



Research Paper

Appendicular dedifferentiated chondrosarcoma: A management and survival study from the SEER database

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HIGHLIGHTS

- Dedifferentiated chondrosarcoma is an aggressive bone tumor with high rates of metastasis that severely impact the patient's prognosis.
- Treatment usually consists of either a limb-salvage procedure or limb amputation, the former being more commonly performed.
- Size of the tumor severely impacts the likelihood of presenting metastasis at diagnosis.
- Female gender appears to be an important protective factor against death.

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ABSTRACT

Introduction: Dedifferentiated chondrosarcoma (DDC) is an aggressive osseous neoplasm with a dismal prognosis. Treatment commonly involves limb-salvage surgery or amputation. In patients with appendicular DDC, we sought to describe demographic, clinical and treatment characteristics (1), analyze risk factors for metastasis (2) and overall death (3), and assess survival rates by treatment (4).

Materials and methods: Two-hundred-and-five patients from the SEER Database were included in our analysis. Demographic, clinical and treatment variables were analyzed. Multivariate regression was performed to identify risk factors. Survival analysis was performed using the Kaplan-Meier method.

Results: Fifty-one (24.9%) of the patients included presented metastasis at diagnosis. The most common locations were the lungs, other sites, and bone. Surgery to the primary site was more common in patients without metastasis (94.2%) than those with (78.2%); limb-salvage procedures were more common than amputations. Tumors >8 cm (T2) and those discontinuous (T3) were more likely to present metastasis at diagnosis (OR = 2.54, p = 0.043 and OR = 7.4, p = 0.008, respectively). Female gender was found to be a protective factor for overall death on crude analysis (OR = 0.33, p = 0.019). Metastases to sites other than the lungs (M1b) had the highest risk of overall death (OR = 49, p = 0.01). Combination of surgery and chemotherapy showed a trend towards higher overall survival in non-metastatic patients (p = 0.1069 and p = 0.1703).

Conclusions: Appendicular DDC displays a high metastatic rate and low survival rates. The most common procedure is a limb-salvage surgery. Tumor size increases the risk of presenting metastases at diagnosis and female gender is a protective factor against death.

1. Introduction:

Dedifferentiated chondrosarcoma (DDC) is a neoplasm of osseous origin that transitions to an undifferentiated neoplasm or transforms to another differentiated phenotype [1]. DDC contains a well differentiated cartilage tumor component with a histologically abrupt transition to a

high grade non-cartilaginous sarcoma component and has a more malignant behavior [2]. In the literature, the reported incidence of chondrosarcoma is about 2.85 per million per year and dedifferentiation develops in 10–15% of patients [3,4]. Moreover, the average age at presentation is between 50 and 60 years presenting later compared to other chondrosarcoma subtypes. This tumor is commonly located in the

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pelvis and long bones, producing symptoms such as pain, swelling, paresthesia, and pathologic fractures [2,5].

The main treatment option for DDC is wide surgical resection with clear margins; however, it is important to take into consideration that metastases might have already developed or evolved shortly after surgery [6,7]. As a result, prognosis is dismal with a 5-year overall survival of 18% [6]. Certain tumor location show an even lower survival rate, as is the case of central DDC with a 2-, 5-, and 10-year disease-specific survival of 28%, 9% and 9%, respectively [3].

Despite its extremely aggressive nature, this tumor has not been studied in detail due to its relative rarity. In our study in patients with DDC, we sought to: 1) describe patient demographic, clinical and treatment characteristics, 2) analyze risk factors for metastatic disease, 3) analyze risk factors for overall death and 4) assess survival rates according to treatment modality.

2. Materials and methods

This retrospective study used the Surveillance, Epidemiology and End Results (SEER), a National Cancer Institute database consisting of 18 population-based cancer registries that account for about 28% of the United States population. All cancer registries, in order to be considered by the SEER, need to comply with rigorous criteria including a minimum 95% successful follow-up rate [8]. To date, the SEER database remains the most widely used tool for assessing cancer incidence and survival rates [9].

