Clinical features of Ewing and chondrosarcoma

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Chapter 7

Outcome of advanced unresectable conventional central chondrosarcoma

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Abstract

Background

For chondrosarcoma patients with unresectable disease, due to tumor location, tumor size or extensive metastatic disease, treatment options are very limited because of relative resistance to radio- and chemotherapy. The overall survival of this patient population is poor, however specific studies are lacking and large series have not been published. Therefore we conducted this retrospective two-center study in order to gain insight in the outcome of patients with advanced unresectable conventional central chondrosarcoma.

Patients and methods

All unresectable conventional central chondrosarcoma patients diagnosed between 1-1-1980 and 31-12-2011 in two major European bone sarcoma centres (Rizzoli Institute Bologna, Leiden University Medical Centre) were selected. Relevant information was collected from the medical records at both centers.

Results

A total of 171 patients met our selection criteria, overall survival for all patients was 48% at 1 year, 24% at 2 years, 12% at 3 years, 6% at 4 years and 2% at 5 years. Patients with unresectable locally advanced disease without distant metastases had a significant better survival than patients with metastatic disease (p=0.0014). Systemic treatment, either doxorubicin based chemotherapy or the non-cytotoxic drugs imatinib and sirolimus, improved survival significantly compared to no treatment (p=0.0487). For patients with locally advanced disease without metastases, radiotherapy was associated with a survival benefit (p=0.0032).

Conclusion

This study provides a standard for overall survival rates after unresectable conventional central chondrosarcoma. Systemic treatment and radiotherapy may improve survival although selection bias due to the retrospective nature of this study may have influenced the outcome. The poor survival underlines the need for new therapeutic options for this patient population.

Introduction

Chondrosarcomas are a heterogeneous diverse group of tumors that share at least the characteristic of chondroid matrix production. After osteosarcoma it is the second most common primary bone tumor in adults and accounts for 20 percent of the new primary bone cancer cases. Conventional central chondrosarcoma is the most common subtype, and the majority is of low histological grade. Histological grade is so far the best prognostic indicator [1-3]. Low grade chondrosarcoma tumors rarely metastasize, grow slowly and have a favorable prognosis after surgery, and therefore in the new WHO classification grade I chondrosarcomas are reclassified as atypical cartilaginous tumours [www.WHO.it]. Approximately 10% of conventional central chondrosarcomas are histologically high grade (grade II or III) with a high risk for distant metastases and/or local recurrence and therefore a poor prognosis after resection alone.

In the last decades there has been no significant improvement in survival for patients with chondrosarcoma. The only treatment option with curative intent is surgical resection [4]. However for some locations in the body, such as the pelvis or the skull, resection with a wide margin is difficult to achieve and so local recurrence and metastatic disease are more common. The currently available systemic therapy options are not believed to improve outcome although randomized studies and large series have not been published. Therefore we conducted this study in order to gain insight in the outcome and the effectiveness of systemic treatment of patients with advanced unresectable conventional central chondrosarcoma.

Materials and methods

For our study we selected all unresectable central chondrosarcoma patients diagnosed between 1-1-1980 and 31-12-2011 in two major European bone sarcoma centres (Rizzoli Institute in Bologna, and Leiden University Medical Centre) in January 2012. Reasons for unresectable disease were: complete resection of primary tumor and/or metastases was not deemed feasible because of technical inability due to the size or location of the primary tumor or extensive metastatic sites, or because complete resection would lead to unacceptable morbidity as judged by the multidisciplinary teams at the referral sites in Bologna and Leiden. Relevant information was retrospectively collected from the archives at both centers. Baseline information consisted of gender, age at first presentation of disease, date of first disease presentation, disease location, type, grade and TNM stage of chondrosarcoma at first diagnosis and at recurrence, treatment received, date of development of local recurrence or metastatic disease, pattern of metastases, overall survival from disease onset and post-relapse survival.

The overall survival (OS) was calculated from the day of non-resectability until death or the last follow-up examination. The day that the decision was taken not to perform surgery in the multidisciplinary sarcoma board meeting was taken as the day of non-resectability. The survival curves were calculated according to the Kaplan and Meier method and compared using the log-rank test.

Results

A total of 171 patients were diagnosed with unresectable central conventional chondrosarcoma in the given timeframe at the two centers: 49 cases at first presentation, 122 cases after one or more relapses. The patient characteristics are shown in Table 7.1. From the 171 unresectable patients 72 (42%) had unresectable metastatic disease in the lungs

Table 7.1 Patient characteristics from the 171 unresectable central conventional chondrosarcoma patients

Male : Female	107 : 64
Age at diagnosis (years)	
Mean	53
Range	17–90
Primary site	
Limb proximal	51
Limb distal	19
Pelvis	63
Rib	14
Scapula	7
Vertebra	9
Other[a]	8
Grade at diagnosis	
1	9
2	118
3	44
Margins of primary surgery	
Wide	87
Marginal	24
Intralesional	28
Inoperable	18
Refused surgery	10
Unknown	4
Unresectable disease localization	
Local	45
Lung	72
Local and lung	39
Multi-organ	15

[a] Other sites = foot, neck, sternum and hand.

