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Prognostic Factors and Treatment Options for Patients with High-Grade Chondrosarcoma

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Data Collection B
Statistical Analysis C
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Background: The goal of this study was to determine the prognostic factors exclusive for high-grade chondrosarcoma and whether adjuvant radiotherapy could achieve better overall survival (OS) or cancer-specific survival (CSS) for patients with high-grade chondrosarcoma.

Material/Methods: Surveillance, Epidemiology, and End Results (SEER) cancer registry database was utilized to extract the chondrosarcoma cases diagnosed between 1973 and 2014. Among these cases, the histological grades of poorly differentiated (grade 3) and undifferentiated (grade 4) were categorized as high-grade and included in this study. Chondrosarcoma OS and CSS were the primary outcomes in the present study. The log-rank test was performed for univariate analysis, and the Cox regression model was conducted for multivariate analysis.

Results: A total of 743 patients with high-grade chondrosarcoma were identified in this study (430 cases were poorly differentiated tumors, and 313 cases were undifferentiated tumors). Age at diagnosis, pathological grade, histo-type, SEER stage, tumor size and surgical resection were identified as independent predictors in both OS and CSS analysis of high-grade chondrosarcoma. When stratified by histological grade, surgical resection remained the effective treatment. Strikingly, radiotherapy was determined as an independent protective factor in both OS and CSS analysis of undifferentiated (grade 4) dedifferentiated chondrosarcoma, and adjuvant radiotherapy combined surgical resection could improve both the OS and CSS of patients with undifferentiated myxoid and dedifferentiated chondrosarcoma compared with other treatment regimens.

Conclusions: Our study first demonstrated that adjuvant radiotherapy combined surgery could improve the survival of patients with undifferentiated myxoid and dedifferentiated chondrosarcoma. These results encourage the application of adjuvant radiotherapy for patients with high-grade chondrosarcoma and maximize the patients' outcome.

MeSH Keywords: Chondrosarcoma • Prognosis • Radiotherapy • SEER Program • Survival Analysis

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Background

Chondrosarcomas represent a heterogeneous group of malignant neoplasms with diverse histopathological features and are characterized by producing cartilaginous matrix [1]. As the second most common primary malignancy of bone, the annual incidence of chondrosarcoma in the United States is about 1 in 200 000 [2]. The prognosis of chondrosarcoma is tightly associated with the histological grade [2–4]. The low-grade chondrosarcoma with abundant cartilage matrix and poor cellularity, is prone to be localized and shows a good prognosis after surgical resection [5]. However, high-grade tumors show little cartilage matrix and high cellularity, and easily metastasize, leading to dismal prognoses [1,6].

Previous studies have analyzed the prognostic factors and treatment regimens for chondrosarcoma. Bindiganavile et al. demonstrated that histological grade and tumor location could predict the outcome of chondrosarcoma, and the patients with high-grade and axial-location tumors suffered the worst prognosis [7]. Arshi et al. elucidated that age at diagnosis, extent of tumor, surgical resection were independent survival determinants for spinal chondrosarcoma [8]. However, almost all of these studies focused on the entire entity of chondrosarcoma rather than on different histological grades, and to our knowledge, the prognostic study exclusive to high-grade chondrosarcoma has not been reported. Given the significant diversity between the low- and high- grade chondrosarcoma, whether these prognostic factors and treatment strategies can also be applied to high-grade tumors is largely unknown. In addition, due to the few dividing cells, rich cartilage matrix, and poor vascularization, chondrosarcoma is resistant to radiotherapy [9–11]. Although some studies have demonstrated that adjuvant radiotherapy could be beneficial for local control of chondrosarcoma, it failed to achieve better overall survival (OS) or cancer-specific survival (CSS) [12–16]. However, whether high-grade chondrosarcoma, which typically shows higher cellularity and less matrix [1], is sensitive to radiotherapy is also unclear. Therefore, it is meaningful to address the prognostic indicators and effective treatment of high-grade chondrosarcoma, which may be beneficial to optimize the treatment regimen and improve patient survival.

The Surveillance, Epidemiology, and End Results (SEER) cancer registry database is maintained by National Cancer Institute, which routinely records the cancer incidence and survival data from 18 population-based cancer registries. The database doesn't include the specific chemotherapy data, and the specific information of radiotherapy and surgery, such as the doses of radiotherapy and the margins of surgical resection. In the SEER cancer registry database, the histological grade includes 4 categories: well differentiated (grade 1), moderately differentiated (grade 2), poorly differentiated (grade 3), and undifferentiated (grade 4). As reported in a previous study [17], we categorized poorly differentiated and undifferentiated as high-grade. The method to classify the grade is an assessment of the similarity between the tumor cells and the normal cells of the original organ. The grade 3 tumor (poorly differentiated) has some, or little similarity to the original organ, while the grade 4 (undifferentiated) tumor has no similarity to the original organ [18].

The following questions were addressed in this study: 1) what is the 5 year-OS and CSS for patients with high-grade chondrosarcoma; 2) what are the prognostic factors exclusive for high-grade chondrosarcoma; 3) whether the application of adjuvant radiotherapy can improve the survival of patients with high-grade tumors; and 4) whether the prognostic factors of poorly differentiated and undifferentiated tumors are different due to the biological and clinical differences.

Material and Methods

Patients selection

Due to public access and no unique identification for patients in the SEER database, ethical review was waived after the discussion by the Ethics Committee of Xi'an Jiaotong University (Xi'an, China). The SEER*Stat software (version 8.3.4) was employed to extract the chondrosarcoma cases diagnosed between 1973 and 2014. The following histologic ICD-O-3 codes (International Classification of Diseases for Oncology, Third Edition) were included: code 9220 (chondrosarcoma not otherwise specified), code 9221 (juxtacortical chondrosarcoma), code 9231 (myxoid chondrosarcoma), code 9240 (mesenchymal chondrosarcoma), code 9242 (clear cell chondrosarcoma) and code 9243 (dedifferentiated chondrosarcoma). According to the definition of ICD-0-3: chondrosarcoma, NOS: the most common subtype of chondrosarcoma, which comprises about 75% of the tumors, and is characterized by the chondromyxoid matrix material [19]; myxoid chondrosarcoma: it is characterized by the formation of myxoid stroma, and includes extraskeletal myxoid chondrosarcoma and the myxoid tumor of skull base [20]; mesenchymal chondrosarcoma: a rare subtype of chondrosarcoma, which is characterized by undifferentiated small round cells in addition to the well differentiated hyaline cartilage [21]; clear cell chondrosarcoma: a rare variant of chondrosarcoma, which is histologically characterized by the presence of bland clear cells [22]; dedifferentiated chondrosarcoma: an aggressive subtype of chondrosarcoma, which contains 2 components, a low-grade cartilage sarcoma and a high-grade tumor without cartilage [23]. The classification of these cases was reviewed and confirmed by one senior pathologist in our hospital.

The following criteria were applied to exclude some cases: 1) chondrosarcoma was not the primary tumor; 2) the tumor

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Table 1. Baseline demographics and clinicopathological characteristics of patients with high-grade chondrosarcoma in the SEER database.

