Clinical Research

Does Resection of the Primary Tumor Improve Survival in Patients With Metastatic Chondrosarcoma?

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Abstract

Background Although surgical resection or amputation has been the mainstay of localized chondrosarcoma management for many decades, its efficacy in patients with metastatic chondrosarcoma remains unknown, and likewise we do not know whether there are any tumor- or patient-related factors associated with better survival after surgery for metastatic chondrosarcoma.

Questions/purposes (1) Is resection of the primary tumor associated with improved survival in patients with metastatic chondrosarcoma? (2) Which subgroups of patients with chondrosarcoma benefit more from resection in terms of survival?

Methods We identified 200 of 222 patients with metastatic chondrosarcoma in the Surveillance, Epidemiology, and End Results (SEER) database between 1988 and 2014 based on the exclusion criteria. Among those patients, 107 (53.5%) underwent primary tumor resection or amputation. Patient information, including demographics (patient age, gender, race, year of diagnosis), tumor characteristics (primary site, histologic subtype, tumor grade, tumor size), and treatment (record of operation and radiation), was collected and included in the study. Kaplan-Meier analyses, log-rank tests, competing risks framework, multivariable Cox regression modeling, and interaction tests were conducted to assess the association of primary tumor resection and survival in the overall cohort and subgroups.

Results Resection of the primary tumor was associated with improved overall survival (hazard ratio [HR], 0.481; 95% confidence interval [CI], 0.340–0.680; p < 0.001) and cancer-specific survival (HR, 0.493; 95% CI, 0.343–0.709; p < 0.001) after controlling for confounding variables. After controlling further for age, histologic subtype, and grade, primary tumor resection was associated with a survival advantage in patients with conventional subtype and Grade II chondrosarcoma (conventional subtype: HR, 0.403; 95% CI, 0.260–0.623 for overall survival and HR, 0.396; 95% CI, 0.250–0.627 for cancer-specific survival). However, primary tumor resection was not associated with increased survival in patients with metastatic chondrosarcoma who had the dedifferentiated subtype and Grade III malignancy.

Conclusions The present study demonstrates a possible favorable association between primary tumor resection and survival in some patients with metastatic chondrosarcoma at initial diagnosis. Specifically, patients with conventional

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subtypes and Grade II malignancies who underwent primary tumor resection had better survival compared with those patients who did not have primary tumor resection. Thus, there might be a benefit from primary tumor resection in these patients, but given the limitations of this database, further prospective studies or randomized trials are needed to confirm our findings. In the meantime, this information might be helpful to consider when discussing surgical options with patients who have conventional, Grade 2 metastatic chondrosarcoma at diagnosis.
Level of Evidence Level III, therapeutic study.

Introduction

Chondrosarcoma is a malignant bone tumor characterized by the production of chondroid matrix [8]. After osteosarcoma, it is the second most common primary bone tumor and accounts for 30% of primary bone sarcomas [3]. Approximately 8% of patients with chondrosarcoma have metastasis at initial presentation [10]. Although relatively uncommon, distant metastasis has been identified as one of the most significant prognostic factors that dramatically reduces the survival time of patients with chondrosarcoma [1, 2, 4, 10].

Because radiation therapy and chemotherapy have limited effects, surgical resection or amputation is the mainstay of localized chondrosarcoma management [9, 11]. However, there is no standard treatment for patients with metastatic chondrosarcoma. The favorable effect of resection of the primary tumor has been reported in patients with metastatic renal cancer, colorectal cancer, and breast cancer [7, 18]. As a result of the rarity of metastatic chondrosarcoma, data regarding the potential association of primary tumor resection with longer survival are nonexistent. Therefore, in this study, we collected a nationwide, population-based cohort from the Surveillance, Epidemiology, and End Results (SEER) database to assess the possible association of primary tumor resection in patients with metastatic chondrosarcoma and to explore whether and for whom primary tumor resection should be considered.

We asked the following questions: (1) Is resection of the primary tumor associated with improved survival in patients with metastatic chondrosarcoma? (2) Which subgroups of patients with chondrosarcoma benefit more from resection in terms of survival?

Patients and Methods

Database and Patient Cohort

The SEER database is the largest publicly available cancer data set, consisting of 18 cancer registries and covering approximately 28% of the total US population. The SEER database has been widely used in clinical cancer research of different cancer types, including chondrosarcoma [6, 10, 14, 17, 18]. We used SEER*Stat software (Version 8.3.4; National Cancer Institute, Bethesda, MD, USA) to extract information from the database.

To be included, 222 patients in total had to have high-grade chondrosarcoma with distant metastasis present at initial diagnosis, chondrosarcoma as the first primary malignancy, be diagnosed between 1988 and 2014 and with no missing data on survival time, have their diagnosis confirmed by histology, and have their primary site limited to a bone only. We excluded patients for the following reasons: if the primary site was limited to the skull or facial bones (n = 6) resulting from the rarity in this subgroup, if they had mesenchymal chondrosarcoma (n = 12) resulting from the rarity in this subgroup, or if it was unknown whether a primary tumor operation or radiation was performed. Finally, 200 of 222 patients with metastatic chondrosarcoma were included in the study (see Figure, Supplemental Digital Content).

