. 2014;120(20):3159–64.
6. Outani H, Hamada K, Imura Y, Oshima K, Sotobori T, Demizu Y, Kakunaga S, Joyama S, Imai R, Okimoto T, et al. Comparison of clinical and functional outcome between surgical treatment and carbon ion radiotherapy for pelvic chondrosarcoma. Int J Clin Oncol. 2016;21(1):186–93.
7. Andreou D, Gilg MM, Gosheger G, Werner M, Hardes J, Pink D, Leithner A, Tunn PU, Streitburger A. Metastatic potential of grade I chondrosarcoma of bone: results of a multi-institutional study. Ann Surg Oncol. 2016;23(1):120–5.
8. Nota SP, Braun Y, Schwab JH, van Dijk CN, Bramer JA. The identification of prognostic factors and survival statistics of conventional central chondrosarcoma. Sarcoma. 2015;2015:623746.
9. Fiorenza F, Abudu A, Grimer RJ, Carter SR, Tillman RM, Ayoub K, Mangham DC, Davies AM. Risk factors for survival and local control in chondrosarcoma of bone. J Bone Joint Surg (Br). 2002;84(1):93–9.
10. Lee FY, Mankin HJ, Fondren G, Gebhardt MC, Springfield DS, Rosenberg AE, Jennings LC. Chondrosarcoma of bone: an assessment of outcome. J Bone Joint Surg Am. 1999;81(3):326–38.
11. Giuffrida AY, Burgueno JE, Koniaris LG, Gutierrez JC, Duncan R, Scully SP. Chondrosarcoma in the United States (1973 to 2003): an analysis of 2890 cases from the SEER database. J Bone Joint Surg Am. 2009;91(5):1063–72.
12. Mochizuki K, Yamaguchi H, Umeda T. The management of pelvic chondrosarcoma in Japan. Japanese Musculo-Skeletal Oncology Group. Int Orthop. 2000;24(2):65–70.
13. Pring ME, Weber KL, Unni KK, Sim FH. Chondrosarcoma of the pelvis. A review of sixty-four cases. J Bone Joint Surg Am. 2001;83-A(11):1630–42.
14. Donati D, El Ghoneimy A, Bertoni F, Di Bella C, Mercuri M. Surgical treatment and outcome of conventional pelvic chondrosarcoma. J Bone Joint Surg (Br). 2005;87(11):1527–30.
15. Weber KL, Pring ME, Sim FH. Treatment and outcome of recurrent pelvic chondrosarcoma. Clin Orthop Relat Res. 2002;397:19–28.
16. Sheth DS, Yasko AW, Johnson ME, Ayala AG, Murray JA, Romsdahl MM. Chondrosarcoma of the pelvis. Prognostic factors for 67 patients treated with definitive surgery. Cancer. 1996;78(4):745–50.
17. Ozaki T, Hillmann A, Lindner N, Blasius S, Winkelmann W. Chondrosarcoma of the pelvis. Clin Orthop Relat Res. 1997;337:226–39.
18. Mermerkaya MU, Bekmez S, Karaaslan F, Danisman M, Kosemehmetoglu K, Gedikoglu G, Ayvaz M, Tokgozoglu AM. Intralesional curettage and cementation for low-grade chondrosarcoma of long bones: retrospective study and literature review. World J Surg Oncol. 2014;12:336.
19. Goud AL, Wuyts W, Bessems J, Bramer J, van der Woude HJ, Ham J. Intraosseous atypical chondroid tumor or chondrosarcoma grade 1 in patients with multiple osteochondromas. J Bone Joint Surg Am. 2015;97(1):24–31.
20. Campanacci DA, Scoccianti G, Franchi A, Roselli G, Beltrami G, Ippolito M, Caff G, Frenos F, Capanna R. Surgical treatment of central grade 1 chondrosarcoma of the appendicular skeleton. J Orthop Traumatol. 2013;14(2):101–7.
21. Leerapun T, Hugate RR, Inwards CY, Scully SP, Sim FH. Surgical management of conventional grade I chondrosarcoma of long bones. Clin Orthop Relat Res. 2007;463:166–72.
22. Di Giorgio L, Touloupakis G, Vitullo F, Sodano L, Mastantuono M, Villani C. Intralesional curettage, with phenol and cement as adjuvants, for low-grade intramedullary chondrosarcoma of the long bones. Acta Orthop Belg. 2011;77(5):666–9.
23. Hanna SA, Whittingham-Jones P, Sewell MD, Pollock RC, Skinner JA, Saifuddin A, Flanagan A, Cannon SR, Briggs TW. Outcome of intralesional curettage for low-grade chondrosarcoma of long bones. Eur J Surg Oncol. 2009;35(12):1343–7.
24. Donati D, Colangeli S, Colangeli M, Di Bella C, Bertoni F. Surgical treatment of grade I central chondrosarcoma. Clin Orthop Relat Res. 2010;468(2):581–9.
25. Verdegaal SH, Brouwers HF, van Zwet EW, Hogendoorn PC, Taminiau AH. Low-grade chondrosarcoma of long bones treated with intralesional curettage followed by application of phenol, ethanol, and bone-grafting. J Bone Joint Surg Am. 2012;94(13):1201–7.