Characteristics	Total N=743	Poorly differentiated N=430	Undifferentiated N=313
Age (years) at diagnosis			
<60	425 (57.2%)	262 (60.9%)	163 (52.1%)
≥60	318 (42.8%)	168 (39.1%)	150 (47.9%)
Race			
White	647 (87.1%)	379 (88.1%)	268 (85.6%)
Black	51 (6.9%)	29 (6.7%)	22 (7.0%)
Other	45 (6.0%)	22 (5.2%)	23 (7.4%)
Sex			
Male	424 (57.1%)	252 (58.6%)	172 (55.0%)
Female	319 (42.9%)	178 (41.4%)	141 (45.0%)
Tumor location			
Axial	212 (28.5%)	135 (31.4%)	77 (24.6%)
Extremities	326 (43.9%)	175 (40.7%)	151 (48.2%)
Other	205 (27.6%)	120 (27.9%)	85 (27.2%)
Histo-type			
Chondrosarcoma, NOS	417 (56.1%)	283 (65.8%)	134 (42.8%)
Myxoid	87 (11.7%)	50 (11.6%)	37 (11.8%)
Mesenchymal	72 (9.8%)	35 (8.2%)	37 (11.8%)
Dedifferentiated	154 (20.7%)	52 (12.1%)	102 (32.5%)
Other	13 (1.7%)	10 (2.3%)	3 (1.1%)
SEER stage			
Localized	224 (30.1%)	138 (32.1%)	86 (27.5%)
Regional	335 (45.1%)	200 (46.5%)	135 (43.1%)
Distant	149 (20.1%)	66 (15.3%)	83 (26.5%)
Unstaged	35 (4.7%)	26 (6.1%)	9 (2.9%)
Tumor size			
≤8 cm	268 (36.1%)	159 (37.0%)	109 (34.8%)
>8 cm	304 (40.9%)	171 (39.8%)	133 (42.5%)
Unknown	171 (23.0%)	100 (23.2%)	71 (22.7%)
Marital status			
Married	434 (58.4%)	255 (59.3%)	179 (57.2%)
Divorced	67 (9.0%)	34 (7.9%)	33 (10.5%)
Single	179 (24.1%)	117 (27.2%)	62 (19.8%)
Widowed	63 (8.5%)	24 (5.6%)	39 (12.5%)

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Table 1 continued. Baseline demographics and clinicopathological characteristics of patients with high-grade chondrosarcoma in the SEER database.

Characteristics	Total N=743	Poorly differentiated N=430	Undifferentiated N=313
Socioeconomic status			
Low-SES	380 (51.1%)	237 (55.1%)	143 (45.7%)
High-SES	363 (48.9%)	193 (44.9%)	170 (54.3%)
Surgery			
Performed	654 (88.0%)	381 (88.6%)	273 (87.2%)
Not performed	89 (12.0%)	49 (11.4%)	40 (12.8%)
Radiotherapy			
Performed	212 (28.5%)	124 (28.8%)	88 (28.1%)
Not performed	531 (71.5%)	306 (71.2%)	225 (71.9%)
Treatment			
Both	172 (23.1%)	99 (23.0%)	73 (23.3%)
Surgery only	482 (64.8%)	282 (65.6%)	200 (63.9%)
Radiotherapy only	40 (5.4%)	25 (5.8%)	15 (4.8%)
None	49 (6.7%)	24 (5.6%)	25 (8.0%)

SEER – Surveillance, Epidemiology, and End Results; NOS – not otherwise specified; SES – socioeconomic status.

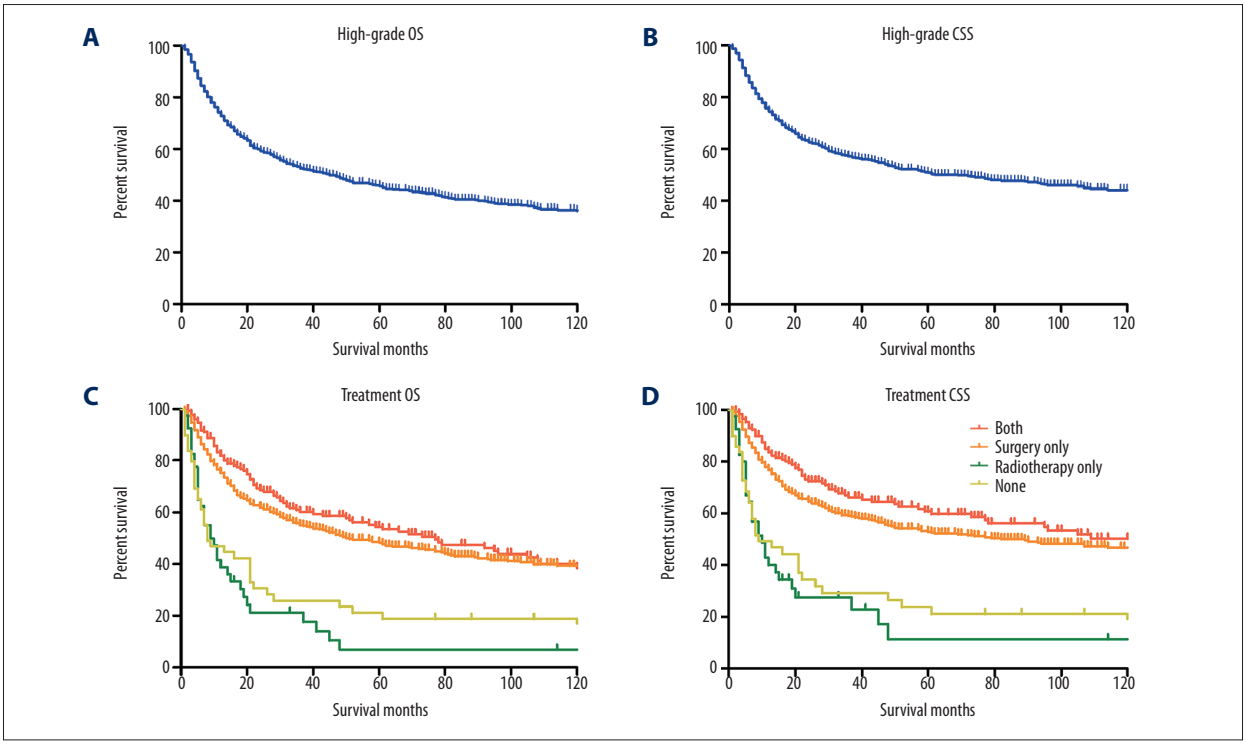

Figure 1. Kaplan-Meier curves for high-grade chondrosarcoma. (**A, B**) The overall survival curve (**A**) and cancer-specific survival curve (**B**) for high-grade chondrosarcoma. (**C, D**) The overall survival curves (**C**) and cancer-specific survival curves (**D**) for high-grade chondrosarcoma according to treatment regimens.

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Table 2. Overall and cancer-specific survival analysis for patients with high-grade chondrosarcoma in the SEER database.