Patient Characteristics

A total of 200 patients with metastatic chondrosarcoma at the time of initial diagnosis were included in our study (Fig. 1). Of the 200 patients, 107 (53%) underwent primary tumor resection or amputation (surgery group), whereas 93 (47%) did not (nonsurgery group). The median age of all patients was 60 years (range, 14-91 years). In all, 92 patients (46%) had a primary lesion in their extremities, and 73 patients (36%) had a primary lesion in the pelvis or spine. The overall cohort was
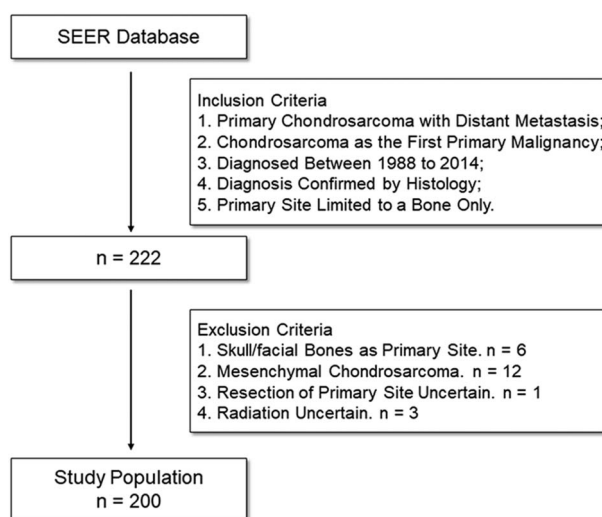

Fig. 1 The flowchart shows the process of collecting patients. Overall, 200 patients with metastatic chondrosarcoma were included.

divided according to whether patients had undergone primary tumor resection. The median survival was 13 months (range, 1-206 months) and 7 months (range, 1-200 months) in the surgery and nonsurgery groups, respectively. We found that patients who had surgery were more likely to be white, to have a tumor located in the appendicular skeleton, to have a dedifferentiated subtype, and were less likely to undergo radiotherapy (Table 1). To account for these baseline differences between the surgery and nonsurgery groups, we performed propensity score matching. With propensity score matching, imbalance regarding race, primary site, histologic subtype, and grade was mitigated (Table 2).

Covariates and Outcomes

We collected data on demographics (patient age, gender, race, year of diagnosis), tumor characteristics (primary site, histologic subtype, tumor grade, tumor size), and treatment (record of primary tumor resection and radiation). Because the anatomic site information in the SEER database is relatively nonspecific—for example, the femur, tibia, and fibula were recorded as long bones of the lower extremities without distinction—primary sites were categorized into four groups: lower extremity, upper extremity, pelvis/spine, and ribs/sternum. Primary tumor resection

Table 1. Baseline characteristics of patients with metastatic chondrosarcoma at diagnosis (unmatched)

Characteristic	Total n = 200	Primary tumor resection n = 107	No primary tumor resection n = 93	p value*
Age (years)				0.189
Median (range)	60 (14-91)	59 (14-88)	62 (15-91)	
Race, number (%)				0.030
White	169 (84)	97 (90)	72 (77)	
Black	18 (9)	5 (5)	13 (14)	
Other[†]	13 (7)	5 (5)	8 (9)	
Gender, number (%)				0.712
Male	122 (61)	64 (60)	58 (62)	
Female	78 (39)	43 (40)	35 (38)	
Year of diagnosis				0.276
1988 to 1999	34 (17)	20 (19)	14 (15)	
2000 to 2009	102 (51)	58 (54)	44 (47)	
2010 to 2014	64 (32)	29 (27)	35 (38)	
Primary site, number (%)				0.002
Lower extremity	67 (34)	46 (43)	21 (23)	
Upper extremity	25 (13)	16 (15)	9 (10)	
Pelvis/spine	73 (36)	28 (26)	45 (48)	
Ribs/sternum	35 (17)	17 (16)	18 (19)	
Histologic subtype, number (%)				0.004
Conventional	143 (72)	66 (62)	77 (83)	
Dedifferentiated	39 (19)	28 (26)	11 (12)	
Myxoid	18 (9)	13 (12)	5 (5)	
Grade, number (%)				< 0.001
II	73 (36)	43 (40)	30 (32)	
III	86 (43)	58 (54)	28 (30)	
Unknown	41 (21)	6 (6)	35 (38)	
Size (cm)[‡]				0.368
Median (range)	11.2 (1.5-50.0)	11.0 (1.5-50.0)	11.8 (1.7-30.0)	
Radiation, number (%)				0.012
No	140 (70)	83 (78)	57 (61)	
Yes	60 (30)	24 (22)	36 (39)	

*Estimated by the Student's t-test or Pearson chi-square test, as indicated.
†including Native American/Alaska Native, Asian/Pacific Islander.
‡61 patients were excluded because of missing data.