26. Meftah M, Schult P, Henshaw RM. Long-term results of intralesional curettage and cryosurgery for treatment of low-grade chondrosarcoma. J Bone Joint Surg Am. 2013;95(15):1358–64.
27. Funovics PT, Panotopoulos J, Sabeti-Aschraf M, Abdolvahab F, Funovics JM, Lang S, Kotz RI, Dominkus M. Low-grade chondrosarcoma of bone: experiences from the Vienna bone and soft tissue tumour registry. Int Orthop. 2011;35(7):1049–56.
28. Schwab JH, Wenger D, Unni K, Sim FH. Does local recurrence impact survival in low-grade chondrosarcoma of the long bones? Clin Orthop Relat Res. 2007;462:175–80.
29. Streitburger A, Ahrens H, Balke M, Buerger H, Winkelmann W, Gosheger G, Hardes J. Grade I chondrosarcoma of bone: the Munster experience. J Cancer Res Clin Oncol. 2009;135(4):543–50.
30. Yoo HJ, Hong SH, Choi JY, Moon KC, Kim HS, Choi JA, Kang HS. Differentiating high-grade from low-grade chondrosarcoma with MR imaging. Eur Radiol. 2009;19(12):3008–14.
31. Douis H, Singh L, Saifuddin A. MRI differentiation of low-grade from high-grade appendicular chondrosarcoma. Eur Radiol. 2014;24(1):232–40.
32. Kendell SD, Collins MS, Adkins MC, Sundaram M, Unni KK. Radiographic differentiation of enchondroma from low-grade chondrosarcoma in the fibula. Skelet Radiol. 2004;33(8):458–66.
33. Bauer HC, Brosjo O, Kreicbergs A, Lindholm J. Low risk of recurrence of enchondroma and low-grade chondrosarcoma in extremities. 80 patients followed for 2-25 years. Acta Orthop Scand. 1995;66(3):283–8.
34. Andreou D, Ruppin S, Fehlberg S, Pink D, Werner M, Tunn PU. Survival and prognostic factors in chondrosarcoma: results in 115 patients with long-term follow-up. Acta Orthop. 2011;82(6):749–55.
35. Rizzo M, Ghert MA, Harrelson JM, Scully SP. Chondrosarcoma of bone: analysis of 108 cases and evaluation for predictors of outcome. Clin Orthop Relat Res. 2001;391:224–33.
36. Soderstrom M, Ekfors TO, Bohling TO, Teppo LH, Vuorio EI, Aro HT. No improvement in the overall survival of 194 patients with chondrosarcoma in Finland in 1971-1990. Acta Orthop Scand. 2003;74(3):344–50.
37. Bjornsson J, McLeod RA, Unni KK, Ilstrup DM, Pritchard DJ. Primary chondrosarcoma of long bones and limb girdles. Cancer. 1998;83(10):2105–19.
38. Angelini A, Guerra G, Mavrogenis AF, Pala E, Picci P, Ruggieri P. Clinical outcome of central conventional chondrosarcoma. J Surg Oncol. 2012; 106(8):929–37.
39. Ozaki T, Hillmann A, Linder N, Blasius S, Winkelmann W. Metastasis of chondrosarcoma. J Cancer Res Clin Oncol. 1996;122(10):629–32.
40. Muller PE, Durr HR, Nerlich A, Pellengahr C, Maier M, Jansson V. Malignant transformation of a benign enchondroma of the hand to secondary chondrosarcoma with isolated pulmonary metastasis. Acta Chir Belg. 2004; 104(3):341–4.
41. Hayashi T, Tsuda N, Iseki M, Kishikawa M, Shinozaki T, Hasumoto M. Primary chondrosarcoma of the lung. A clinicopathologic study. Cancer. 1993;72(1):69–74.
42. Bindiganavile S, Han I, Yun JY, Kim HS. Long-term outcome of chondrosarcoma: a single institutional experience. Cancer Res Treat. 2015; 47(4):897–903.
43. Gitelis S, Bertoni F, Picci P, Campanacci M. Chondrosarcoma of bone. The experience at the Istituto Ortopedico Rizzoli. J Bone Joint Surg Am. 1981; 63(8):1248–57.
44. Gronchi A, Miceli R, Fiore M, Collini P, Lozza L, Grosso F, Mariani L, Casali PG. Extremity soft tissue sarcoma: adding to the prognostic meaning of local failure. Ann Surg Oncol. 2007;14(5):1583–90.
45. Brennan MF. The enigma of local recurrence. The Society of Surgical Oncology. Ann Surg Oncol. 1997;4(1):1–12.
46. Cho WH, Song WS, Jeon DG, Kong CB, Koh JS, Kim JI, Lee SY. Oncologic impact of the curettage of grade 2 central chondrosarcoma of the extremity. Ann Surg Oncol. 2011;18(13):3755–61.

Veröffentlichung II

Fromm *et al. World Journal of Surgical Oncology* (2019) 17:155
https://doi.org/10.1186/s12957-019-1695-4

World Journal of Surgical Oncology

RESEARCH Open Access

Survival and prognostic factors in conventional G1 chondrosarcoma

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

Abstract

Background: Chondrosarcoma is the second most frequent malignant bone tumor. Grade I chondrosarcoma (syn.: atypical cartilaginous tumor) is classified as an intermediately and locally aggressive neoplasm and typically is treated less aggressively (i.e., by intralesional curettage). Does the data regarding local recurrence (LR) and metastatic disease justify this?

Methods: From 1982 to 2014, 37 consecutive patients with G1 chondrosarcoma had been resected or curetted. The margin was defined as R0 (wide resection) or R1 (marginal resection). All patients were followed for evidence of local recurrence or metastatic disease. Overall and recurrence-free survival were calculated, and various potentially prognostic factors were evaluated.

Results: In 23 patients (62%), the tumor was widely (R0) resected, whereas in 14 patients, (38%) the resection was marginal (R1). Overall survival was 97% after 5 years, 92% after 10 years, and 67% after 20 years. Five-year local recurrence-free survival was 96%. Ten-year local recurrence-free survival was 83%. Local recurrence-free survival showed a significant correlation to margin status but no correlation to location or age. None of the patients with local recurrence died during the follow-up. One patient had metastatic disease at initial presentation, and a further five patients developed metastatic disease during follow-up. Metastatic disease proofed to be a highly significant factor for survival but was not correlated to local recurrence.

Conclusions: There was no significant correlation between the outcome and the primary tumor location. Marginal resection was a risk factor for LR, but there was no significant difference in the overall survival in patients with or without LR. Metastatic disease (16%) was more common than expected from the literature and a significant predictor for poor overall survival.

Keywords: Chondrosarcoma, Low-grade, Surgery, Curettage, Margin status, Recurrence, Prognostic factors

Background

Representing more than 20% of all malignant tumors of the bone, chondrosarcoma (CS) is the third most common primary malignant bone tumor following osteosarcoma and multiple myeloma [1]. Chondrosarcomas are most often seen in adult age and are a very heterogenous group with a diverse behavior depending on the histological subtype. The most common subtype is conventional CS. Clear cell CS appears to have the best prognosis while dedifferentiated CS has the worst outcome [2]. For conventional CS, tumor grading and anatomic location are the main predictors of outcome [2–4].