Variable	Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)		Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)	
	5-year OS	*P*	HR (95% CI)	*P*	5-year CSS	*P*	HR (95% CI)	*P*
Age at diagnosis		<0.001				<0.001		
<60	54.5%		Reference		57.1%		Reference	
≥60	33.7%		1.85 (1.50–2.30)	<0.001	40.9%		1.54 (1.22–1.94)	<0.001
Race		0.401				0.675		
White	45.0%				50.3%			
Black	46.5%				51.3%			
Other	51.5%				53.6%			
Sex		0.135				0.198		
Male	43.1%				48.5%			
Female	48.8%				52.5%			
Tumor location		0.004				0.001		
Axial	40.5%		Reference		45.2%		Reference	
Extremities	42.0%		0.99 (0.79–1.25)	0.952	46.5%		0.98 (0.77–1.27)	0.909
Other	55.2%		0.95 (0.71–1.28)	0.747	63.0%		0.88 (0.63–1.22)	0.438
Pathological grade		<0.001				<0.001		
Poorly differentiated	54.2%		Reference		60.1%		Reference	
Undifferentiated	33.1%		1.40 (1.14–1.72)	0.001	37.1%		1.38 (1.10–1.73)	0.005
Histo-type		<0.001				<0.001		
Chondrosarcoma, NOS	46.3%		Reference		52.5%		Reference	
Myxoid	49.2%		0.97 (0.70–1.34)	0.855	54.1%		0.93 (0.65–1.35)	0.718
Mesenchymal	57.9%		0.68 (0.45–1.03)	0.070	61.6%		0.70 (0.45–1.11)	0.127
Dedifferentiated	27.3%		1.33 (1.02–1.72)	0.032	30.4%		1.46 (1.10–1.92)	0.007
Other	63.5%		0.85 (0.31–2.33)	0.758	70.4%		0.74 (0.23–2.35)	0.611
SEER stage		<0.001				<0.001		
Localized	60.7%		Reference		67.8%		Reference	
Regional	47.3%		1.45 (1.13–1.87)	0.003	52.3%		1.68 (1.25–2.24)	0.001
Distant	14.9%		3.12 (2.34–4.15)	<0.001	16.3%		3.95 (2.87–5.43)	<0.001
Unstaged	56.1%		0.97 (0.57–1.65)	0.921	69.8%		0.91 (0.47–1.77)	0.783
Tumor size		<0.001				<0.001		
≤8 cm	59.6%		Reference		64.3%		Reference	
>8 cm	36.5%		1.42 (1.11–1.81)	0.006	42.0%		1.45 (1.11–1.90)	0.007
Unknown	36.7%		1.37 (1.03–1.83)	0.030	42.2%		1.38 (1.00–1.90)	0.049

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Table 2 continued. Overall and cancer-specific survival analysis for patients with high-grade chondrosarcoma in the SEER database.

Variable	Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)		Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)	
	5-year OS	*P*	HR (95% CI)	*P*	5-year CSS	*P*	HR (95% CI)	*P*
Marital status		<0.001				<0.001		
Married	46.4%		Reference		50.9%		Reference	
Divorced	40.3%		1.17 (0.83–1.65)	0.358	47.5%		1.12 (0.77–1.64)	0.551
Single	51.2%		1.02 (0.79–1.32)	0.889	57.6%		0.95 (0.72–1.26)	0.727
Widowed	19.5%		1.42 (1.04–1.93)	0.028	25.7%		1.39 (0.99–1.97)	0.059
Socioeconomic status		0.025				0.112		
Low-SES	41.9%		Reference		47.7%			
High-SES	49.6%		0.90 (0.74–1.09)	0.273	54.3%			
Surgery		<0.001				<0.001		
Performed	49.8%		Reference		54.9%		Reference	
Not performed	13.9%		2.00 (1.51–2.66)	<0.001	17.6%		2.06 (1.53–2.78)	<0.001
Radiotherapy		0.928				0.573		
Performed	44.9%				51.4%			
Not performed	45.7%				50.1%			
Treatment		<0.001	NA			<0.001	NA	
Both	54.3%				59.8%			
Surgery only	47.6%				52.5%			
Radiotherapy only	7.2%				11.5%			
None	18.8%				21.1%			

SEER – Surveillance, Epidemiology, and End Results; OS – overall survival; CSS – cancer-specific survival; HR – hazard ratio; CI – confidence interval; NOS – not otherwise specified; SES – socioeconomic status; NA – the analysis is not available because of the covariance.

was diagnosed without histopathology confirmed; 3) the survival time was not clear; 4) the histological grade was well- or moderately-differentiated.

Study variables

Demographic variables, such as age, race, sex, marital status and socioeconomic status (SES), was analyzed in this study. Age was categorized as: <60 years old and ≥60 years old. Race was recoded as white, black and other in the SEER database. Marital status was divided into 4 categories: married, divorced, single, and widowed. Socioeconomic status was created by standard 2000 US Census SES variables as previous studies [24,25] and further categorized as low-SES and high-SES. Tumor-related variables, such as histological grade, tumor location, tumor size, SEER stage, and treatment options, were extracted from the database. The histological grade included 2 categories: poorly differentiated (grade 3) and undifferentiated (grade 4), according to the SEER database. To simplify the analysis, the histo-type was divided into: chondrosarcoma not otherwise specified, myxoid chondrosarcoma, mesenchymal chondrosarcoma, dedifferentiated chondrosarcoma, and other (including juxtacortical chondrosarcoma and clear cell chondrosarcoma). Tumor location was classified as axial (including pelvic bones, sacrum, coccyx, ribs, sternum, and vertebral columns), extremities (including bones of the upper and lower extremities) and other group (including bones of skull, mandible, and other atypical locations) as previous study [24]. As coded in the SEER program, the SEER stage was divided into localized, regional, distant, and unstaged. Tumor size was categorized as: ≤8 cm, >8 cm, and unknown. With regards to surgery and radiotherapy, both were divided into performed