Table 2. Baseline characteristics of patients with metastatic chondrosarcoma (after propensity score matching)

Characteristic	Total n = 175	Primary tumor resection n = 107	No primary tumor resection n = 68	p value*
Age (years)				0.293
Median (range)	60 (14-91)	59 (14-88)	60.5 (15-91)	
Race, number (%)				0.063
White	150 (86)	97 (90)	53 (78)	
Black	13 (7)	5 (5)	8 (12)	
Other†	12 (7)	5 (5)	7 (10)	
Gender				0.797
Male	106 (61)	64 (60)	42 (62)	
Female	69 (39)	43 (40)	26 (38)	
Year of diagnosis				0.150
1988 to 1999	31 (18)	20 (19)	11 (16)	
2000 to 2009	87 (50)	58 (54)	29 (43)	
2010 to 2014	57 (32)	29 (27)	28 (41)	
Primary site				0.294
Lower extremity	67 (38)	46 (43)	21 (31)	
Upper extremity	25 (14)	16 (15)	9 (13)	
Pelvis/spine	54 (31)	28 (26)	26 (38)	
Ribs/sternum	29 (17)	17 (16)	12 (18)	
Histologic subtype				0.076
Conventional	119 (68)	66 (62)	53 (78)	
Dedifferentiated	39 (22)	28 (26)	11 (16)	
Myxoid	17 (10)	13 (12)	4 (6)	
Grade				0.069
II	73 (42)	43 (40)	30 (44)	
III	86 (49)	58 (54)	28 (41)	
Unknown	16 (9)	6 (6)	10 (15)	
Size (cm)‡				0.722
Median (range)	12.2 (1.5-50.0)	12.1 (1.5-50.0)	12.3 (1.7-30.0)	
Radiation				0.040
No	126 (72)	83 (78)	43 (63)	
Yes	49 (28)	24 (22)	25 (37)	

*Estimated by Student's t-test or Pearson chi-square test, as indicated.
†including Native American/Alaska Native, Asian/Pacific Islander.
‡a multiple imputation procedure was used for 53 patients with missing data.

referred to resection of the primary lesion. Because metastasectomy was performed in only two patients, this variable was not included in our study. Eligible patients were grouped according to whether they had undergone primary tumor resection.

The major endpoints of interest were overall survival (OS) and cancer-specific survival (CSS). OS was defined as the time from diagnosis until death from all possible causes or last followup. CSS was defined as the time from diagnosis until death attributed to chondrosarcoma or last followup.

Statistical Analysis

We compared between-group differences with the Student's t-test for continuous variables and Pearson's chi-square test for categorical variables. We used a multiple imputation method to analyze the missing data for tumor size. Survival curves were drawn and compared using the Kaplan-Meier method and log-rank analysis. Cumulative incidence curves were drawn and compared under a competing risk framework. The initial Cox regression analysis involved a simple univariate model for each variable,

including primary tumor resection, age, race, gender, year of diagnosis, primary site, histologic subtype, grade, size, and radiation. We created a multivariable Cox regression model by selecting only those variables with a substantial measure of association (< 0.10). The first multivariable model included primary tumor resection, age, histologic subtype, and grade. Then, we created a second multivariable model that included all collected variables to verify the stability of our findings.

We conducted the Student's t-test, Pearson's chi-square test, multiple imputation, univariate and multivariable Cox regression analyses, and interaction test using SPSS 22.0 (IBM Corp, Armonk, NY, USA). The Kaplan-Meier survival curves and log-rank analysis were performed using GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA). Propensity score matching, cumulative incidence curves, and Gray tests were conducted in R version 3.3.1 (http://www.r-project.org/). Forest plots summarizing the results of subgroup multivariable analyses were drawn using Stata 14.0 (StataCorp, College Station, TX, USA). All p values were two-sided and p < 0.05 was considered statistically significant except for the interaction test (a threshold at 0.10 was set).

Results

Association Between Resection of the Primary Tumor and Survival in the Overall Cohort

Patients who underwent surgery had improved OS at 2 years compared with those who did not (36.5% [95% confidence interval {CI}, 27.3%-45.7%] versus 9.9% [95% CI, 2.1%-17.7%]; p < 0.001) (Fig. 2A). Likewise, patients who underwent surgery had improved cancer-specific survival at 2 years compared with those who did not (38.0% [95% CI, 28.6%-47.4%] versus 11.3% [95% CI, 2.5%-20.1%]; p = 0.005) (Fig. 2B).

After controlling for resection of the primary tumor, age, histologic subtype, and grade revealed that primary tumor resection was associated with improved OS (hazard ratio [HR], 0.481; 95% CI, 0.340–0.680; p < 0.001) (Table 3). Likewise, primary tumor resection was associated with improved CSS (HR, 0.493; 95% CI, 0.343–0.709; p < 0.001) (Table 4).