Therapy consists mainly of surgical resection. In critical locations, radiotherapy in high dosage (if applicable) is effective as an adjuvant or as the sole therapy [5] while chemotherapy appears to be less effective [6, 7]. The definition of adequate surgical margins varies within the literature [4]. In high-grade chondrosarcomas, a wide resection is the standard to prevent local recurrence. In low-grade chondrosarcoma, intralesional curettage is commonly used although controversial [8–10]. In a large literature review in 2017, Chen et al. found only 1.2% metastatic disease and no difference in local recurrence with respect to surgical margins [11].

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

The WHO classification of grade I chondrosarcoma (atypical cartilaginous tumor) as an intermediately and locally aggressive neoplasm implies that there is no or only rarely metastatic disease with low-grade chondrosarcoma [12]. This definition comprises the benign clinical behavior of the lesions, but it is known that even grade I CS carries a risk of metastasis in up to 6% of cases [12].

With intralesional curettage becoming more and more common in low-grade chondrosarcoma, it appears important to take a closer look at the influence of less aggressive (intralesional) surgical margins and outcomes in grade I CS. Does a wider margin prevent metastases or local recurrence in low-grade CS? Is the location of the lesion a predictor of outcome in low-grade lesions as it is in high-grade CS [13, 14]?

The main aim of this retrospective study hence was to have a closer look at this very selective and homogenous group of patients with primary low-grade conventional CS treated at a single tumor center to determine prognostic factors for overall and recurrence-free survival. The secondary aim was a comparison of our data to the literature for quality-of-care reasons.

Materials and methods

Patients

From 1982 through 2014, 87 consecutive patients with central chondrosarcoma of the extremities, the pelvis, and the trunk wall were treated at our institution. All patients had a diagnosis of chondrosarcoma based on histological, radiological, and clinical features.

Preoperatively, mainly magnetic resonance imaging (MRI) and in some cases computed tomography (CT) were used to define size and location of the tumor. A CT scan of the chest was obtained to rule out or prove metastatic disease.

Margins and inclusion criteria

All patients underwent surgical resections. The margin was defined as R0 if a rim of healthy tissue around the lesion was present (wide resection) or R1 if the margins were contaminated as in close resections or curettages. From those 87 patients, 37 showed a low-grade (G1) histology and were classified as atypical cartilaginous tumors. Inclusion criteria for this study were therefore a histology-proven G1 grading in the resected specimen with or without proven metastatic disease.

Statistical analysis

All patients were followed for evidence of local recurrence or distant metastasis in general by MRI scans and chest x-rays. Due to the long investigation period with considerable changes in the ability to detect small metastases, especially in the lungs, and small local recurrences, the number of metastatic cases as also local recurrences might be underestimated. Subsequently, recurrence-free survival would be overestimated. Therefore, in addition, overall survival is calculated from the time of surgery to last follow-up or death in deceased patients. Overall and recurrence-free survival were calculated by the Kaplan-Meier method. Significance analysis was performed using the log-rank test or the chi-square test. The data analysis software used was SPSS 24®.

Results

The mean age of the 12 female and 25 male patients was 47.1 years (range 17–84 years). The upper extremity was involved in 4 cases (humerus 2, radius 1, hand 1), and the lower extremity in 23 cases (femur 15, tibia 4, fibula 2, feet 2). Five patients had the lesion in the trunk (scapula 4, ribs 1), and five in the pelvis (4 os ilium, 1 os pubis). Sixteen (43%) showed extraosseous tumor growth.

The median duration of symptoms was 19.8 months (range 0–153 months). Nineteen patients (51%) complained of pain, 3 (8%) complained about swelling, and 5 (11%) suffered from a pathological fracture, and in 6 cases (16%), the lesion was found as an incidental finding. Occasionally, there were neurological symptoms or a loss of the range of motion. Thirty-one patients (84%) had a biopsy taken before surgery. In four cases, the biopsies showed benign cartilaginous lesions, later classified as false negatives. Six patients had undergone intralesional surgery elsewhere with either intramedullary nails or endoprostheses prior to presenting to our institution, and the tumor had been overlooked or underestimated in these cases. One patient had metastatic disease at the time of diagnosis.

In 28 patients, the tumor was resected or curetted and the defect, as necessary, was filled with allogenic bone graft. A reconstruction with megaendoprostheses was performed in 8 (22%), and an amputation in 1 case (2%). In 23 patients (64%), the tumor was widely (R0) resected, whereas in 14 patients (38%), the resection was marginal (R1). There were no R2 resections. Histology showed a conventional low-grade chondrosarcoma in all patients. In pelvic lesions, 66% were marginal resections compared to 92% at the lower extremities and 33% at the upper extremities. There were no marginal resections at the trunk.

In five patients (14%), revisions due to complications had to be performed. The complications included loosening of an endoprosthesis in two, neurological impairment because of a malpositioned osteosynthesis screw, additional and more aggressive tumor resection, and deep wound infection in one case each.

The mean follow-up in our series was 127.9 months (range 0–344 months). Only 3 patients had a follow-up time of less than 24 months, and 13 patients (35%) had a

follow-up of less than 5 years. Five patients died during the follow-up: one within the first year, one after 7 years, and three after more than 15 years (Fig. 1).

Overall survival was 97% after 5 years, 92% after 10 years, and 67% after 20 years (Fig. 1). Five-year local recurrence-free survival was 96%. Ten-year local recurrence-free survival was 83%. In total, 5 (14%) patients developed local recurrences: only 1 of them during the first 5 years and 4 after 10 years. In our patients, local recurrence-free survival showed a significant correlation with the margin status (Fig. 2; $p = 0.035$) but no correlation with the location or the patients' age. This was confirmed by means of multivariate analysis (Table 1).

None of the patients with local recurrence (LR) died during the follow-up, and only one showed LR and metastatic disease (MD).

Six patients (16%) in our study developed metastases, whereas one patient had an initial spinal metastasis but remained free of disease after resection of that lesion. In five patients (14%), metastatic disease developed during follow-up (four pulmonary, one bone). Mean metastasis-free survival was 86% after 5 years and 75% after 20 years. Four of our patients deceased during the follow-up period (Fig. 3). In the multivariate analysis, there was no correlation between the surgical margins and the location in respect to metastatic disease.