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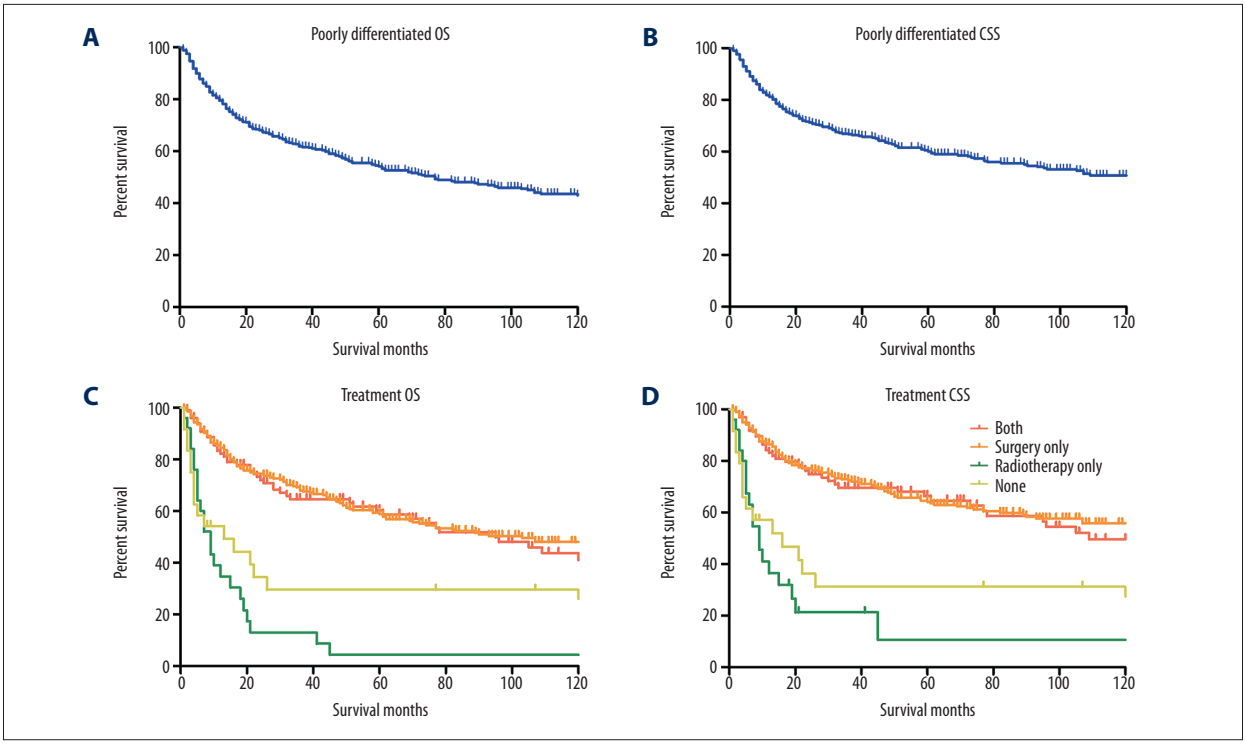

Figure 2. Kaplan-Meier curves for poorly differentiated chondrosarcoma. (**A, B**) The overall survival curve (**A**) and cancer-specific survival curve (**B**) for poorly differentiated chondrosarcoma. (**C, D**) The overall survival curves (**C**) and cancer-specific survival curves (**D**) for poorly differentiated chondrosarcoma according to treatment regimens.

and not performed. For the treatment regimen, we included 4 groups: radiotherapy combined surgery, surgery only, radiotherapy only, and no treatment.

Statistical analysis

In this study, OS and chondrosarcoma CSS were the primary outcomes. As described in the SEER database, the deaths caused by chondrosarcoma were considered as events for CSS, and the deaths from any cause were considered as events for OS. Descriptive analysis was carried out to assess the distribution of demographic and tumor-related variables. The Kaplan-Meier method was used to estimate the 5-year OS and CSS. The log-rank test was performed for univariate analysis, and the Cox regression model was conducted for multivariate analysis. The aforementioned statistical analyses were performed using SPSS statistics software, version 20 (IBM, SPSS, Inc., Chicago, IL, USA). All *P* values were 2-sided, and $P<0.05$ indicated the significant difference.

Results

Baseline patient characteristics

A total of 743 patients with high-grade chondrosarcoma were identified in this study, of which 430 cases were diagnosed as poorly differentiated tumors and 313 cases were classified as undifferentiated tumors. Of these cases with high-grade chondrosarcoma, the majority were found in younger age (57.2%, n=425), white race (87.1%, n=647) and male (57.1%, n=424). The most common SEER stage of high-grade chondrosarcoma was regional (45.1%, n=335), followed by localized (30.1%, n=224) and distant (20.1%, n=149). Most patients were married (58.4%, n=434), followed by single (24.1%, n=179) and divorced (9.0%, n=67). Most patients underwent surgical resection (88.0%, n = 654), while the minority received radiotherapy (28.5%, n=212). The most common treatment regimens were surgery only (64.8%, n=482) and adjuvant radiotherapy combined surgery (23.1%, n=172). Similar distributions of patient demographics and tumor characteristics were found in poorly differentiated tumors and undifferentiated tumors. The baseline characteristics of this study were shown in Table 1.

Survival analysis for patients with high-grade chondrosarcoma

Kaplan-Meier curves (Figure 1A, 1B) showed that the 5-year OS and CSS for patients with high-grade chondrosarcoma were 45.7% and 50.8%, respectively. Adjuvant radiotherapy combined surgery didn't make a difference on the survival of patients compared with surgery-only group, and surgical resection could significantly improve the outcomes of patients

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Table 3. Overall and cancer-specific survival analysis for patients with poorly differentiated chondrosarcoma in the SEER database.

Variable	Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)		Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)	
	5-year OS	*P*	HR (95% CI)	*P*	5-year CSS	*P*	HR (95% CI)	*P*
Age (years) at diagnosis		<0.001				0.001		
<60	61.3%		Reference		64.9%		Reference	
≥60	42.4%		1.59 (1.16–2.18)	0.004	51.3%		1.50 (1.07–2.09)	0.018
Race		0.911				0.775		
White	54.8%				60.8%			
Black	48.7%				57.9%			
Other	51.8%				51.8%			
Sex		0.381				0.269		
Male	52.9%				58.4%			
Female	56.1%				61.3%			
Tumor location		0.079				0.032		
Axial	46.0%				51.8%		Reference	
Extremities	54.1%				58.5%		0.81 (0.57–1.15)	0.242
Other	62.8%				70.9%		0.89 (0.57–1.40)	0.611
Histo-type		<0.001				<0.001		
Chondrosarcoma, NOS	53.8%		Reference		60.2%		Reference	
Myxoid	57.9%		0.99 (0.64–1.54)	0.953	65.8%		0.92 (0.54–1.57)	0.749
Mesenchymal	60.4%		1.27 (0.71–2.25)	0.423	63.1%		1.35 (0.71–2.56)	0.357
Dedifferentiated	25.1%		1.84 (1.22–2.75)	0.003	35.9%		2.00 (1.30–3.08)	0.002
Other	71.4%		0.64 (0.16–2.67)	0.546	85.7%		0.39 (0.05–2.88)	0.358
SEER stage		<0.001				<0.001		
Localized	66.2%		Reference		75.2%		Reference	
Regional	54.4%		1.36 (0.97–1.91)	0.082	58.9%		1.84 (1.22–2.78)	0.004
Distant	18.8%		3.01 (1.97–4.60)	<0.001	21.8%		4.48 (2.79–7.21)	<0.001
Unstaged	62.9%		0.78 (0.41–1.51)	0.461	78.5%		0.76 (0.32–1.78)	0.525
Tumor size		<0.001				<0.001		
≤8 cm	68.8%		Reference		74.4%		Reference	
>8 cm	46.4%		1.49 (1.06–2.08)	0.021	52.8%		1.72 (1.16–2.54)	0.007
Unknown	41.7%		1.69 (1.12–2.54)	0.012	47.7%		1.89 (1.20–2.97)	0.006

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Table 3 continued. Overall and cancer-specific survival analysis for patients with poorly differentiated chondrosarcoma in the SEER database.