Demographic, clinicopathological, therapeutic, and survival data was retrieved from the Research Plus Data 18 released in April 2021. Data from patients diagnosed between 2000 and 2018 was obtained using the SEER*Stat version 8.4.0. For certain variables such as metastases to distant sites, the analysis was restricted to the period from 2010 onwards, as these variables were not available before. A total of 297 patients diagnosed with dedifferentiated chondrosarcoma by positive histology according to the ICD-O-3 classification were extracted from the database. Inclusion criteria included primary location in the bone, location in the upper or lower limbs, and fulfillment of criteria for primary tumor by international rules. We excluded 63 patients due to incomplete follow-up data and tumor location not on the upper or lower limb, and 29 patients due to missing metastatic data. Axial location of the tumor (spine and pelvis) was excluded due to direct contradiction between the SEER database and the available literature on the prognosis of axial DDC, which might be misleading to the reader. At the end, 205 patients (69% of total) were included.

Demographic variables included patient age, gender, race, marital status, and follow-up time. Clinicopathological variables included primary location of the tumor, laterality, TNM stage, AJCC stage (8th edition), histological grade, current status (live or dead), history of previous malignancy, and cause of death, when appropriate. Although LN involvement is commonly considered loco-regional metastasis, the SEER database differentiates between regional and distant LN involvement. The variable LN compromise/involvement, an important component of this analysis, refers uniquely to the regional LN. Distant LN involvement, referring to compromise of LNs that do not directly drain tumor, are instead classified into the metastasis variable. Regarding metastatic disease, the SEER database only displayed information on metastasis located in the lung, liver, brain, bone, and distant lymph nodes. Metastases located in different sites to the aforementioned were displayed in the "Other sites" category and their specific anatomical location could not be retrieved due to database limitations.

Regarding surgery to the primary site, the SEER database was rather imprecise defining the criteria for each non-amputation procedure such as resection and excision. We therefore defined 2 categories for the variable surgery to the primary site: limb-salvage procedure and amputation. Additionally, we assessed surgery to the lymph nodes, surgery to another distant site (indirect for surgery to the metastasis), radiotherapy and chemotherapy.

2.1. Statistical analysis

Statistical analysis was performed using Stata software (StataCorp LLC, Texas, USA). Demographic and clinical characteristics were analyzed using descriptive statistics. Overall 1, 2 and 5-year survival was calculated using the Kaplan-Meier method. Survival difference was assessed using the log-rank test.

Multivariate analysis was performed using Cox proportional hazard regression to determine significant risk factors for metastases. Additional multivariate analysis was also performed to identify risk factors for overall death among patients with dedifferentiated chondrosarcoma. Variables analyzed in the multivariate analysis included age at diagnosis, gender, history of previous malignancy, primary tumor location, TNM stage, metastatic pattern, surgery to the primary site, LN and/or another site, and use of chemotherapy and/or radiotherapy. A *p* value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Patient demographic and clinical characteristics

We analyzed a total of 205 patients, out of which 61 (24.9%) had metastatic DDC at diagnosis. Among patients with metastatic DDC, median age was 68 years, median follow-up 6 months and 47.1% (24/51) of them were male (Table 1). Patients with non-metastatic DDC had a slightly higher median age, 70.5 years, median follow-up was longer (10 months) and the male population predominated (57.8%, 89/154). Caucasian/White was the most common race among both non-metastatic (85.7%, 132/154) and metastatic (76.5%, 46/51) DDC, followed by Hispanic race.

The most common tumor location was the lower limb in patients with either metastatic (76.5%, 39/51) or non-metastatic (69.5%, 107/154) disease. The laterality of the primary tumor slightly favored the right in patients with non-metastatic DDC (51.3%, 79/154), and the left in patients with metastatic disease (51%, 26/51); however, the differences were not statistically significant ($p = 0.339$).

Regarding the TNM score, 68% (34/50) of patients with metastatic disease had a tumor > 8 cm (T2 score) in its largest dimension. In comparison, 54.5% (84/154) of patients without metastases had a T2 score. T3 score, which indicates discontinuous tumors in the primary bone site, was rather uncommon in both non-metastatic (3.2%, 5/54) and metastatic (6%, 6/50) groups. There was no significant difference in the rates of regional LN involvement between patients with and without metastases ($p = 0.968$). In patients with metastatic DDC, 52.9% (27/51) had lung metastases (M1a score) and 43.1% (22/51) had metastases to the bone or other distant sites (M1b score). History of previous malignancy was reported in 13.7% (7/51) and 20.8% (32/154) of patients with and without metastases, respectively.