Metastasis proved to be a significant predictive factor for survival (Fig. 3; $p < 0.0001$). Age over 50 showed a trend in respect to worse overall survival, but this failed significance testing (Fig. 4; $p = 0.078$). Only one of the patients (5%) without soft tissue extension died during the follow-up period compared to four patients (27%) with extraosseous infiltration (n.s.) (Fig. 5; $p = 0.07$). Local recurrence and lesion location showed no significance in predicting overall survival.

Discussion

Grade I chondrosarcoma is generally assumed to be an entity of low malignancy with 5-year survival rates of 90% and more and with little to no metastatic disease [12, 15]. There is, however, no consensus on prognostic factors (i.e., location of the lesion) or the influence of surgical margins (wide resection vs. curettage) and the clinical outcomes in grade I CS.

Although tumor location and patient age have been identified as being strong predictive factors for overall survival in patients with conventional chondrosarcoma in previous publications [16, 17], in our series of patients with low-grade CS, we observed no statistically significant correlation between overall survival and patient age at diagnosis ($p = 0.078$) or tumor location ($p = 0.238$).

A 14% LR rate in our group of patients is similar to previously published numbers of LR in low-grade CS, ranging between 0 and 26% [18–21]. Marginal resection was a significant predictor for LR ($p = 0.037$) in our series. It is known that local recurrence in high-grade chondrosarcoma is associated with poorer outcome, but there is still some debate about whether this is true for low-grade chondrosarcoma as well [22–25]. We were not able to demonstrate a significant correlation between local recurrence and overall survival in this group of patients ($p = 0.6$). Several authors have described a

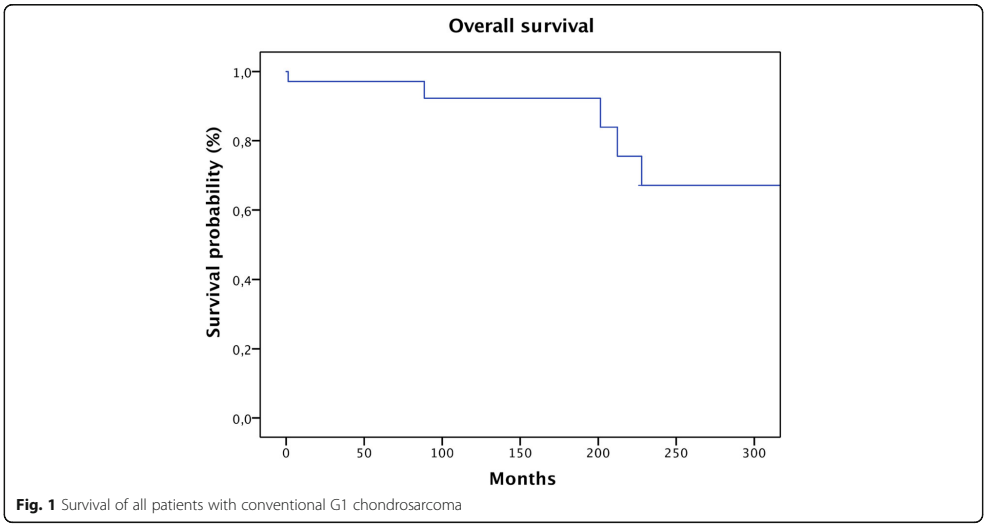

Fig. 1 Survival of all patients with conventional G1 chondrosarcoma

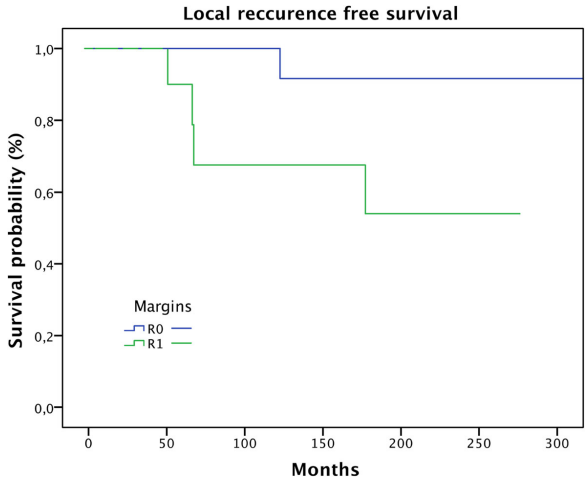

Fig. 2 Influence of surgical margins on local recurrence-free survival ($p = 0.035$)

progression of the tumor and the occurrence of distant metastases in association with local recurrence [12, 22, 26, 27]. However, there also are studies that were unable to find such a correlation between LR and MD [23, 24]. In our patients, there was also no correlation between LR and MD with only one patient having both LR and MD. This discrepancy to some of the published literature might be due to the limited mean follow-up of the patients with LR in our group of only 77 months, especially since Schwab et al. described that poor outcomes in patients with LR become significant only beyond 10 years [22].

As mentioned above, there is no consensus on whether or not LR has any significance when it comes to overall survival in low-grade CS. However, many studies have shown that inadequate surgical margins lead to a higher rate of LR, necessitating further surgery with additional risks [10, 23, 24, 27]. Some studies suggest to combine intralesional curettage with adjuvant measures such as the application of poly-methyl-methacrylat (PMMA) or cryosurgery to reduce LR rates [20, 28, 29].

The metastatic potential of low-grade CS is controversially discussed in the literature with rates ranging between 0 and 6% [18, 24, 28, 30]. In our study, one patient already had MD at initial assessment and five patients developed MD during follow-up (16%). A possible reason for this observation could be the longer follow-up of our study with a mean metastasis-free survival of 76 months. Studies which did not describe any MD often report a much shorter follow-up period [31, 32]. However, there are also published studies with a long follow-up and little or no MD as well [9, 20]. This might reflect the difficulty in differentiating between atypical chondrogenic tumors and benign chondromas.