Resection of the Primary Tumor on Survival in Different Subgroups

Resection of the primary tumor was associated with improved OS at 2 years in patients with the conventional subtype (40.8% [95% CI, 28.7%-52.9%] versus 11.2% [95% CI, 2.2%-20.2%]; p < 0.001), Grade II malignancy (60.0% [95% CI, 45.2%-74.8%] versus 17.5% [95% CI, 3.6%-31.4%]; p < 0.001), and an age younger than 65 years old (39.9% [95% CI, 28.2%-51.6%] versus 11.3% [95% CI, 0.1%-22.5%]; p < 0.001) (Fig. 3). Likewise, primary tumor resection was associated with improved CSS at 2 years in those subgroups (conventional subtype: 42.8% [95% CI, 30.5%-55.1%] versus 13.1% [95% CI, 2.7%-23.5%], p = 0.004; Grade II malignancy: 63.7% [95% CI, 49.7%-77.7%] versus 21.8% [95% CI, 5.2%-38.4%], p = 0.014; younger than 65 years old: 40.8% [95% CI, 28.7%-52.9%] versus 11.7% [95% CI, 0.2%-23.2%], p < 0.001) (Fig. 4). However, in patients with dedifferentiated subtype or Grade III malignancy, resection of the primary tumor did not improve OS at 6 months (dedifferentiated subtype: 42.9% [95% CI, 33.5%-52.3%] versus 45.5% [95% CI, 30.5%-60.5%], p = 0.703; Grade III malignancy: 51.1% [95% CI, 38.2%-64.0%] versus 57.1% [95% CI, 47.7%-66.5%], p = 0.217). It is

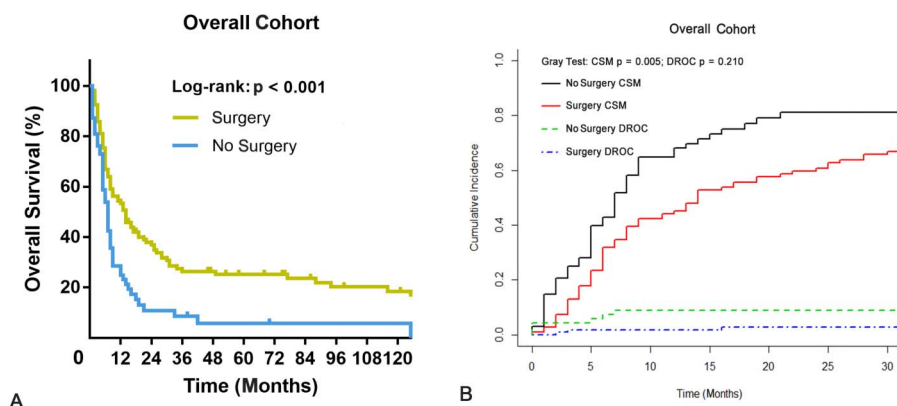**Fig. 2 A-B** The graphs show Kaplan-Meier and cumulative incidence curves of (**A**) overall and (**B**) cancer-specific survival according to whether patients underwent primary tumor surgery in the overall cohort. CSM = cancer-specific mortality; DROC = death resulting from other causes.

Table 3. Factors associated with overall survival of patients with metastatic chondrosarcoma

Characteristic	Model 1 (unadjusted)*		Model 2† n = 175		Model 3‡ n = 175	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Resection of the primary tumor						
No	Reference		Reference		Reference	
Yes	0.501 (0.357-0.703)	< 0.001	0.481 (0.340-0.680)	< 0.001	0.458 (0.316-0.664)	< 0.001
Age						
For each 1-year increase	1.019 (1.008-1.029)	< 0.001	1.012 (1.001-1.023)	0.030	1.013 (1.002-1.025)	0.024
Race						
White	Reference				Reference	
Black	0.998 (0.551-1.806)	0.994			1.150 (0.574-2.306)	0.693
Other	1.122 (0.600-2.097)	0.718			1.038(0.536-2.011)	0.912
Gender						
Male	Reference				Reference	
Female	1.153 (0.828-1.607)	0.399			1.012 (0.709-1.445)	0.948
Year of diagnosis						
1988 to 1999	Reference				Reference	
2000 to 2009	1.091 (0.703-1.693)	0.696			0.889 (0.547-1.444)	0.635
2010 to 2014	1.181 (0.725-1.925)	0.504			0.764 (0.434-1.346)	0.351
Primary site						
Lower extremity	Reference				Reference	
Upper extremity	0.995 (0.605-1.637)	0.984			1.015 (0.600-1.717)	0.956
Pelvis/spine	0.776 (0.528-1.142)	0.198			0.973 (0.628-1.506)	0.901
Ribs/sternum	0.517 (0.308-0.868)	0.013			0.675 (0.383-1.190)	0.174
Histologic subtype						
Conventional	Reference		Reference		Reference	
Dedifferentiated	1.857 (1.256-2.744)	0.002	1.418 (0.931-2.160)	0.104	1.526 (0.946-2.463)	0.083
Myxoid	0.652 (0.370-1.148)	0.139	0.711 (0.401-1.262)	0.244	0.671 (0.356-1.264)	0.217
Grade						
II	Reference		Reference		Reference	
III	1.829 (1.280-2.615)	0.001	1.751 (1.191-2.574)	0.004	1.614 (1.083-2.406)	0.019
Unknown	3.542 (2.003-6.265)	< 0.001	2.857 (1.553-5.255)	0.001	2.398 (1.252-4.594)	0.008
Size						
For each 1-cm increase	1.013 (0.988-1.038)	0.308			1.004 (0.976-1.033)	0.773
Radiation						
No	Reference				Reference	
Yes	1.277 (0.893-1.826)	0.181			1.065 (0.727-1.560)	0.746