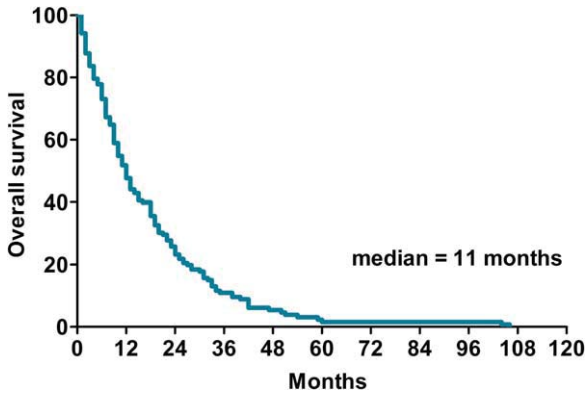

Figure 7.1 Median overall survival for all included patients calculated from the time point of non-resectability till death or last patient contact.

only, 45 (26%) had only local unresectable disease, 39 (23%) had local and unresectable lung disease and 15 (9%) had multi-organ involvement. The median OS was 11 months with a range of 1 to 106 months (Figure 7.1).

OS for all patients was 48% at 1 year, 24% at 2 years, 12% at 3 years, 6% at 4 years and 2% at 5 years. The OS was additionally analysed according to location of the disease. For patients with only local unresectable disease OS was 26% after 3 years compared to 7% in patients with only lung involvement and 8% for patients with lung and local disease involvement. Patients with multi-organ involvement had an OS of 0% after 2 years with a mean survival time of 7 months (Figure 7.2). The difference between OS of patients with only local unresectable disease and patients with metastatic disease is significant with a p-value of 0.0014.

The OS after 3 years was the same for the patients who received only cytotoxic drugs and the patients who received systemic treatment, this is probably due to the small group of patients who were treated with these drugs. It was not possible to calculate the progression free survival because patients were often not followed by scans as this is a palliative setting, and if scans were made they were not done with standard time intervals.

Next we investigated which variables may influence survival after unresectable disease. Both age below 40 years (p=0.001) and grade II (p=0.022) were correlated with a better OS, no correlation with OS was found for gender, site and resectable versus non-resectable at primary diagnosis (data not shown).

Of the 171 patients 37 received systemic treatment, most patients received doxorubicin-based chemotherapy, but also the non-chemotherapy based agents imatinib and sirolimus

were adopted. This group had an OS of 26% after 3 years compared to 8% for the patients without systemic treatment ($p \leq 0.05$) (Figure 7.3) with a median OS of 20 months for the patients with systemic treatment versus 15 months for the patients without treatment.

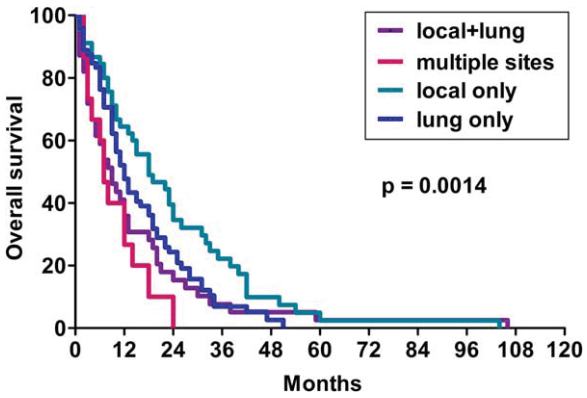

Figure 7.2 Median overall survival calculated from the time point of non-resectability till death or last patient contact for the patients subdivided in the groups local disease involvement only, local and lung, lung only and multiple sites.

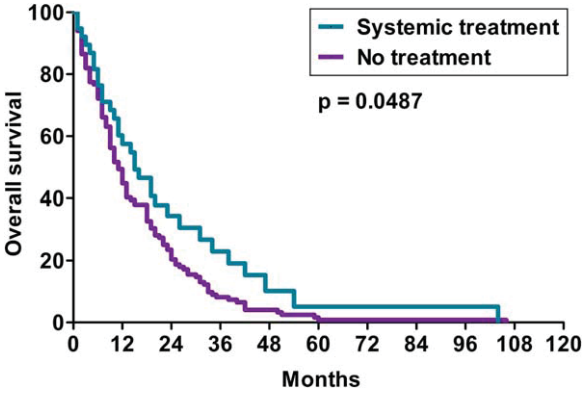

Figure 7.3 For the included patients median overall survival is correlated to systemic treatment. Patients were subdivided in those who received systemic treatment versus patients who received no treatment.