In this study, MD proved to be a significant predictor for a poor outcome ($p < 0.0001$) which is consistent with the findings of other authors. However, we found no significant correlation between the surgical procedure and

Table 1 Local recurrence in relation to surgical margins and tumor location

Local recurrence	No	Yes	*p* value	5-year LRFS (%)	10-year LRFS (%)	15-year LRFS (%)	*p* value
R0	22 (96%)	1 (4%)	0.037	100	92	92	0.035
R1	10 (71%)	4 (29%)		90	79	54	
Upper extremity	4 (100%)	0 (0%)	0.097	100	100	100	0.238
Lower extremity	18 (78%)	5 (22%)		94	71	60	
Pelvis	5 (100%)	0 (0%)		100	100	100	
Trunk	5 (100%)	0 (0%)		100	100	100	

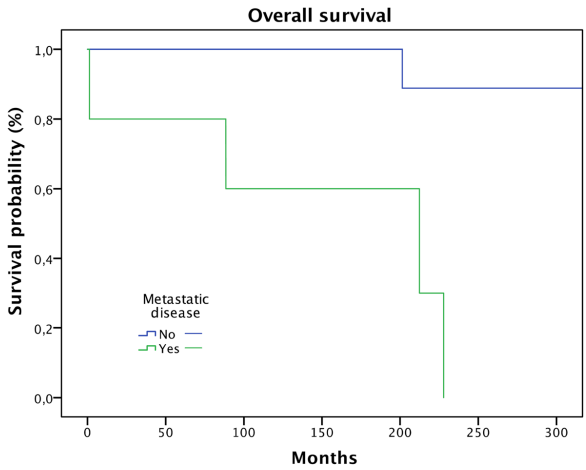

Fig. 3 Metastatic disease has a significant negative influence on overall survival ($p < 0.0001$)

MD. Interestingly, 2 out of 8 patients with intralesional curettage and 4 out of 16 patients with extraosseous tumor growth developed MD but there was no statistically significant correlation between surgical margins and MD ($p = 0.45$) or extraosseous growth and MD ($p = 0.21$).

Although not statistically significant, the high rate of MD and the higher mortality suggests that extraosseous tumor growth may be a different subtype of CS after all, since it appears to behave differently than regular low-grade CS.

Conclusion

While the location of the primary tumor is a strong prognostic factor for high-grade CS (i.e., pelvic lesions have a worse prognosis), in this study, there was no significant difference between patients' outcomes and

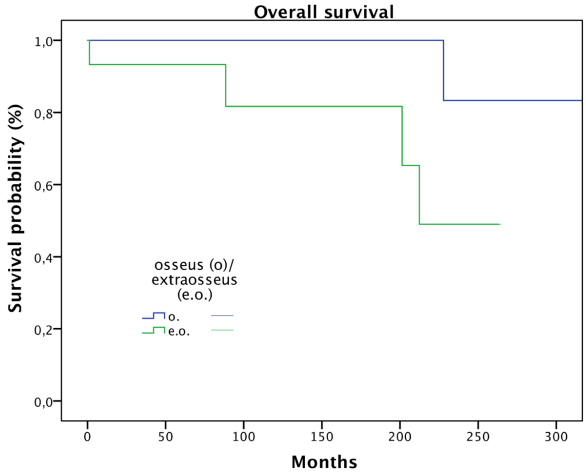

Fig. 4 Overall survival of patients in relation to patient age (≤ 50 vs. > 50 years) (n.s.)

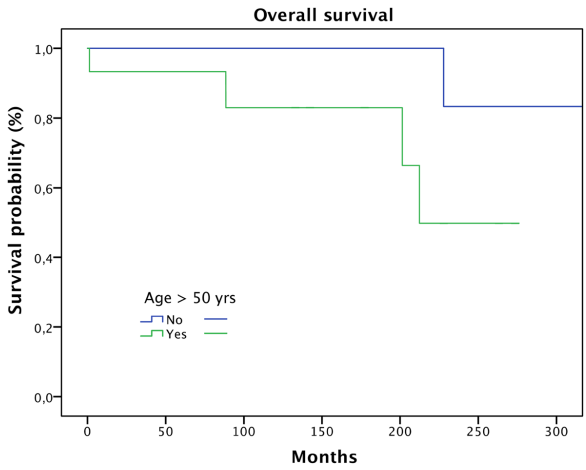

Fig. 5 Comparison of overall survival of patients with and without extraosseous tumor involvement (n.s.)

the tumor location. Marginal resection (R1) was a risk factor for LR, but compared to high-grade CS, there was no significant difference in the overall survival of patients with or without LR. Patients with soft tissue extension of the tumor showed a worse prognosis, but this failed significance testing. MD was more common (16%) than expected and a significant predictor for poor overall survival.

Abbreviations

CS: Chondrosarcoma; CT: Computed tomography; G1, G2, G3: Grading according to the French Federation of Cancer Centers' grading system; LR: Local recurrence; MD: Metastatic disease; MRI: Magnetic resonance imaging; n.s.: Not significant; PMMA: Poly-methyl-methacrylate; R0, R1, R2: Resection margin

Acknowledgements

Not applicable.

Conflict of interest statement

All authors disclose no financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work. This study did not have any grants or funding despite the academic setting of the institutions and authors.

Authors' contributions

JF is a student doing his thesis on chondrosarcomas. He contacted the patients, acquired the data, and is involved in the drafting and revising of the manuscript. AK is a surgeon on many of the cases and is involved in the drafting and revising of the manuscript. AB-M is a radiologist reviewing the radiologic investigations and is involved in the drafting and revising of the manuscript. TK is a pathologist reviewing the pathologic investigations and is involved in the drafting and revising of the manuscript. LL is an oncologist and is involved in drafting and revising of the manuscript. Every patient was discussed in the interdisciplinary panel, and the final decision regarding chemotherapy was based on this. CB is a surgeon on many of the cases, is a reviewer of the manuscript, and is involved in the drafting and revising of the manuscript. FR reviewed the radiotherapy, decided which patient to treat or not to treat, and is involved in the drafting and revising of the manuscript. VJ is a surgeon on many of the cases, is a reviewer of the manuscript, and is involved in the drafting and revising of the manuscript. HRD is the corresponding author, developed the study concept, did the final data analysis, and provided the major clinical input in the 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.

Funding

This study did not have any grants or funding despite the academic setting of the institutions and authors.

