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Prognosis of Primary and Recurrent Chondrosarcoma of the Rib

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ABSTRACT

Background. Chondrosarcoma of the rib is a rare disease. Although surgery is the only curative treatment option, rib resection with an adequate margin can be challenging and local recurrence is a frequent problem. In this study, the prognosis of primary and recurrent chondrosarcoma of the rib is reported.

Methods. Retrospective analysis was performed of patients treated for chondrosarcoma of the rib between 1984 and 2014 in three major tertiary referral centers in The Netherlands. Clinical and histopathological features were analyzed for their prognostic value using Kaplan–Meier and Cox proportional hazard analysis. Endpoints were set at local recurrent disease, metastasis rate, or death.

Results. Overall, 76 patients underwent a resection for a primary chondrosarcoma, and 26 patients underwent a resection for a recurrent chondrosarcoma. Five-year overall survival in the primary group was 90 %, local recurrence rate was 17 %, and metastasis rate was 12 %. The 5-year outcome after recurrent chondrosarcoma was lower, with an overall survival of 65 %, local recurrence rate of 27 %, and metastasis rate of 27 %. For primary chondrosarcoma, tumor size >5 cm and a positive resection margin were correlated with worse overall survival [hazard ratio (HR) 3.28, 95 % confidence interval (CI) 1.03–10.44; HR 2.92, 95 % CI 1.03–8.25). A higher histological grade was correlated with a higher local recurrence and metastasis rate (HR 5.92, 95 % CI 1.11–31.65; HR 6.96, 95 % CI 1.15–42.60).

Conclusion. Surgical resection of both primary and recurrent chondrosarcoma of the rib is an effective treatment strategy. The oncological outcome after surgery is worse in tumors >5 cm, in tumors with positive resection margins and grade 3 chondrosarcoma.

Chondrosarcoma is a rare type of cancer derived from cartilage-producing malignant mesenchymal cells, and occurs in both the appendicular and the axial skeleton. It is the second most frequent malignant bone tumor, with an incidence of 0.79/(million year).[1,2] Biological behavior varies widely depending on grade and anatomical location.[3–6] Since chondrosarcoma is notoriously resistant to conventional chemotherapy and radiation, surgical resection remains the only curative treatment, although new treatment modalities are currently under investigation.[7] Low-grade chondrosarcoma typically has low metastatic potential and is therefore treated with intralesional surgery or curettage in combination with local adjuvant therapy such as phenol.[8] The 10-year survival rate for low-grade chondrosarcoma ranges from 80 to 90 %.[1,2] In contrast, high-grade chondrosarcoma has a 10-year survival rate of approximately 40–70 % and is treated with radical resection.[9–11]

The site of origin may affect outcome in chondrosarcoma, with some anatomic locations such as the pelvis known to predict a worse prognosis than others. This may be due to differences in biological behavior, or may reflect the difficulty achieving an R0 resection in these locations.[1]

Chondrosarcoma of the chest wall accounts for only 15 % of all chondrosarcomas, arising frequently in the rib.[12–14] Since tumor growth of rib chondrosarcomas is

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often intramedullary and immediately adjacent to the pleural cavity, obtaining adequate resection margins is often challenging.[15,16] Prognosis and prognostic factors of patients with chondrosarcoma of the rib are rarely described.[12,15,16] Most series of chest-wall chondrosarcomas are small and include tumors arising from various chest-wall locations. Only one Scandinavian study of 106 patients evaluated prognostic factors of chondrosarcoma of the chest wall.[12] Here, we report a multicenter study of patients with chondrosarcoma of the rib only. To our knowledge, this is the only report to date analysing prognosis and prognostic factors of rib chondrosarcoma specifically. The aim of this study was to evaluate the effectiveness of chest-wall resection for primary and recurrent chondrosarcoma of the rib, and to identify clinical and pathological prognostic factors. As local recurrence is a frequent problem in chondrosarcoma,[17] outcome of patients with recurrent chondrosarcoma of the rib is also evaluated.