Patients with only metastatic disease, thus excluding patients with local disease or local disease with metastases, had a better OS if they received any systemic or radiotherapy treatment compared to the patients who received no treatment ($p=0.0082$) (Figure 7.4). The patient characteristics of these subpopulations are shown in Table 7.2.

Thirty-three patients received radiotherapy mainly with palliative intent. Patients were treated with radiotherapy according to the standard protocol in the centers. A broad range of dose fractionation schedules was used ranging from 66 Gy in 2 Gy fractions in an attempt to maximize local control to 24 Gy in 8 Gy fractions when the intent was palliative in patients with a poor prognosis. These patients had an OS of 27% after 3 years versus 8% for the patients without radiotherapy treatment. After separating the 33 patients receiving radiotherapy in groups depending on the disease location a survival benefit for patients with only local disease was shown with a p-value of 0.0032 (Figure 7.5). The patient characteristics of these subpopulations are shown in Table 7.3.

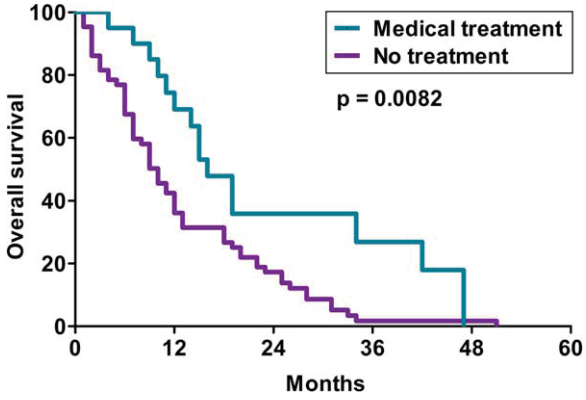

Figure 7.4 A subpopulation was defined with patients with only metastatic disease, patients with local or local and metastatic disease were excluded. Patients were subdivided in those who received treatment (systemic and/or radiotherapy) and those who received no treatment.

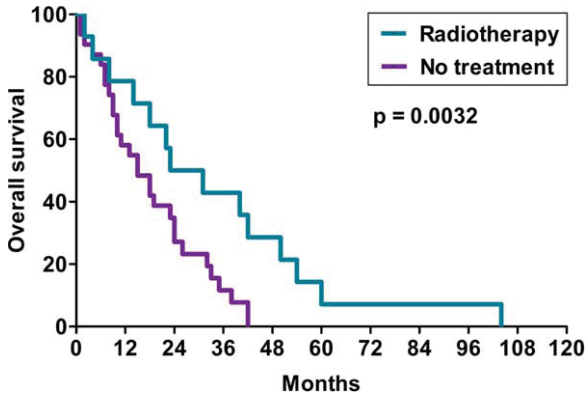

Figure 7.5 A subpopulation was defined with patients with only locally advanced unresectable disease. The median overall survival for these patients is better after radiotherapy versus no radiotherapy.

Table 7.2 Patients characteristics comparing the subpopulation of metastatic only patients who receive treatment (systemic and/or radiotherapy) versus those who received no treatment

	Metastatic only patients	
	Systemic treatment	No systemic treatment
Male : Female	15 : 24	49 : 25
Age at diagnosis (years)		
Mean	49	49
Range	27–68	17–90
Primary site		
Limb proximal	12	25
Limb distal	1	15
Pelvis	6	9
Rib	2	4
Scapula	1	4
Vertebra	2	0
Other [a]	1	5
Grade at diagnosis		
1	2	1
2	18	32
3	6	28
Outcome first surgery		
Wide	14	48
Marginal	6	8
Intralesional	4	6
Inoperable	0	0
Refused surgery	0	0
Unknown	1	0

Patients are compared for gender, age primary site, histological grade at diagnosis and outcome of first surgery.
[a] Other sites = sternum, foot, hand, calcaneus.

Discussion

Conventional central chondrosarcoma is a primary bone tumor which, if the grade is low, can be treated with surgery with curative intent. However the patients who present or develop unresectable disease have a poor prognosis. In the present study the outcome of all patients diagnosed with unresectable conventional central chondrosarcoma at two major bone sarcoma centres was evaluated, in order to explore the OS in this condition and to set the standard for future studies.