Availability of data and materials

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

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 irreversibly anonymized for statistical evaluation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

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

Received: 5 May 2019 Accepted: 16 August 2019
Published online: 03 September 2019

References

1. Doyle LA. Sarcoma classification: an update based on the 2013 World Health Organization classification of tumors of soft tissue and bone. Cancer. 2014;120:1763–74.
2. Bindiganavile S, Han I, Yun JY, Kim HS. Long-term outcome of chondrosarcoma: a single institutional experience. Cancer Res Treat. 2015;47:897–903.
3. Di Giorgio L, Touloupakis G, Vitullo F, Sodano L, Mastantuono M, Villani C. Intralesional curettage, with phenol and cement as adjuvants, for low-grade intramedullary chondrosarcoma of the long bones. Acta Orthop Belg. 2011; 77:666–9.
4. Puri A, Shah M, Agarwal MG, Jambhekar NA, Basappa P. Chondrosarcoma of bone: does the size of the tumor, the presence of a pathologic fracture, or prior intervention have an impact on local control and survival? J Cancer Res Ther. 2009;5:14–9.
5. Outani H, Hamada K, Imura Y, Oshima K, Sotobori T, Demizu Y, Kakunaga S, Joyama S, Imai R, Okimoto T, et al. Comparison of clinical and functional outcome between surgical treatment and carbon ion radiotherapy for pelvic chondrosarcoma. Int J Clin Oncol. 2016;21:186–93.
6. van Maldegem AM, Gelderblom H, Palmerini E, Dijkstra SD, Gambarotti M, Ruggieri P, Nout RA, van de Sande MA, Ferrari C, Ferrari S, et al. Outcome of advanced, unresectable conventional central chondrosarcoma. Cancer. 2014; 120:3159–64.
7. Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, Bovee JV. The clinical approach towards chondrosarcoma. Oncologist. 2008;13:320–9.
8. Donati D, Colangeli S, Colangeli M, Di Bella C, Bertoni F. Surgical treatment of grade I central chondrosarcoma. Clin Orthop Relat Res. 2010;468:581–9.
9. Chen YC, Wu PK, Chen CF, Chen WM. Intralesional curettage of central low-grade chondrosarcoma: a midterm follow-up study. J Chin Med Assoc. 2017;80:178–82.
10. Fiorenza F, Abudu A, Grimer RJ, Carter SR, Tillman RM, Ayoub K, Mangham DC, Davies AM. Risk factors for survival and local control in chondrosarcoma of bone. J Bone Joint Surg Br. 2002;84:93–9.
11. Chen X, Yu LJ, Peng HM, Jiang C, Ye CH, Zhu SB, Qian WW. Is intralesional resection suitable for central grade 1 chondrosarcoma: a systematic review and updated meta-analysis. Eur J Surg Oncol. 2017;43:1718–26.
12. Andreou D, Gilg MM, Gosheger G, Werner M, Hardes J, Pink D, Leithner A, Tunn PU, Streitburger A. Metastatic potential of grade I chondrosarcoma of bone: results of a multi-institutional study. Ann Surg Oncol. 2016;23:120–5.
13. Bergh P, Gunterberg B, Meis-Kindblom JM, Kindblom LG. Prognostic factors and outcome of pelvic, sacral, and spinal chondrosarcomas: a center-based study of 69 cases. Cancer. 2001;91:1201–12.
14. Jodi M, Carter CYI. Conventional chondrosarcoma: old controversies and new insights. Diagn Histopathol. 2014;20:181–90.
15. Funovics PT, Panotopoulos J, Sabeti-Aschraf M, Abdolvahab F, Funovics JM, Lang S, Kotz RI, Dominkus M. Low-grade chondrosarcoma of bone: experiences from the Vienna Bone and Soft Tissue Tumour Registry. Int Orthop. 2011;35:1049–56.
16. Bjornsson J, McLeod RA, Unni KK, Ilstrup DM, Pritchard DJ. Primary chondrosarcoma of long bones and limb girdles. Cancer. 1998;83:2105–19.
17. Giuffrida AY, Burgueno JE, Koniaris LG, Gutierrez JC, Duncan R, Scully SP. Chondrosarcoma in the United States (1973 to 2003): an analysis of 2890 cases from the SEER database. J Bone Joint Surg Am. 2009;91:1063–72.
18. de Camargo OP, Baptista AM, Atanasio MJ, Waisberg DR. Chondrosarcoma of bone: lessons from 46 operated cases in a single institution. Clin Orthop Relat Res. 2010;468:2969–75.
19. Hanna SA, Whittingham-Jones P, Sewell MD, Pollock RC, Skinner JA, Saifuddin A, Flanagan A, Cannon SR, Briggs TW. Outcome of intralesional curettage for low-grade chondrosarcoma of long bones. Eur J Surg Oncol. 2009;35:1343–7.
20. Meftah M, Schult P, Henshaw RM. Long-term results of intralesional curettage and cryosurgery for treatment of low-grade chondrosarcoma. J Bone Joint Surg Am. 2013;95:1358–64.
21. Kim W, Han I, Kim EJ, Kang S, Kim HS. Outcomes of curettage and anhydrous alcohol adjuvant for low-grade chondrosarcoma of long bone. Surg Oncol. 2015;24:89–94.
22. Schwab JH, Wenger D, Unni K, Sim FH. Does local recurrence impact survival in low-grade chondrosarcoma of the long bones? Clin Orthop Relat Res. 2007;462:175–80.
23. Lee FY, Mankin HJ, Fondren G, Gebhardt MC, Springfield DS, Rosenberg AE, Jennings LC. Chondrosarcoma of bone: an assessment of outcome. J Bone Joint Surg Am. 1999;81:326–38.
24. Donati D, El Ghoneimy A, Bertoni F, Di Bella C, Mercuri M. Surgical treatment and outcome of conventional pelvic chondrosarcoma. J Bone Joint Surg Br. 2005;87:1527–30.
25. Sheth DS, Yasko AW, Johnson ME, Ayala AG, Murray JA, Romsdahl MM. Chondrosarcoma of the pelvis. Prognostic factors for 67 patients treated with definitive surgery. Cancer. 1996;78:745–50.
26. Pant R, Yasko AW, Lewis VO, Raymond K, Lin PP. Chondrosarcoma of the scapula: long-term oncologic outcome. Cancer. 2005;104:149–58.
27. Weber KL, Pring ME, Sim FH. Treatment and outcome of recurrent pelvic chondrosarcoma. Clin Orthop Relat Res. 2002;397:19-28.
28. Streitburger A, Ahrens H, Balke M, Buerger H, Winkelmann W, Gosheger G, Hardes J. Grade I chondrosarcoma of bone: the Munster experience. J Cancer Res Clin Oncol. 2009;135:543–50.
29. Ahlmann ER, Menendez LR, Fedenko AN, Learch T. Influence of cryosurgery on treatment outcome of low-grade chondrosarcoma. Clin Orthop Relat Res. 2006;451:201–7.
30. Andreou D, Ruppin S, Fehlberg S, Pink D, Werner M, Tunn PU. Survival and prognostic factors in chondrosarcoma: results in 115 patients with long-term follow-up. Acta Orthop. 2011;82:749–55.
31. Mermerkaya MU, Bekmez S, Karaaslan F, Danisman M, Kosemehmetoglu K, Gedikoglu G, Ayvaz M, Tokgozoglu AM. Intralesional curettage and cementation for low-grade chondrosarcoma of long bones: retrospective study and literature review. World J Surg Oncol. 2014;12:336.
32. Campanacci DA, Scoccianti G, Franchi A, Roselli G, Beltrami G, Ippolito M, Caff G, Frenos F, Capanna R. Surgical treatment of central grade 1 chondrosarcoma of the appendicular skeleton. J Orthop Traumatol. 2013;14:101–7.