Variable	Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)		Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)	
	5-year OS	*P*	HR (95% CI)	*P*	5-year CSS	*P*	HR (95% CI)	*P*
Marital status		0.034				0.609		
Married	53.3%		Reference		58.5%			
Divorced	49.1%		0.91 (0.55–1.53)	0.849	60.9%			
Single	56.7%		0.84 (0.59–1.21)	0.333	62.4%			
Widowed	32.1%		1.30 (0.79–2.15)	0.299	43.4%			
Socioeconomic status		0.024				0.588		
Low-SES	49.1%		Reference		56.6%			
High-SES	59.8%		0.76 (0.57–1.01)	0.062	63.6%			
Surgery		<0.001				<0.001		
Performed	59.1%		Reference		64.7%		Reference	
Not performed	17.3%		2.58 (1.72–3.88)	<0.001	23.3%		2.35 (1.55–3.56)	<0.001
Radiotherapy		0.055				0.086		
Performed	48.5%				56.2%			
Not performed	56.6%				61.6%			
Treatment		<0.001	NA			<0.001	NA	
Both	60.2%				66.3%			
Surgery only	58.8%				64.1%			
Radiotherapy only	4.4%				10.6%			
None	22.2%				23.4%			

SEER – Surveillance, Epidemiology, and End Results; OS – overall survival; CSS – cancer-specific survival; HR – hazard ratio; CI – confidence interval; NOS – not otherwise specified; SES – socioeconomic status; NA – the analysis is not available because of the covariance.

compared with radiotherapy-only or non-treatment groups (OS *P*<0.00, Figure 1C; CSS *P*<0.001, Figure 1D). In addition, both the OS and CSS analysis demonstrated that undifferentiated pathological grade, dedifferentiated histo-type, distant SEER stage, larger tumor size, and widowhood were associated with dismal prognoses. The multivariate analysis identified that pathological grade, histo-type, SEER stage, tumor size, and surgical resection were independent predictors for both OS and CSS of high-grade chondrosarcoma, and widowhood was an independent predictor for chondrosarcoma OS. Patients with undifferentiated chondrosarcoma suffered a remarkably higher risk of overall mortality (Hazard ratio [HR] 1.40, 95% confidence interval [CI] 1.14–1.72, *P*=0.001) and cancer-specific mortality (HR 1.38, 95% CI 1.10–1.73, *P*=0.005). Similarly, patients without surgical resection also had a dramatical increase in the risk of overall mortality (HR 2.00, 95% CI 1.51–2.66, *P*<0.001) and cancer-specific mortality (HR 2.06, 95% CI 1.53–2.78, *P*<0.001). The details of log-rank test and Cox regression were shown in Table 2.

Subgroup survival analysis for patients with poorly differentiated chondrosarcoma

To further determine the therapeutic effects of surgical resection and radiotherapy on poorly differentiated chondrosarcoma, we performed the Kaplan-Meier curves and log-rank test to

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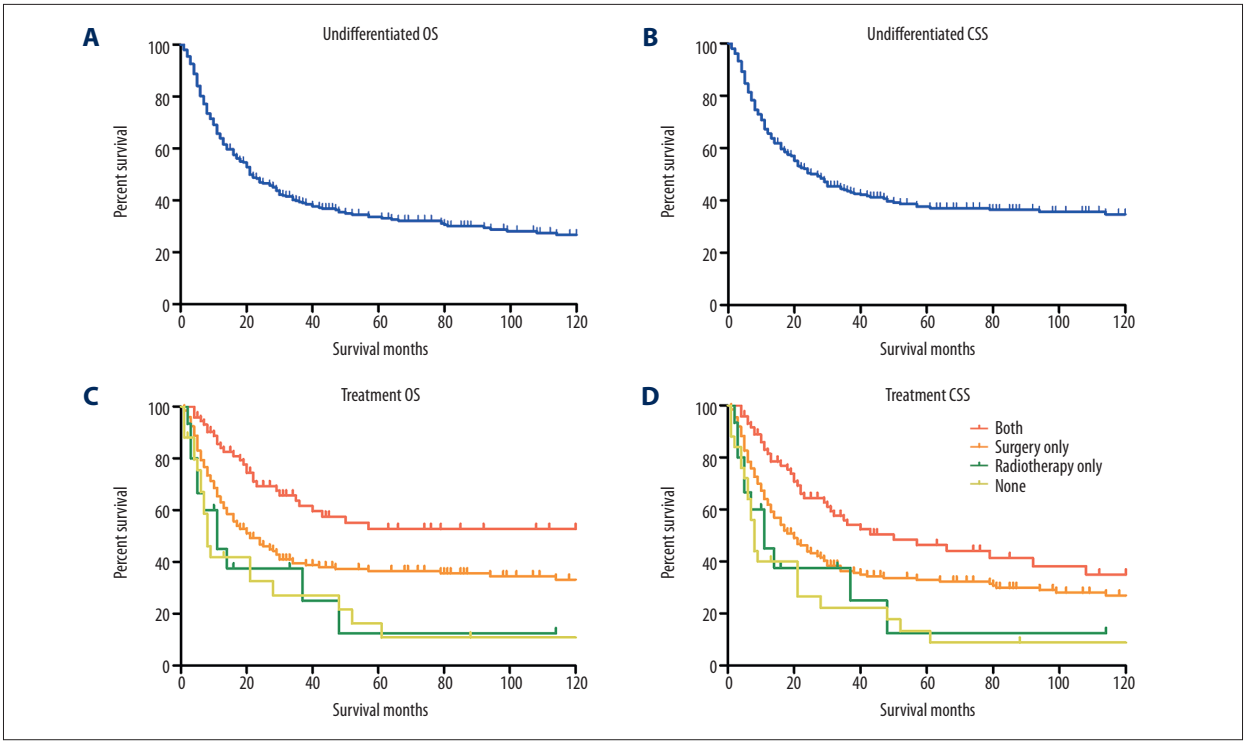

Figure 3. Kaplan-Meier curves for undifferentiated chondrosarcoma. (**A, B**) The overall survival curve (**A**) and cancer-specific survival curve (**B**) for undifferentiated chondrosarcoma. (**C, D**) The overall survival curves (**C**) and cancer-specific survival curves (**D**) for undifferentiated chondrosarcoma according to treatment regimens.

evaluate the OS and CSS. The Kaplan-Meier curves revealed that the 5-year OS and CSS for patients with poorly differentiated chondrosarcoma were 54.2% and 60.1%, respectively (Figure 2A, 2B). Adjuvant radiotherapy combined surgery didn't significantly improve the patient outcomes compared with surgery-only group, and surgical resection could dramatically improve the survival rate of patients (OS $P<0.001$, Figure 2C; CSS $P<0.001$, Figure 2D). Similar with the survival analysis of high-grade tumors, greater age, dedifferentiated histo-type, distant SEER stage, and larger tumor size were associated with dismal prognoses in both OS and CSS. Widowhood and low-SES were associated with poor outcomes in OS analysis. By multivariate analysis, histo-type, SEER stage, tumor size, and surgical resection were determined as independent prognostic factors for both OS and CSS of poorly differentiated chondrosarcoma. The mortality risk of patients without surgical resection was more than 2 times than that of patients receiving surgical resection in OS (HR 2.58, 95% CI 1.72–3.88, $P<0.001$) and CSS analysis (HR 2.35, 95% CI 1.55–3.56, $P<0.001$). The results of survival analysis were shown in Table 3.