PATIENTS AND METHODS

Patients

All patients who were discussed at The Netherlands Committee on Bone Tumors between 1984 and 2014 were reviewed. In The Netherlands, patients with a malignant bone tumor will be discussed in this review panel, consisting of radiologists, pathologists, and dedicated sarcoma surgeons. Patients with chondrosarcoma of the rib who were treated with surgical resection were identified from the archives of this committee. Clinical information was obtained from the hospital records of all patients who were diagnosed and/or treated in one of the following referral hospitals in The Netherlands: the Daniel den Hoed/Erasmus Medical Centre, Rotterdam; the Netherlands Cancer Institute, Amsterdam; or the Leiden University Medical Center, Leiden.

Selection Criteria

A total of 165 patients with a histologically confirmed diagnosis of chondrosarcoma of the rib were identified from the archives of the committee. The diagnosis of chondrosarcoma was based on large-core needle biopsies or surgical specimens and were reviewed in regional sarcoma boards. From these patients, two were excluded for having Ollier's disease, and from the remaining patients we identified 76 patients with primary chondrosarcoma and 26 patients with recurrent chondrosarcoma who underwent surgical resection. All other patients were treated in smaller community hospitals or other referral hospitals.

Clinical and Pathological Data

Clinical and pathological features were analyzed for their association with local recurrence, metastasis formation, and overall survival in the primary chondrosarcoma cohort. Patient's files were used for obtaining demographic data, information about follow-up, and information about the surgical procedure and results. Histopathological data were obtained from pathology reports, including size of the tumor and resection margin. The resection margins were categorized as macroscopically incomplete (R2), microscopically incomplete (R1), or complete (R0, no ink was seen on the margin on the tumor).

Statistical Analysis

The study was designed as a retrospective cohort study. Endpoints were set at overall survival, local recurrence, or distant metastasis formation. Survival curves were created using the Kaplan–Meier method. Differences between the groups were assessed using the log-rank test, and Cox proportional hazards models were used to obtain hazard ratios (HRs) for different tumor characteristics in relation to outcome. Significance levels were set at $p < 0.05$. All statistical tests were performed using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient Characteristics

The cohort consisted of 76 patients with primary chondrosarcoma and 26 patients with recurrent chondrosarcoma. Clinical characteristics of the patients are shown in Table 1. Of the 76 patients with a primary tumor, 39 were male. The median age in this cohort was 53 years (range 19–86), and the median tumor size was 6 cm (range 2–25). We found 26 patients with a recurrent chondrosarcoma, of whom 10 were recurrent at presentation. Median age of this cohort was 57 years (range 25–80), 15 patients were male, and median tumor size was 5 cm (range 2–25) [Table 1].

Survival After Primary or Recurrent Chondrosarcoma

Of all 76 patients with primary chondrosarcoma, 13 (17 %) patients had a local recurrence within 5 years, with a median time to recurrent disease of 34 months. In addition, 9 (12 %) patients developed distant metastases, with a median time to metastatic disease of 39 months. Eight patients died within 5 years, resulting in a 5-year mortality rate of 10 % (Table 2). From the eight deceased patients, six died of disease.

TABLE 1 Patient characteristics

	Primary CHS $n = 76$	Recurrent CHS $n = 26$
Median age range (years)	53 (19–86)	58 (25–80)
Sex		
Male	39 (51 %)	15 (58 %)
Female	37 (49 %)	11 (42 %)
Resection type		
Partial rib	49 (65 %)	11 (42 %)
Total rib	17 (22 %)	4 (15 %)
Unknown	10 (13 %)	11 (32 %)
Number of ribs resected		
1–3 ribs	67 (88 %)	23 (89 %)
4–6 ribs	6 (8 %)	0 (0 %)
>6 ribs	2 (3 %)	1 (4 %)
Unknown	1 (1 %)	2 (8 %)
Histological grade		
Grade I	29 (38 %)	9 (35 %)
Grade II	42 (55 %)	13 (50 %)
Grade III	5 (7 %)	3 (12 %)
Unknown	0 (0 %)	1 (4 %)
Median tumor size (range) cm	6 (2–25)	5 (2–25)
<5 cm	35 (46 %)	12 (46 %)
>5 cm	36 (50 %)	13 (50 %)
Unknown	3 (4 %)	1 (4 %)
Adjuvant therapy		
Radiotherapy	4 (5 %)	4 (15 %)
Chemotherapy	0 (0 %)	0 (0 %)
Postoperative complications	7 (9 %)	3 (12 %)

Of all 26 patients with recurrent chondrosarcoma, seven (27 %) patients had a second local recurrence within 5 years, with a median time to re-recurrent disease of 17 months. One patient developed a third recurrence. Of these 26 patients, seven (27 %) developed distant metastases, with a median time to metastasis development of 24 months. A total of nine patients died; the 5-year mortality was 35 % (Table 2). From this group of nine patients, eight died of disease.