The overall survival for all patients is poor, with a 3 year OS of 12%. The patients with only local unresectable disease had a better prognosis as compared to patients with metastatic disease, with an OS of 26% after 3 years. Comparing these figures with the published overall survival data for resectable chondrosarcoma the difference with our

Table 7.3 Patients characteristics comparing the subpopulation of locally advanced only patients who receive radiotherapy versus those who received no radiotherapy

	Locally advanced only patients	
	RT	No RT
Male : Female	8 : 6	19 : 12
Age at diagnosis (years)		
Mean	49	59
Range	26–81	26–89
Primary site		
Limb proximal	1	5
Limb distal	0	2
Pelvis	8	20
Rib	1	0
Scapula	0	0
Vertebra	3	4
Other[a]	1	0
Grade at diagnosis		
1	0	4
2	14	27
3	0	0
Outcome first surgery		
Wide	3	10
Marginal	0	2
Intralesional	6	4
Inoperable	2	8
Refused surgery	3	6
Unknown	0	1

Patients are compared for gender, age primary site, histological grade at diagnosis and outcome of first surgery.
[a] Other sites = neck.

patient population is striking: 5-years OS of 99% for grade I tumours and 77% for grade III tumours [5]. The results of our study show how urgent the need for new therapeutic options is in this patient population. Currently trials with targeted single agent or combinations are being conducted to address this unmet medical need. A phase II study for unresectable or metastatic conventional chondrosarcoma patients treated with saridegib had to be terminated because the interim analyses showed no treatment benefit compared to placebo. A phase II study testing the hedgehog inhibitor GDC-0449 in patients with advanced chondrosarcoma showed some activity and was well tolerated [6]. A phase II study investigating pazopanib for unresectable or metastatic conventional chondrosarcoma patients (NCT01330966) and a phase II study with imatinib in advanced conventional chondrosarcoma patients (NCT00928525) are still recruiting.

Because of the dismal survival for patients with unresectable disease it is important to determine prognostic factors able to identify the subpopulation of chondrosarcoma patients at high risk of developing unresectable disease. Several studies have already been conducted to search for prognostic factors [1, 7, 8]. So far, no molecular marker has been shown that is independent from and superior to histological grading in combination with clear margins in predicting outcome.

In contrast to what is generally stated in literature we found that for metastatic patients there is a survival benefit when receiving chemotherapy: various regimes of alkylating drugs were being used. Due to heterogeneity of the chemotherapy treatments employed it was not possible to do sub-analysis on type of treatment. We did compare the patients who received cytotoxic drugs to those who got non-cytotoxic drugs, but the difference was not significant (p=0.436). This outcome may not be representative because of the small number of patients and the wide time range in which the patients were treated. The general result of improved survival after chemotherapy is rather unexpected because the common opinion is that chondrosarcoma patients do not benefit from non-surgical treatment. However some preclinical studies have already shown promising data that contradicts this assumption [9]. Moreover, patients with only locally advanced unresectable disease have a survival benefit from radiotherapy, although this benefit disappears when patients have metastatic disease. We were also interested in the progression free survival after radiotherapy. However, no routine scans were made after radiotherapy, most likely due to the palliative intent of radiotherapy in many patients. This hampers correct interpretation of time to progression and thus the progression free survival endpoint in this retrospective study. The results of these non-surgical treatment could however be affected by selection bias which may have played a role in this retrospective study of two bone tumor referral centers.

The patients with only locally advanced disease eventually die because of local problems due to increasing tumor load, local tumor pressure on important structures and side effects of the tumor like increasing need of pain medication like morphine and anemia.

Italiano et al very recently published an article in which they retrospectively describe the survival data of advanced chondrosarcoma patients [10]. One hundred and eighteen advanced chondrosarcoma patients were analyzed and the median PFS was 4.7 months with a median OS 18 months. Performance status, number of metastatic sites and palliative surgery were all associated with OS. Their population is heterogeneous due to the different subtypes of chondrosarcoma included and thereby different expected outcome. The authors also mention this as they find a significant difference in objective response rate for the different histological subtypes. This is why we decided to study outcomes in a larger cohort of a homogenous population of central conventional chondrosarcoma.

Also our study has some limitations. Our retrospective study, despite using data from two experienced bone cancer centers in Europe may have encountered some difference in the definition of unresectability between the centers which may have had limited impact on the outcome of this study. Differences in risk-benefit ratio may be perceived differently between sites and surgeons, and patients. Also due to the retrospective nature of this study not all possible prognostic items could be reliably retrieved from the records, such as performance status which had been found in earlier studies to be related to OS [10].

In conclusion, our study adds significantly to the limited data available on overall survival for both locally and metastatic unresectable conventional central chondrosarcoma. Our data show that chemotherapy in unresectable chondrosarcoma patients may increase survival, but further studies are warranted. Radiotherapy shows a survival advantage and is common practice for locally advanced conventional central chondrosarcomas in both reference centers.

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