Subgroup survival analysis for patients with undifferentiated chondrosarcoma

We next evaluated the therapeutic effects of surgical resection and adjuvant radiotherapy on undifferentiated chondrosarcoma by log-rank test and Cox regression analysis. The results showed that the 5-year OS and CSS for patients with undifferentiated chondrosarcoma were 33.1% and 37.1%, respectively (Figure 3A, 3B). Similar with the results of high-grade chondrosarcoma and poorly differentiated chondrosarcoma, surgical resection remained the effective treatment option for patients with undifferentiated chondrosarcoma. Strikingly, adjuvant radiotherapy combined surgery could significantly improve the outcomes of patients with undifferentiated chondrosarcoma in both OS and CSS analysis (OS $P<0.001$, Figure 3C; CSS $P<0.001$, Figure 3D), which was in contrast with the results in high-grade chondrosarcoma and poorly differentiated. Besides, greater age, extremities location, dedifferentiated histo-type, distant SEER stage, larger tumor size, and widowhood were associated with dismal prognoses in both OS and CSS. The Cox regression analysis demonstrated that radiotherapy was an independent protective factor for patients with undifferentiated chondrosarcoma in both OS (HR 1.57, 95% CI 1.09–2.27, $P=0.017$) and CSS (HR 1.66, 95% CI 1.11–2.50, $P=0.016$). In addition, age at diagnosis, tumor location, histo-type, SEER stage, tumor size, marital status, and surgical resection were also identified as independent prognostic factors for both OS and CSS. The results of survival analysis were shown in Table 4.

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Table 4. Overall and cancer-specific survival analysis for patients with undifferentiated chondrosarcoma in the SEER database.

Variable	Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)		Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)	
	5-year OS	P	HR (95% CI)	P	5-year CSS	P	HR (95% CI)	P
Age (years) at diagnosis		<0.001				<0.001		
<60	43.4%		Reference		44.6%		Reference	
≥60	21.6%		2.16 (1.58–2.97)	<0.001	28.3%		1.75 (1.25–2.45)	0.001
Race		0.037				0.089		
White	30.6%		Reference		34.8%			
Black	43.3%		0.80 (0.43–1.49)	0.485	43.3%			
Other	50.6%		0.44 (0.23–0.84)	0.012	54.8%			
Sex		0.098				0.321		
Male	28.3%				33.1%			
Female	38.7%				41.3%			
Tumor location		0.003				0.001		
Axial	31.6%		Reference		35.0%		Reference	
Extremities	25.7%		1.14 (0.80–1.62)	0.474	29.9%		1.13 (0.77–1.64)	0.543
Other	45.6%		1.08 (0.67–1.73)	0.763	51.5%		0.89 (0.53–1.51)	0.679
Histo-type		0.007				0.008		
Chondrosarcoma, NOS	29.5%		Reference		36.2%		Reference	
Myxoid	37.5%		1.03 (0.63–1.67)	0.912	39.5%		1.11 (0.65–1.88)	0.712
Mesenchymal	55.5%		0.52 (0.29–0.92)	0.026	60.3%		0.52 (0.27–1.01)	0.053
Dedifferentiated	24.0%		1.07 (0.77–1.50)	0.681	27.8%		1.08 (0.75–1.55)	0.680
Other	NA*		1.41 (0.33–6.05)	0.647	NA*		1.61 (0.37–7.02)	0.527
SEER stage		<0.001				<0.001		
Regional	37.2%		1.66 (1.13–2.43)	0.010	41.8%		1.54 (1.00–2.36)	0.048
Distant	11.6%		3.41 (2.25–5.16)	<0.001	12.1%		3.66 (2.35–5.72)	<0.001
Unstaged	33.3%		1.23 (0.42–3.59)	0.711	38.9%		1.18 (0.35–3.99)	0.791
Tumor size		0.001				0.001		
≤8 cm	46.0%		Reference		50.8%		Reference	
>8 cm	23.2%		1.29 (0.89–1.86)	0.179	26.8%		1.28 (0.87–1.89)	0.219
Unknown	29.9%		1.17 (0.76–1.79)	0.471	34.6%		0.96 (0.59–1.54)	0.850
Marital status		0.001				0.001		
Married	35.8%		Reference		39.3%		Reference	
Divorced	32.1%		1.17 (0.71–1.91)	0.538	33.1%		1.21 (0.72–2.03)	0.465
Single	38.3%		1.12 (0.74–1.68)	0.591	48.0%		0.98 (0.62–1.54)	0.922
Widowed	10.7%		1.54 (1.01–2.34)	0.045	13.1%		1.65 (1.06–2.57)	0.027

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Table 4 continued. Overall and cancer-specific survival analysis for patients with undifferentiated chondrosarcoma in the SEER database.

Variable	Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)		Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)	
	5-year OS	P	HR (95% CI)	P	5-year CSS	P	HR (95% CI)	P
Socioeconomic status		0.559				0.584		
Low-SES	31.8%				35.2%			
High-SES	35.0%				39.6%			
Surgery		0.003				0.001		
Performed	36.1%		Reference		40.9%		Reference	
Not performed	10.8%		1.84 (1.17–2.89)	0.008	12.4%		1.90 (1.19–3.04)	0.008
Radiotherapy		0.015				0.004		
Performed	41.1%		Reference		46.2%		Reference	
Not performed	30.0%		1.57 (1.09–2.27)	0.017	33.4%		1.66 (1.11–2.50)	0.016
Treatment		<0.001	NA#			<0.001	NA#	
Both	46.3%				52.8%			
Surgery only	32.3%				36.5%			
Radiotherapy only	12.5%				12.5%			
None	8.3%				10.9%			

SEER – Surveillance, Epidemiology, and End Results; OS – overall survival; CSS – cancer-specific survival; HR – hazard ratio; CI – confidence interval; NOS – not otherwise specified; SES – socioeconomic status; NA* – the analysis is not available because of the small sample size; NA# – the analysis is not available because of the covariance.