Since the standard of care for patients with recurrent chondrosarcoma is also surgical resection, we compared the outcome of recurrent chondrosarcoma with primary chondrosarcoma. We compared the two groups in terms of local recurrent disease and overall survival. Overall survival of patients with recurrent chondrosarcoma seems slightly worse in comparison to patients with primary chondrosarcoma, although this difference was not significant. However, local recurrence is significantly higher after resection of recurrent chondrosarcoma when compared with resection of primary chondrosarcoma (Fig. 1). The patients in our study developing a 2nd recurrence were all treated with salvage surgery.

TABLE 2 Outcome data of patients with primary chondrosarcoma and recurrent chondrosarcoma

	5 year event rate	Median time to event in months	Total even rate
Primary CHS			
Local recurrence	13 (17 %)	34	16 (21 %)
Metastasis	9 (12 %)	39	12 (16 %)
Morality	8 (10 %)	54	13 (17 %)
Recurrent CHS			
Local recurrence	7 (27 %)	17	8 (31 %)
Metastasis	7 (27 %)	24	8 (31 %)
Morality	9 (35 %)	40	9 (35 %)

Analysis of Prognostic Factors for Local Recurrent Disease, Distant Metastasis, and Overall Survival After Treatment for Primary Chondrosarcoma

Different parameters were analyzed for their relation to outcome in primary rib chondrosarcoma. First, overall survival after local recurrent chondrosarcoma or metastasis formation was determined (Fig. 2). Local recurrence in the group of patients with primary chondrosarcoma is not significantly correlated with worse overall survival. However, metastasis formation is significantly correlated with poor overall survival ($p < 0.01$).

Table 3 displays an overview of different clinical and pathological factors in relation to local recurrent disease, metastasis formation, and overall survival. Fig. 3 shows Kaplan–Meier curves of different factors significantly correlated with worse outcome.

Tumor size >5 cm was significantly correlated with worse overall survival (HR 3.28, 95 % confidence interval [CI] 1.03–10.44) and showed a trend towards a higher metastasis rate (HR 2.19, 95 % CI 0.66–7.29); however, this was not significant (Fig. 3). Grade III tumors were significantly correlated with a higher metastasis rate (HR 6.96, 95 % CI 1.15–42.60) and local recurrent disease (HR 5.92, 95 % CI 1.11–31.65), but not with worse overall survival.[18] In our group, positive resection margins were a significant predictor of worse overall survival (HR 2.92, 1.03–8.25). Of note, no significant correlations were obtained for the number of ribs involved or the extension of the rib resection (complete or partial).

DISCUSSION

In this retrospective, multicenter study, we included 76 patients with primary chondrosarcoma of the rib and 26 patients with recurrent chondrosarcoma of the rib, selected from the archives of The Netherlands Committee on Bone

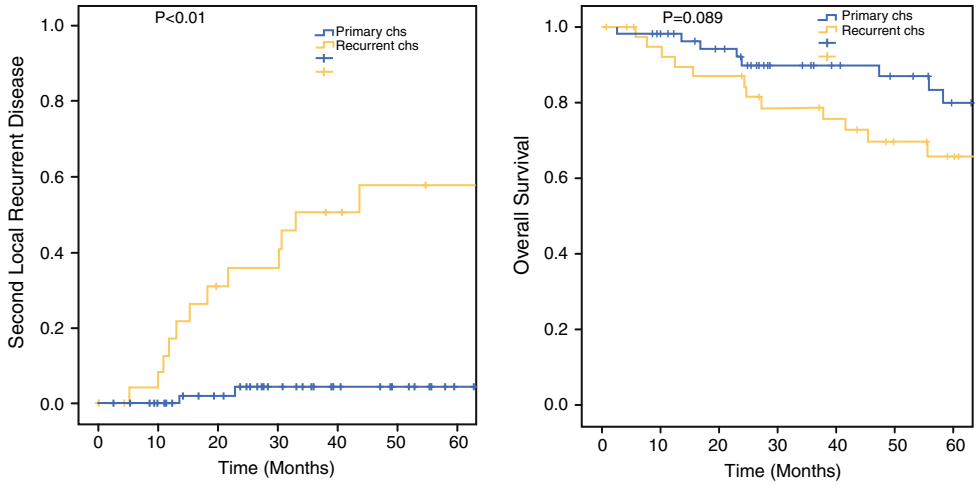

FIG. 1 Kaplan–Meier curves for local recurrence rate and overall survival for primary and recurrent chondrosarcoma