Publisher's Note

Eigenanteil

Der Eigenanteil von Herrn Fromm, der bei den beiden Veröffentlichungen „Survival and prognostic factors in conventional central chondrosarcoma“ und „Survival and prognostic factors in conventional GI chondrosarcoma“ als Erstautor auftritt, umfasst die selbstständige Datenerhebung und -auswertung, die Kontaktaufnahme mit den Patienten, die Literaturrecherche und das Verfassen der Manuskripte der vorliegenden Arbeiten. Die Studienplanung erfolgte durch Professor H.R. Dürr. Die klinische Interpretation der Daten erfolgte durch Herrn Fromm in Zusammenarbeit mit Herrn Professor Dürr. Herr Professor Dürr unterstützte den Doktoranden zusätzlich bei der Korrektur des Manuskripts.

Literaturverzeichnis

1. Rozeman, L.B., A.M. Cleton-Jansen, and P.C. Hogendoorn, *Pathology of primary malignant bone and cartilage tumours.* Int Orthop, 2006. **30**(6): p. 437-44.
2. Leerapun, T., et al., *Surgical management of conventional grade I chondrosarcoma of long bones.* Clin Orthop Relat Res, 2007. **463**: p. 166-72.
3. van Praag Veroniek, V.M., et al., *Incidence, outcomes and prognostic factors during 25 years of treatment of chondrosarcomas.* Surg Oncol, 2018. **27**(3): p. 402-408.
4. Verdegaal, S.H., et al., *Incidence, predictive factors, and prognosis of chondrosarcoma in patients with Ollier disease and Maffucci syndrome: an international multicenter study of 161 patients.* Oncologist, 2011. **16**(12): p. 1771-9.
5. Gelderblom, H., et al., *The clinical approach towards chondrosarcoma.* Oncologist, 2008. **13**(3): p. 320-9.
6. Coindre, J.M., *[New WHO classification of tumours of soft tissue and bone].* Ann Pathol, 2012. **32**(5 Suppl): p. S115-6.
7. Geirnaerdt, M.J., et al., *Usefulness of radiography in differentiating enchondroma from central grade 1 chondrosarcoma.* AJR Am J Roentgenol, 1997. **169**(4): p. 1097-104.
8. Schiller, A.L., *Diagnosis of borderline cartilage lesions of bone.* Semin Diagn Pathol, 1985. **2**(1): p. 42-62.
9. Ferrer-Santacreu, E.M., et al., *Enchondroma versus Low-Grade Chondrosarcoma in Appendicular Skeleton: Clinical and Radiological Criteria.* J Oncol, 2012. **2012**: p. 437958.
10. Ferrer-Santacreu, E.M., et al., *Enchondroma versus Chondrosarcoma in Long Bones of Appendicular Skeleton: Clinical and Radiological Criteria-A Follow-Up.* J Oncol, 2016. **2016**: p. 8262079.
11. Di Giorgio, L., et al., *Intralesional curettage, with phenol and cement as adjuvants, for low-grade intramedullary chondrosarcoma of the long bones.* Acta Orthop Belg, 2011. **77**(5): p. 666-9.
12. Andreou, D., et al., *Metastatic Potential of Grade I Chondrosarcoma of Bone: Results of a Multi-institutional Study.* Ann Surg Oncol, 2016. **23**(1): p. 120-5.
13. Streitburger, A., et al., *Grade I chondrosarcoma of bone: the Munster experience.* J Cancer Res Clin Oncol, 2009. **135**(4): p. 543-50.
14. Xu, J., et al., *Mesenchymal chondrosarcoma of bone and soft tissue: a systematic review of 107 patients in the past 20 years.* PLoS One, 2015. **10**(4): p. e0122216.
15. Giuffrida, A.Y., et al., *Chondrosarcoma in the United States (1973 to 2003): an analysis of 2890 cases from the SEER database.* J Bone Joint Surg Am, 2009. **91**(5): p. 1063-72.