Subgroup survival analysis for patients with different histo-types of undifferentiated chondrosarcoma

To explore which histo-type of undifferentiated chondrosarcoma was sensitive to the adjuvant radiotherapy, the log-rank test and Cox regression analysis were performed. The log-rank test of undifferentiated myoxid chondrosarcoma showed both the 5-year OS and CSS of patients with adjuvant radiotherapy were much higher than that of patients without radiotherapy, although the differences were not significant (Figure 4A, 4B). The univariate analysis of undifferentiated dedifferentiated chondrosarcoma demonstrated that the adjuvant radiotherapy could remarkably benefit the OS and CSS (OS P=0.015, Figure 4C; CSS P=0.007, Figure 4D), and the Cox regression analysis demonstrated that radiotherapy was an independent protective factor for patients in both OS (HR 2.64, 95% CI 1.17–5.95, P=0.019) and CSS (HR 3.56, 95% CI 1.39–9.15, P=0.008) analysis. While the survival analysis showed that the adjuvant radiotherapy did not benefit the survival of patients with undifferentiated chondrosarcoma (NOS) and mesenchymal chondrosarcoma. Together, these results determined that the adjuvant radiotherapy combined with surgery could benefit the patients with undifferentiated myxoid and dedifferentiated chondrosarcoma rather than those with undifferentiated chondrosarcoma (NOS) and mesenchymal chondrosarcoma. The results of survival analysis were shown in Table 5.

Discussion

Since most prognostic studies focus on the entire entity of chondrosarcoma [2,26–28], the prognostic factors and optimal treatment for high-grade chondrosarcoma remain poorly understood. Given the significant diversity between different histopathology grades and the dismal prognosis of high-grade chondrosarcomas, prognostic studies specifically for high-grade tumors are imperative. In this study, we demonstrated that age at diagnosis, pathological grade, histo-type, SEER stage, tumor size and surgical resection were independent prognostic factors in OS and CSS analysis for the entire high-grade tumor group. While radiotherapy was identified as a protective factor in both OS and CSS analysis of patients with undifferentiated (grade 4) dedifferentiated chondrosarcoma, and adjuvant radiotherapy combined with surgery could improve both

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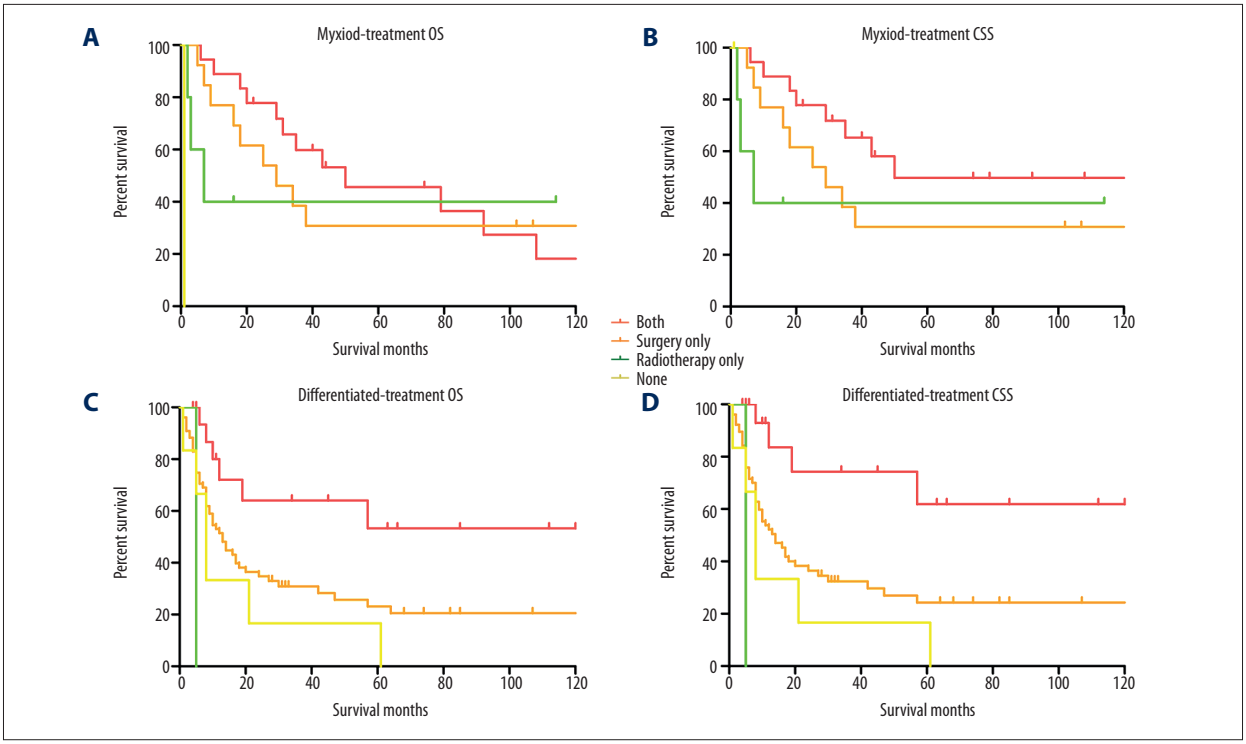

Figure 4. Kaplan-Meier curves for undifferentiated myxoid and dedifferentiated chondrosarcoma. (**A, B**) The overall survival curves (**A**) and cancer-specific survival curves (**B**) for undifferentiated myxoid chondrosarcoma according to treatment regimens. (**C, D**) The overall survival curves (**C**) and cancer-specific survival curves (**D**) for undifferentiated dedifferentiated chondrosarcoma according to treatment regimens.

the OS and CSS of patients with undifferentiated (grade 4) myxoid and dedifferentiated chondrosarcoma, which encourage the application of adjuvant radiotherapy for patients with undifferentiated chondrosarcoma.

With an 88.5% CSS at 5 years [24], the low-grade chondrosarcoma is often considered as an indolent cancer. However, the survival of patients with high-grade chondrosarcoma, especially the undifferentiated chondrosarcoma was unfavorable. In this study, the 5-year OS and CSS for poorly-differentiated chondrosarcoma were 54.2% and 60.1%, respectively, and the OS and CSS for undifferentiated chondrosarcoma were 33.1% and 37.1%, respectively, emphasizing the clinical difference between the poorly-differentiated and undifferentiated tumor. In consistent with our survival data, Fiorenza et al. found that the 5-year OS rate of grade-2 chondrosarcoma was 53%, and the survival rate of grade-3 tumor was 38% [29]. Similarly, the study by Giuffrida et al. reported a 37% 5-year disease-specific survival rate of high-grade chondrosarcoma [2]. However, a single institutional study including 31 patients with high-grade chondrosarcoma revealed that the 5-year disease-specific survival was 82.5% [7], which was much higher than our study and other studies. The reason for the huge gap may be attributed to the small sample size in this single institutional study.

It seems that almost all previous studies on chondrosarcoma elucidated that radiotherapy and chemotherapy are not beneficial to the patients' outcome, and the surgical resection is the only effective treatment for patients with chondrosarcoma [30–32]. In the present study, we also found that surgical resection could benefit the OS and CSS of patients with high-grade chondrosarcoma. However, our study firstly demonstrated that the adjuvant radiotherapy combined with surgery could benefit both OS and CSS of patients with undifferentiated myxoid and dedifferentiated chondrosarcoma compared with other treatment regimens. Similar to our findings, a large-scale SEER study by Koshy et al. analyzed 6960 cases of high-grade soft tissue sarcomas, which included 154 cases of osseous and chondromatous neoplasms, suggesting that the radiotherapy was associated with improved 3-year OS [33]. Some studies have shown radiotherapy could benefit the local tumor control and reduce the recurrence rate, but these studies failed to show the advantage of radiotherapy on survival. Drilon et al. identified 73 cases of localized myxoid chondrosarcoma and found that the patients with adjuvant radiotherapy exhibited a lower incidence of distant metastasis [20]. Kawaguchi et al. retrospectively reviewed 43 cases of mesenchymal chondrosarcoma, which has higher malignant biological behavior than other histo-types and enhanced the effect of adjuvant radiotherapy on local tumor control, but no benefit on OS and disease-free

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Table 5. Subgroup survival analysis for patients with different histo-types of undifferentiated chondrosarcoma in the SEER database.