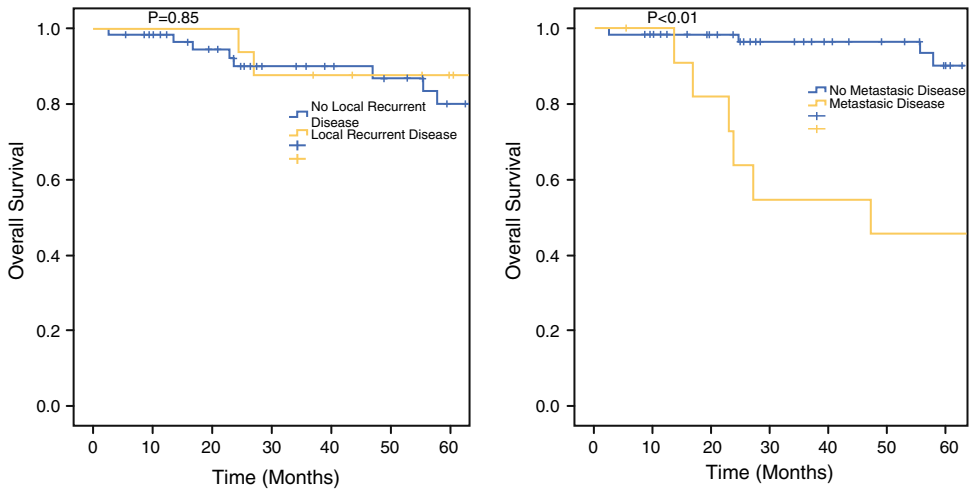

FIG. 2 Kaplan–Meier overall survival curves after local recurrence and metastasis formation

Tumors and treated in one of three major tertiary referral hospitals in The Netherlands. To our knowledge, there are no other studies reporting the outcome of patients with rib chondrosarcoma specifically. The findings in this study demonstrate that resection of primary chondrosarcoma and even recurrent chondrosarcoma of the rib is an effective treatment strategy with relatively favorable prognosis. The outcome of the cohort of primary chondrosarcoma of the rib is relatively favorable when compared with other chondrosarcoma studies, with a 5-year mortality of 10 %, local recurrence rate of 17 %, and metastasis rate of 12 %. In two studies describing chondrosarcoma of the thoracic wall in general, percentages of mortality, local recurrence, and metastasis formation are slightly higher.[12,15,17] This difference might be due to the fact that in these studies the tumor localization was more heterogeneous and included sternal, scapular, clavicular, and vertebral chondrosarcoma. Other studies relating to chondrosarcoma in all anatomical locations show even higher mortality (20–40 %), local recurrence (34–50 %), and metastasis rate (20–29 %);[12,15,17,19,20] however, the prognosis of chondrosarcoma varies widely between different anatomical locations.[9,12,19,20] Worse overall survival in these studies can also be explained by a number of untreatable local diseases included in these studies.[15,19] In addition, resection of low-grade chondrosarcoma at other anatomical sites often includes excochleation of the medulla, leaving the cortex intact.[20–22] However, in the rib, surgery almost always consists of partial or complete resection of the rib, including resection of the cortex. Complete or partial rib resection including the cortex, instead of leaving the cortex in situ, might result in less microscopic residual disease throughout the rib, leading to lower local recurrences when compared with excochleation of chondrosarcomas elsewhere. Of note, in this

TABLE 3 Univariable analysis for factors influencing overall survival, local recurrent disease and metastasis formation