*Univariate Cox regression analysis.
†multivariate Cox regression analysis controlling for primary tumor surgery, age, histologic subtype, and tumor grade.
‡multivariate Cox regression analysis controlling for primary tumor surgery, age, race, gender, year of diagnosis, primary site, histologic subtype, tumor grade, tumor size, and radiotherapy; HR = hazard ratio; CI = confidence interval.

noteworthy that patients 65 years old or older had prolonged OS but not CSS at 2 years after resection of the primary tumor (OS: 30.0% [95% CI, 22.4%-37.6%] versus 8.0% [95% CI, 2.6%-13.4%], p = 0.040; CSS: 31.8% [95% CI, 23.9%-39.7%] versus 10.9% [95% CI, 3.8%-18.0%], p = 0.123).

After controlling for age, histologic subtype, and grade, resection of the primary tumor was associated with increased survival in patients with the conventional subtype (OS: HR, 0.403, 95% CI, 0.260–0.623, p < 0.001; CSS: HR, 0.396, 95% CI, 0.250–0.627, p < 0.001) and Grade II chondrosarcoma (OS: HR, 0.382, 95% CI, 0.205–0.713, p = 0.002; CSS: HR, 0.353, 95% CI, 0.180–0.692, p = 0.002), but not in patients with the dedifferentiated subtype (OS: HR, 0.738, 95% CI, 0.326–1.670, p = 0.466; CSS: HR, 0.832, 95% CI, 0.355–1.951, p = 0.673) or Grade III chondrosarcoma (OS: HR, 0.673, 95% CI, 0.404–1.123,

Table 4. Factors associated with cancer-specific survival of patients with metastatic chondrosarcoma

Characteristic	Model 1 (unadjusted)*		Model 2† n = 175		Model 3‡ n = 175	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Resection of the primary tumor						
No	Reference		Reference		Reference	
Yes	0.523 (0.366-0.747)	< 0.001	0.493 (0.343-0.709)	< 0.001	0.477 (0.323-0.706)	< 0.001
Age						
For each 1-year increase	1.015 (1.004-1.025)	0.008	1.007 (0.996-1.019)	0.204	1.008 (0.996-1.020)	0.183
Race						
White	Reference				Reference	
Black	1.046 (0.577-1.897)	0.882			1.158 (0.570-2.351)	0.685
Other	0.699 (0.307-1.590)	0.393			0.637 (0.271-1.493)	0.299
Gender						
Male	Reference				Reference	
Female	1.130 (0.798-1.600)	0.491			1.032 (0.711-1.498)	0.868
Year of diagnosis						
1988 to 1999	Reference				Reference	
2000 to 2009	1.153 (0.723-1.840)	0.550			0.868 (0.521-1.446)	0.587
2010 to 2014	1.231 (0.735-2.060)	0.430			0.752 (0.415-1.363)	0.348
Primary site						
Lower extremity	Reference				Reference	
Upper extremity	0.997 (0.590-1.683)	0.990			1.041 (0.597-1.813)	0.888
Pelvis/spine	0.817 (0.545-1.224)	0.327			1.061 (0.669-1.685)	0.800
Ribs/sternum	0.552 (0.323-0.944)	0.030			0.761 (0.421-1.377)	0.367
Histologic subtype						
Conventional	Reference		Reference		Reference	
Dedifferentiated	1.932 (1.290-2.892)	0.001	1.427 (0.924-2.203)	0.109	1.556 (0.949-2.552)	0.080
Myxoid	0.681 (0.378-1.224)	0.199	0.714 (0.394-1.293)	0.266	0.666 (0.344-1.290)	0.228
Grade						
II	Reference		Reference		Reference	
III	2.039 (1.397-2.976)	< 0.001	1.928 (1.284-2.897)	0.002	1.843 (1.208-2.810)	0.005
Unknown	3.879 (2.141-7.027)	< 0.001	3.308 (1.749-6.257)	< 0.001	2.820 (1.424-5.584)	0.003
Size						
For each 1-cm increase	1.018 (0.993-1.043)	0.159			1.007 (0.979-1.036)	0.626
Radiation						
No	Reference				Reference	
Yes	1.339 (0.926-1.937)	0.121			1.131 (0.763-1.678)	0.540

*Univariate Cox regression analysis.
†multivariate Cox regression analysis controlling for primary tumor surgery, age, histologic subtype, and tumor grade.
‡multivariate Cox regression analysis controlling for primary tumor surgery, age, race, gender, year of diagnosis, primary site, histologic subtype, tumor grade, tumor size, and radiotherapy; HR = hazard ratio; CI = confidence interval.

p = 0.130; CSS: HR, 0.691, 95% CI, 0.411–1.161, p = 0.162) (Fig. 5). For patients < 65 years old and ≥ 65 years old, respectively, we observed an association between primary tumor resection and improved survival (< 65 years: OS–HR, 0.469, 95% CI, 0.298–0.738, p = 0.001; CSS–HR, 0.476, 95% CI, 0.299–0.757, p = 0.002; ≥ 65 years: OS–HR, 0.462, 95% CI, 0.258–0.829, p = 0.010;

CSS–HR, 0.498, 95% CI, 0.265–0.934, p = 0.030). Interaction tests were further carried out to investigate the potential differential effect of resection in different subgroups. With the numbers available, we could not demonstrate a differential surgical effect between conventional and dedifferentiated subtypes (p = 0.078 for OS, p = 0.048 for CSS).