Histo-type	Variable	Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)		Univariate analysis (log-rank test)		Multivariate analysis (Cox regression)	
		5-year OS	*P*	HR (95% CI)	*P*	5-year CSS	*P*	HR (95% CI)	*P*
Chondrosarcoma, NOS	Radiotherapy		0.642				0.709		
	Performed	27.8%				32.0%			
	Not performed	31.0%				37.1%			
	Treatment		0.064				0.085		
	Both	27.9%				40.8%			
	Surgery only	34.9%				39.1%			
	Radiotherapy only	1.0%				1.4%			
	None	8.0%				11.5%			
Myxoid	Radiotherapy		0.608				0.211		
	Performed	42.7%				52.9%			
	Not performed	28.6%				28.6%			
	Treatment		0.000				0.000		
	Both	45.6%				58.0%			
	Surgery only	30.8%				30.8%			
	Radiotherapy only	NA*				NA*			
	None	NA*				NA*			
Mesenchymal	Radiotherapy		0.934				0.883		
	Performed	53.7%				59.7%			
	Not performed	56.7%				60.2%			
	Treatment		0.703				0.380		
	Both	60.9%				69.6%			
	Surgery only	61.4%				65.1%			
	Radiotherapy only	1.0%				1.0%			
	None	33.3%				33.3%			
Dedifferentiated	Radiotherapy		0.020				0.005		
	Performed	50.2%		Reference		58.3%		Reference	
	Not performed	20.6%		2.64 (1.17–5.95)	0.019	21.5%		3.56 (1.39–9.15)	0.008
	Treatment		0.015	NA#			0.007	NA#	
	Both	53.3%				61.9%			
	Surgery only	23.6%				24.3%			
	Radiotherapy only	NA*				NA*			
	None	NA*				NA*			

SEER – Surveillance, Epidemiology, and End Results; OS – overall survival; CSS – cancer-specific survival; HR – hazard ratio; CI – confidence interval; NOS – not otherwise specified; NA* – the analysis is not available because of the small sample size; NA# – the analysis is not available because of the covariance.

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survival was identified [13]. Similarly, a systematic review by Xu et al. revealed that adjuvant radiotherapy may reduce local recurrence of mesenchymal chondrosarcoma but cannot improve the OS [12]. The study of Holliday et al. included 19 patients with spinal chordoma and chondrosarcoma, noting that early postoperative adjuvant radiotherapy may contribute to 2-year local control [14]. Together, these findings encourage the application of adjuvant radiotherapy in the treatment of high-grade chondrosarcoma, especially the undifferentiated myxoid and dedifferentiated chondrosarcoma.

Previous studies on chondrosarcoma have shown that anatomical location, tumor size, and stage can predict patient outcomes [34–37]. Similar to these studies, we demonstrated that tumor size and tumor stage were independent prognostic factors for high-grade tumors in OS and CSS analyses. However, we failed to determine the anatomical location as an independent prognostic factor of high-grade chondrosarcoma, indicating the different nature of high-grade tumors. Additionally, the present study showed that older age was associated with a significant worse survival in high-grade chondrosarcoma group and other 2 subgroups. Consistent with our findings, Giuffrida et al. reported that an age larger than 50 years was associated with a significant worse OS [2]. Our previous study also determined age as an independent prognostic factor in CSS analysis [24]. Together, these results reinforced the role of age in the management of chondrosarcoma. With regard to the marital status, the present study determined that widowhood was an independent risk factor in the subgroup of undifferentiated chondrosarcoma but not in the subgroup of poorly differentiated chondrosarcoma, suggesting the spousal support [38] and psychosocial factors [39–41] play more important roles in higher malignant tumors. The spousal support could increase the frequency of medical screening and the adherence to the treatment [38,42]. Besides, the widowhood status poses psychosocial stress on the surviving companions. The study by van Grootheest et al. revealed that the widowed people exhibited a high level of depression for a long time [40]. It is well known that the psychosocial disorders exert adverse effects on the immune and endocrine systems and contribute to the dismal survival [43]. Therefore, the widowhood patients with undifferentiated chondrosarcoma need more psychiatric intervention to improve the patients' outcome.

The surgical margins play a critical role in the control of the tumor local recurrence. Stevenson et al. demonstrated that the surgical margins determined the local recurrence in all grades of chondrosarcoma [44]. Besides, our study determined that the adjuvant radiotherapy could benefit the patients with undifferentiated chondrosarcoma, while the radiation doses are also important for the treatment regimen [45]. Due to the inherent characteristics of the SEER database, this study couldn't analyze the impact of surgical margins and radiotherapy doses on patients' survival. Moreover, chemotherapy may benefit the outcomes of patients with mesenchymal and dedifferentiated chondrosarcoma, but not other subtypes such as the conventional chondrosarcoma [46]. In our study, we didn't include the chemotherapy due to the lack of the specific data in the database, which may lead to incomplete analysis of the optimal treatment regimen for patients with chondrosarcoma. Finally, the 4-grade system in the SEER database is not commonly used for chondrosarcoma, thus the application of our results may be compromised. Although with these limitations, our study was the first large series to investigate the effect of adjuvant radiotherapy on high-grade chondrosarcoma, and has observed the survival benefit on patients with undifferentiated myxoid and dedifferentiated tumors, which may enhance the confidence of applying adjuvant radiotherapy on high-grade chondrosarcoma, and maximize the patients' outcome.

Conclusions

Our study first demonstrated that radiotherapy was an independent protective factor in both OS and CSS for undifferentiated (grade 4) dedifferentiated chondrosarcoma, and adjuvant radiotherapy combined with surgery can improve both the OS and CSS of patients with undifferentiated (grade 4) myxoid and dedifferentiated chondrosarcoma. In addition, we determined that age at diagnosis, pathological grade, histo-type, SEER stage, tumor size, and surgical resection were independent prognostic factors in OS and CSS analysis for the entire high-grade tumor group. Our findings encourage the application of adjuvant radiotherapy for patients with high-grade chondrosarcoma, especially the undifferentiated myxoid and dedifferentiated chondrosarcoma.

Ethical Statement

The SEER program database is publicly available and contains no unique identification for patients such as name, date of birth, or Social Security number. As such, a formal ethical review was waived after the discussion by the Ethics Committee of Xi'an Jiaotong University (Xi'an, China).

Conflicts of interest

None.

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