	No of patients	Univariate analysis		
		Overall survival HR (95 % CI)	Local recurrent disease HR (95 % CI)	Metastaic disease HR (95 % CI)
Age (>50)	76	2.39 (0.77–7.46)	3.54 (1.00–12.50)	1.70 (0.51–5.68)
Sex				
Male	39	Ref	Ref	Ref
Female	37	2.21 (0.67–7.33)	0.48 (0.50–1.58)	2.85 (0.75–10.77)
Histological grade				
Grade I	29	Ref	Ref	Ref
Grade II	42	1.78 (0.56–5.70)	1.04 (0.35–2.96)	1.37 (0.25–5.37)
Grade III	5	3.95 (0.42–37.07)	**5.92 (1.11–31.65)**	**6.98 (1.15–42.60)**
Size				
<5 cm	35	Ref	Ref	Ref
>5 cm	36	**3.28 (1.03–10.44)**	0.89 (0.33–2.42)	2.19 (0.66–7.30)
Type of rib resection				
Partial rib resection	49	Ref	Ref	Ref
Complete rib resection	17	0.48 (0.10–2.30)	0.20 (0.03–1.52)	0.73 (0.15–3.55)
Surgical margins				
R0	62	Ref	Ref	Ref
R1/R2	13	**2.92 (1.03–8.25)**	2.81 (0.92–8.64)	2.29 (0.68–7.59)

All values are presented as HRs with 95 % confidence intervals in parentheses

Bold values indicate statistically significant

study, patients were treated in tertiary referral centers only, possibly leading to a bias in patient selection and thus in outcome. In the selected population, the number of more difficult cases might be over represented, while the number of inadequate resection margins might be underestimated when compared with the national population.

This study is limited by the relatively low number of patients, which did not allow for a multivariable survival analysis for all available factors. Obviously, there might be confounding factors that were not accounted for in our statistical analysis. Furthermore, there is a high risk of type II errors due to the low number of events. Another weakness of the study is the possible selection bias due to its retrospective character. In the archive of The Netherlands Committee on Bone Tumors, many patients were treated in a number of smaller hospitals with no available hospital records and were therefore excluded. Nevertheless, 76 patients were analyzed for primary rib chondrosarcoma and 26 patients for recurrent rib chondrosarcoma.

The results of this study underline the value of adequate surgical resection as an effective strategy for both primary and recurrent disease. As expected, the outcome after treatment of recurrent disease is worse when compared with primary disease. This might be due to the technically more demanding resection for recurrent disease, but it might also reflect less favorable biology of recurrent chondrosarcoma. This is in accordance with previous studies on chondrosarcoma of the thorax reporting worse outcome of local recurrent disease.[1,5,8] Of note, metastasis rates in patients with recurrent disease are slightly lower in this study when compared with earlier studies (27 vs. 42–49 %).[12,13,15,23]

Interestingly, local recurrence did not lead to worse overall survival. In contrast, metastatic disease is strongly correlated with worse overall survival. This is in line with the outcome of extremity soft tissue sarcoma, where local recurrences—when treated with salvage surgery—only slightly decreases overall survival, whereas metastasis formation is strongly correlated with decreased overall survival.[24,25] Since mortality is not altered after resection of recurrent disease, we do recommend treating recurrent chondrosarcoma with surgical resection. It is probable that recurrent and also re-recurrent disease is due to residual disease after primary and secondary surgery, and is thus caused by positive resection margins. Therefore, taking margins as wide as possible is recommended for both primary and recurrent rib chondrosarcoma. This would include performing a larger partial rib resection or even a complete rib resection.