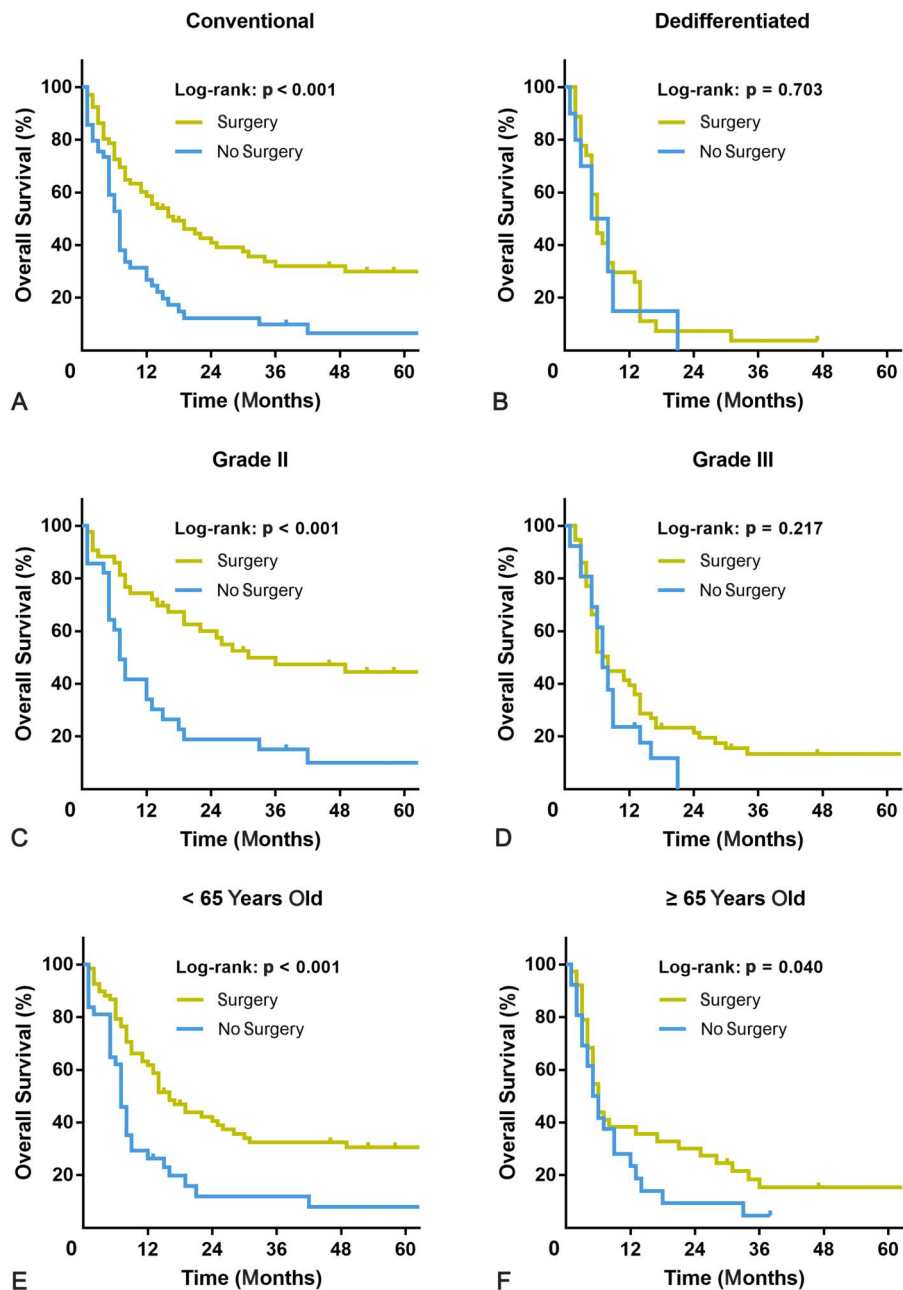Wolters Kluwer

Fig. 3 A-F The graphs show Kaplan-Meier curves of overall survival according to whether patients underwent primary tumor surgery in (**A**) the conventional subtype, (**B**) dedifferentiated subtype, (**C**) Grade II malignancy, (**D**) Grade III malignancy, (**E**) patients < 65 years old, or (**F**) patients ≥ 65 years old.