16. de Camargo, O.P., et al., *Chondrosarcoma of bone: lessons from 46 operated cases in a single institution.* Clin Orthop Relat Res, 2010. **468**(11): p. 2969-75.
17. Fiorenza, F., et al., *Risk factors for survival and local control in chondrosarcoma of bone.* J Bone Joint Surg Br, 2002. **84**(1): p. 93-9.
18. Angelini, A., et al., *Clinical outcome of central conventional chondrosarcoma.* J Surg Oncol, 2012. **106**(8): p. 929-37.
19. Meis-Kindblom, J.M., et al., *Extraskeletal myxoid chondrosarcoma: a reappraisal of its morphologic spectrum and prognostic factors based on 117 cases.* Am J Surg Pathol, 1999. **23**(6): p. 636-50.
20. Kawaguchi, S., et al., *Extraskeletal myxoid chondrosarcoma: a Multi-Institutional Study of 42 Cases in Japan.* Cancer, 2003. **97**(5): p. 1285-92.
21. Chaabane, S., et al., *Periosteal chondrosarcoma.* AJR Am J Roentgenol, 2009. **192**(1): p. W1-6.
22. Papagelopoulos, P.J., et al., *Survivorship analysis in patients with periosteal chondrosarcoma.* Clin Orthop Relat Res, 2006. **448**: p. 199-207.
23. Weinberg, J., et al., *Periosteal chondrosarcoma in a 9-year-old girl with osteochondromatosis.* Skeletal Radiol, 2005. **34**(9): p. 539-42.
24. Kenan, S., et al., *Lesions of juxtacortical origin (surface lesions of bone).* Skeletal Radiol, 1993. **22**(5): p. 337-57.
25. Hatano, H., et al., *Periosteal chondrosarcoma invading the medullary cavity.* Skeletal Radiol, 1997. **26**(6): p. 375-8.
26. Bjornsson, J., et al., *Clear cell chondrosarcoma of bone. Observations in 47 cases.* Am J Surg Pathol, 1984. **8**(3): p. 223-30.
27. Itala, A., et al., *An institutional review of clear cell chondrosarcoma.* Clin Orthop Relat Res, 2005. **440**: p. 209-12.
28. Staals, E.L., P. Bacchini, and F. Bertoni, *Dedifferentiated central chondrosarcoma.* Cancer, 2006. **106**(12): p. 2682-91.
29. Dickey, I.D., et al., *Dedifferentiated chondrosarcoma: the role of chemotherapy with updated outcomes.* J Bone Joint Surg Am, 2004. **86-A**(11): p. 2412-8.
30. Mitchell, A.D., et al., *Experience in the treatment of dedifferentiated chondrosarcoma.* J Bone Joint Surg Br, 2000. **82**(1): p. 55-61.
31. Mercuri, M., et al., *Dedifferentiated chondrosarcoma.* Skeletal Radiol, 1995. **24**(6): p. 409-16.
32. Frassica, F.J., et al., *Dedifferentiated chondrosarcoma. A report of the clinicopathological features and treatment of seventy-eight cases.* J Bone Joint Surg Am, 1986. **68**(8): p. 1197-205.
33. Huvos, A.G., et al., *Mesenchymal chondrosarcoma. A clinicopathologic analysis of 35 patients with emphasis on treatment.* Cancer, 1983. **51**(7): p. 1230-7.
34. Frezza, A.M., et al., *Mesenchymal chondrosarcoma: prognostic factors and outcome in 113 patients. A European Musculoskeletal Oncology Society study.* Eur J Cancer, 2015. **51**(3): p. 374-81.

35. Schneiderman, B.A., S.A. Kliethermes, and L.M. Nystrom, *Survival in Mesenchymal Chondrosarcoma Varies Based on Age and Tumor Location: A Survival Analysis of the SEER Database.* Clin Orthop Relat Res, 2017. **475**(3): p. 799-805.

36. Nota, S.P., et al., *The Identification of Prognostic Factors and Survival Statistics of Conventional Central Chondrosarcoma.* Sarcoma, 2015. **2015**: p. 623746.

37. Donati, D., et al., *Surgical treatment and outcome of conventional pelvic chondrosarcoma.* J Bone Joint Surg Br, 2005. **87**(11): p. 1527-30.

38. Gitelis, S., et al., *Chondrosarcoma of bone. The experience at the Istituto Ortopedico Rizzoli.* J Bone Joint Surg Am, 1981. **63**(8): p. 1248-57.

39. Andreou, D., et al., *Survival and prognostic factors in chondrosarcoma: results in 115 patients with long-term follow-up.* Acta Orthop, 2011. **82**(6): p. 749-55.

40. Lee, F.Y., et al., *Chondrosarcoma of bone: an assessment of outcome.* J Bone Joint Surg Am, 1999. **81**(3): p. 326-38.

41. Donati, D., et al., *Surgical treatment of grade I central chondrosarcoma.* Clin Orthop Relat Res, 2010. **468**(2): p. 581-9.

42. Funovics, P.T., et al., *Low-grade chondrosarcoma of bone: experiences from the Vienna Bone and Soft Tissue Tumour Registry.* Int Orthop, 2011. **35**(7): p. 1049-56.

43. Meftah, M., P. Schult, and R.M. Henshaw, *Long-term results of intralesional curettage and cryosurgery for treatment of low-grade chondrosarcoma.* J Bone Joint Surg Am, 2013. **95**(15): p. 1358-64.

44. Bauer, H.C., et al., *Low risk of recurrence of enchondroma and low-grade chondrosarcoma in extremities. 80 patients followed for 2-25 years.* Acta Orthop Scand, 1995. **66**(3): p. 283-8.

45. Aarons, C., et al., *Extended intralesional treatment versus resection of low-grade chondrosarcomas.* Clin Orthop Relat Res, 2009. **467**(8): p. 2105-11.

46. Schwab, J.H., et al., *Does local recurrence impact survival in low-grade chondrosarcoma of the long bones?* Clin Orthop Relat Res, 2007. **462**: p. 175-80.

Danksagungen

Besonderer Dank gilt an erster Stelle meinem Doktorvater Herr Professor H. R. Dürr, der mir zu über den gesamten Prozess mit Rat und Tat zur Seite stand. Ohne seine Geduld und sein Vertrauen wäre diese Arbeit nicht möglich gewesen.

Mein weiterer Dank gilt allen an der Entstehung dieser Arbeit beteiligten Ko-Autoren und Mitarbeitern des Schwerpunkts Tumororthopädie der Klinik für Orthopädie, Physikalische Medizin und Rehabilitation des Klinikums der Ludwig-Maximilians-Universität München.

Ich möchte meiner Familie für Ihre bedingungslose Unterstützung danken. Meinem Vater besonders für sein Interesse und unsere Gespräche, die mich stets motivierten. Meiner Mutter danke ich für ihre aufmerksamen Fragen und ihren journalistisch geschulten Blick, der mir sehr geholfen hat. Meiner Schwester Hannah möchte ich für die Geduld danken, mit der sie die regelmäßigen und detaillierten Berichte über die Arbeit ertragen hat.

Meiner Freundin Christina danke ich für ihr Interesse, ihre Ruhe und die positive Energie, mit der sie mich nicht nur bei dieser Arbeit unterstützt hat, sondern Tag für Tag mein Leben bereichert.

Meinen Freund/Innen Gabi, Tim und Lukas danke ich für ihre Korrekturen, sowie die Unterstützung, die Geduld und das Vertrauen mit der sie die ganze Zeit für mich da waren.