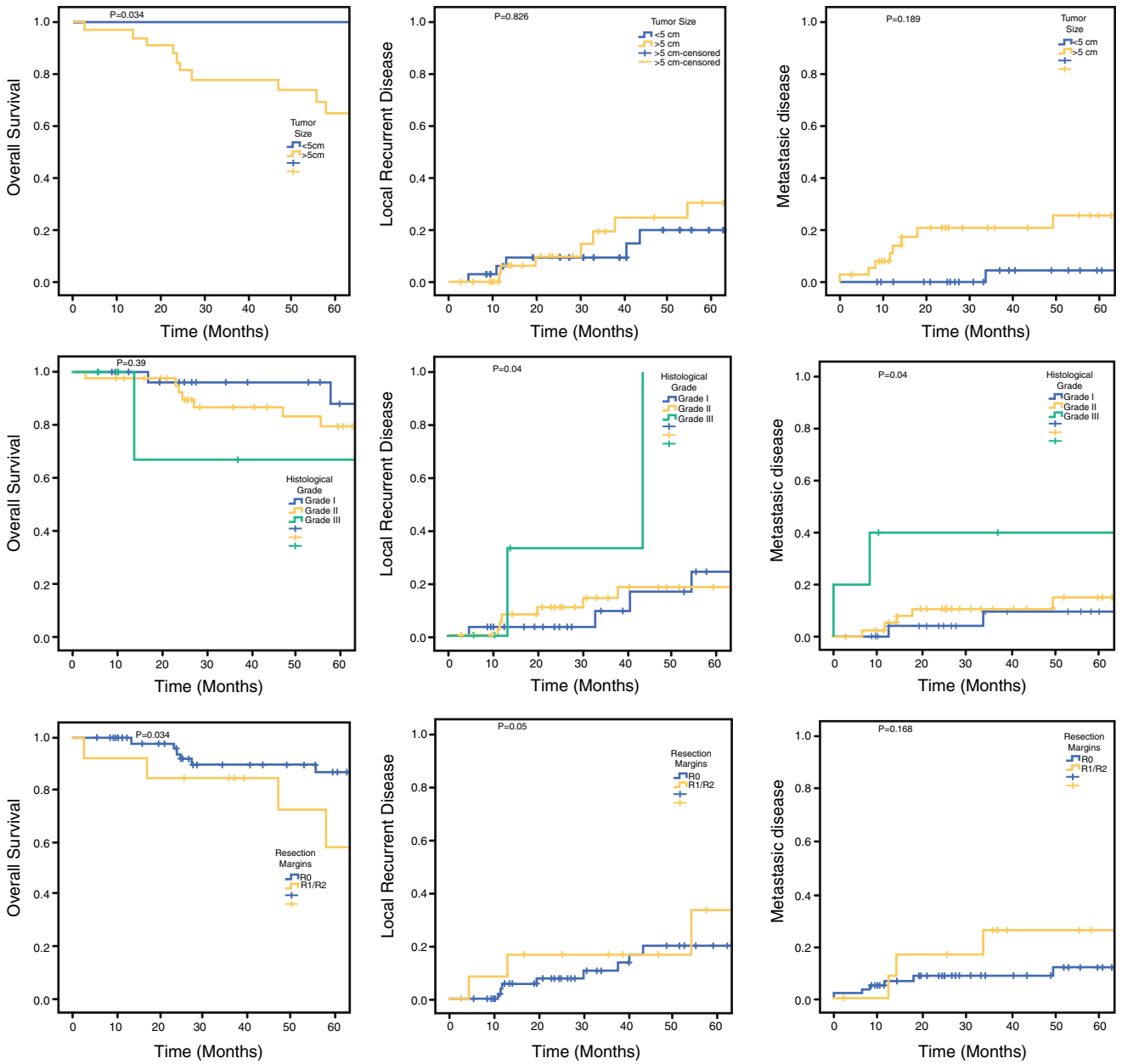

FIG. 3 Kaplan–Meier curves for overall survival, local recurrent disease, and metastasis of histological grade, tumor size, and resection margins

In the clinical setting, knowledge of prognostic factors is useful for optimal treatment planning and patient communication. In this study, the only significant clinical prognostic factors for worse overall survival were a tumor size >5 cm and positive resection margins. This underlines the importance of an adequate surgical margin and therefore more substantial resection of the rib. It might be more challenging to obtain adequate surgical margins in larger tumors, which partly explains the worse overall survival for tumors >5 cm. It is known from several other sarcoma studies and other types of cancer that larger tumors have a higher risk of metastasizing.[1,11,26] In our study, the only factor significantly correlated with a higher recurrence rate and higher metastasis rate was histological grade III, but it was not accompanied by significantly worse survival. This is probably due to the very small number of patients with grade III (five patients). In other studies, higher grade was significantly correlated with higher local recurrence rate, metastasis formation, and worse survival.[18–20]

It has been reported that chondrosarcomas are relatively refractory to radiotherapy;[20] however, in this study the number of patients receiving radiotherapy is too low for proper analysis of the role of radiotherapy.

CONCLUSIONS

This is a unique report describing the outcome and prognostic factors of primary and recurrent chondrosarcoma of the rib as a specific entity. Although recurrent disease is associated with a slightly worse prognosis, surgical resection is still an effective way of treatment. Prognostic factors for worse outcome after treatment for primary chondrosarcoma are tumor size >5 cm, positive resection margins, and high histological grade of the tumor. Obtaining adequate surgical margins when possible is therefore of vital importance.

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