Discussion

For many decades, because radiotherapy or chemotherapy is not considered effective as a result of the extracellular matrix and poor vascularity, the primary treatment option with curative intent has been surgical resection [9, 10, 15, 20]. However, for patients with metastatic chondrosarcoma, no

standard treatment has been established, and whether surgery still confers a survival advantage is worth further investigation. Our investigation demonstrates that there is an association between primary tumor resection in patients with metastatic chondrosarcoma and longer survival based on a large patient cohort. More importantly, the present study also finds that patients with metastatic chondrosarcoma with
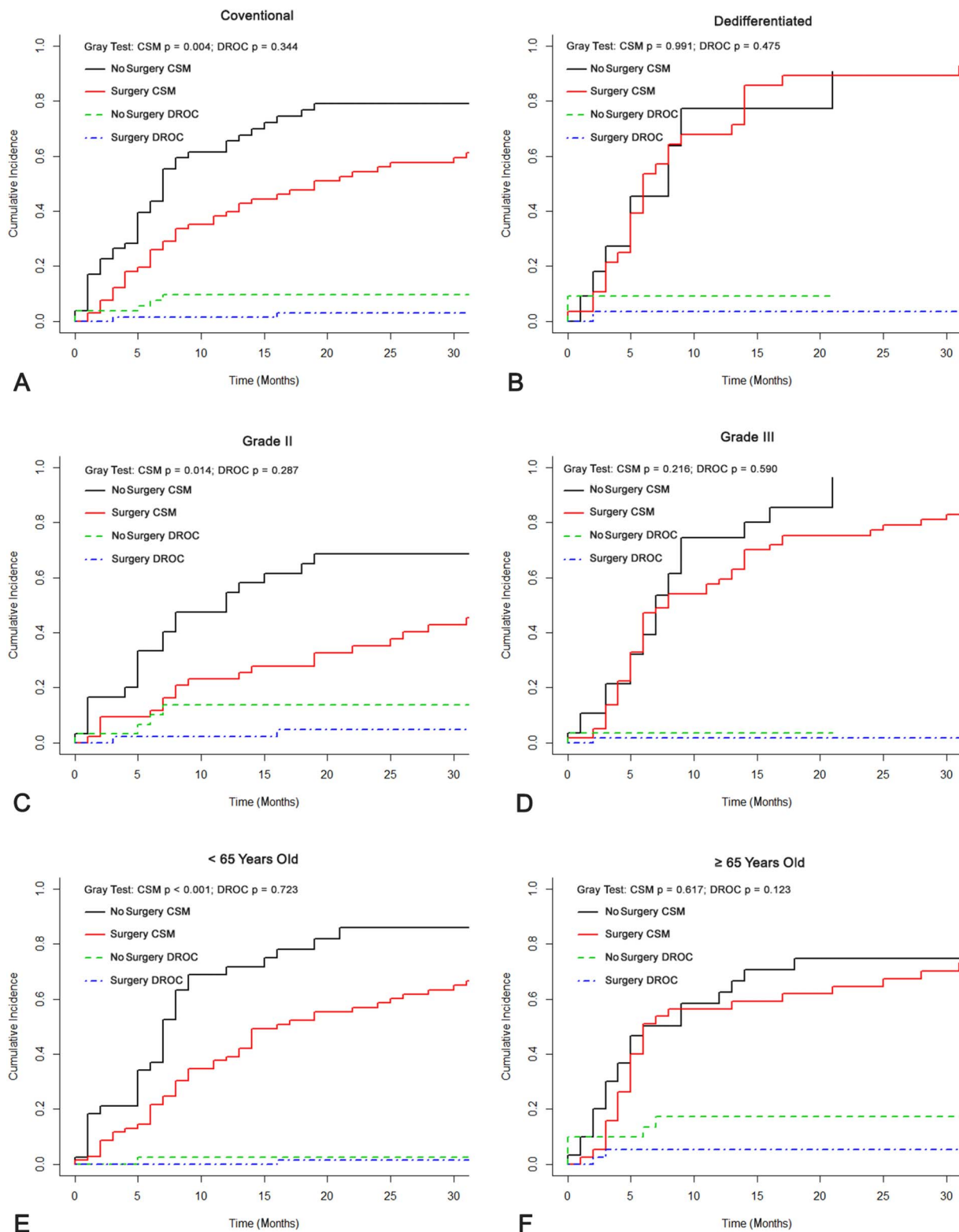
Fig. 4 A-F The graphs show cumulative incidence curves of cancer-specific survival according to whether patients underwent primary tumor surgery in (**A**) the conventional subtype, (**B**) dedifferentiated subtype, (**C**) Grade II malignancy, (**D**) Grade III malignancy, (**E**) patients < 65 years old, or (**F**) patients ≥ 65 years old. CSM = cancer-specific mortality; DROC = death resulting from other causes.
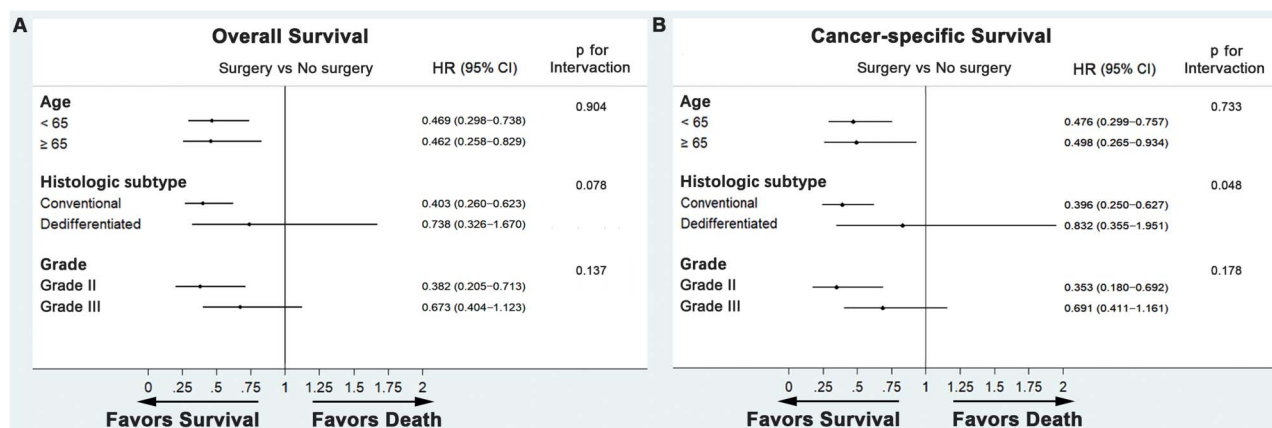
Fig. 5 A-B Forest plots summarize the HRs and 95% CIs of (**A**) overall and (**B**) cancer-specific survival according to whether patients underwent primary tumor surgery in subgroup analyses.

conventional subtypes and Grade II malignancies who underwent primary tumor resection had better survival compared with those patients who did not have primary tumor resection. This information might be helpful to consider when discussing surgical options with patients who have conventional, Grade 2 metastatic chondrosarcoma at diagnosis.

We would like to acknowledge the limitations of the present study. First, at baseline, the surgical groups were dissimilar in important ways, including race (surgery was more common in white patients than in nonwhite patients), tumor location (resections were more common in appendicular lesions than axial ones), histologic subtype (resections were more common in dedifferentiated and myxoid subtypes), tumor grade (resections were more common in Grade III cases), and use of radiation (resections were common in patients who did not undergo radiotherapy). In addition, the nature of the SEER registry does not provide information about how the decision on whether to operate was made. To address these issues, we performed propensity score matching, multivariable analyses, and further subgroup analyses with interaction tests to reduce potential confounding. Second, some unidentified prognostic factors such as the extent of metastatic disease, surgical margin, and location of the metastases (only available between 2010 and 2014) were not collected in the SEER registry and may have contributed to the observed results. Nevertheless, considering the use of multiple methods to investigate the association and the large beneficial effect of primary tumor resection on survival, it seems unlikely that such effect was solely the result of unadjusted confounding. Third, 53 patients (30%) had missing tumor size data. However, we accounted for these missing data with a multiple imputation procedure. Based on the assumption that the data were missing at random, multiple imputation could reconstruct the missing values using the information from observed data to decrease bias resulting from missing size. Finally, our study is based on registry data, which is retrospective by nature and lack validated tools to explain not merely whether those patients are surviving, but also whether they are functioning well.

We observed that patients with chondrosarcoma presenting with metastases at diagnosis who had resection of their primary tumor had longer survival than patients who did not have the primary tumor resected. We do not know the reason for this association in these patients, but accumulating studies have been reported to justify primary tumor resections for patients with metastatic cancer. The possible mechanism of the association we found could be that resection of the primary tumor may reduce the tumor burden [12, 13], remove the "seed source" to retard cancer progression [16], reverse systemic inflammation [19], or restore immunomodulation by removing a potential source of immunosuppression from the primary tumor site [5]. However, to our knowledge, these theories have not been corroborated in patients with metastatic chondrosarcoma.

We also found that patients with conventional chondrosarcoma benefited from resection of the primary tumor, but patients with dedifferentiated chondrosarcoma did not. Interaction tests suggest a differential surgical effect might exist between conventional and dedifferentiated subtypes. Because conventional chondrosarcoma constitutes approximately 85% of all chondrosarcomas, our findings are applicable to most patients who have metastatic chondrosarcoma. Primary tumor resection was associated with prolonged survival in patients with Grade II chondrosarcoma but not in patients with Grade III chondrosarcoma. The results could be partially explained by the limited efficacy of primary tumor resection on a higher degree of malignancy. It is also possible that this observation is the result of selection bias because we do not know how patients were chosen to receive resection nor do we know the metastatic extent in these patients. It is possible that patients with higher grade tumors had more extensive metastatic disease and larger tumors; these patients

might have been considered less likely to benefit from surgical resection of their primary tumor. Competing risks framework suggests that older patients (≥ 65 years old) did not have prolonged CSS after primary tumor resection. After controlling for confounding variables, including histologic subtype and tumor grade, primary tumor resection was found to be associated with a survival advantage in both younger patients (< 65 years old) and older patients (≥ 65 years old) regarding OS and CSS. Interaction tests showing no differential surgical effect between younger and older groups supports the finding in the subgroup analyses.

In summary, the present study demonstrates an association of primary tumor resection on survival in some patients with metastatic chondrosarcoma at initial diagnosis, especially those with Grade 2 chondrosarcoma. We also found that resection of the primary tumor was not associated with improved survival for high-grade chondrosarcoma. We hope that our study will stimulate prospective studies to confirm our observations because we could not determine metastatic burden or the decision-making considerations for tumor resection in these patients, but our findings might be considered when counseling patients with metastatic chondrosarcoma.

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