We also analyzed what organs were involved by DDC metastases, to the extent allowed by the SEER database (Table 2). Out of 205 patients analyzed, lung was the most commonly affected site (14.6%, 30/205). After the lung, other sites (8.3%, 17/205) and bone (2.9%, 6/205) were most commonly involved.

3.2. Treatment modalities for DDC

Surgery to the primary site occurred more frequently in non-metastatic (94.2%, 130/138) than in metastatic DDC (78.3%, 36/46) (Table 3). Limb-salvage procedures were performed more frequently than amputations. Amputation, including both limb and major amputation, was done in 21.7% of patients in both metastatic and non-metastatic groups.

LN surgery was more common in patients without metastasis, since the frequency of LN involvement was also higher in this group. However, this difference was not statistically significant ($p = 0.09$). Surgery to another distant site was almost 4 times more common in metastatic

Table 1

Demographic characteristics of patients with dedifferentiated chondrosarcoma (DDC) by metastatic status. IQR: interquartile range, AJCC: American Joint Committee on Cancer.

	Total (n = 205)	Non-metastatic DDC (n = 154)	Metastatic DDC (n = 51)	p value
Age* (years)	70 (58–78)	70.5 (60–78)	68 (56–77)	0.417
Follow-up* (months)	9 (5–19)	10 (5–22)	6 (3–9)	0.001
Gender				0.182
Male	113 (55.1)	89 (57.8)	24 (47.1)	
Female	92 (44.9)	65 (42.2)	27 (52.9)	
Race				0.386
Hispanic	25 (12.2)	17 (11.04)	8 (15.7)	
Caucasian/White	171 (83.4)	132 (85.7)	39 (76.5)	
African American	5 (2.4)	3 (1.95)	2 (1.3)	
Asian or Pacific Islander	4 (1.95)	2 (1.3)	2 (1.3)	
Primary location				0.339
Upper limb	59 (28.8)	47 (30.5)	12 (23.5)	
Lower limb	146 (71.2)	107 (69.5)	39 (76.5)	
Laterality				0.778
Right	104 (50.7)	79 (51.3)	25 (49)	
Left	101 (49.3)	75 (48.7)	26 (51)	
T score				0.008
T0	0 (0)	0 (0)	0 (0)	
T1	55 (26.96)	47 (30.5)	8 (16)	
T2	118 (57.8)	84 (54.5)	34 (68)	
T3	11 (5.4)	5 (3.2)	6 (12)	
Tx	20 (9.8)	18 (11.7)	2 (4)	
N score				0.968
N0	192 (93.7)	144 (93.5)	48 (94.1)	
N1	5 (2.4)	4 (2.6)	1 (1.96)	
NX	8 (3.9)	6 (3.9)	2 (3.9)	
M score				<0.001
M0	154 (75.1)	154 (100)	0 (0)	
M1	51 (24.9)	0 (0)	51 (100)	
M1a	27 (13.2)	0 (0)	27 (52.9)	
M1b	22 (10.7)	0 (0)	22 (43.1)	
M1 NOS	2 (0.98)	0 (0)	2 (3.9)	
M1 sub-analysis by primary location	51 (24.9)	0 (0)	51 (100)	
Upper limb	12 (5.9 %)	0 (0)	12 (23.5 %)	
Lower limb	39 (19 %)	0 (0)	39 (76.5 %)	
Stage				<0.001
IA	9 (4.95)	9 (6.8)	0 (0)	
IB	11 (6.04)	11 (8.3)	0 (0)	
IIA	36 (19.8)	36 (27.3)	0 (0)	
IIB	69 (37.9)	69 (52.3)	0 (0)	
III	3 (1.7)	3 (2.3)	0 (0)	
IVA	28 (15.4)	0 (0)	28 (56)	
IVB	26 (14.3)	4 (3.03)	22 (44)	

Table 1 (continued)

	Total (n = 205)	Non-metastatic DDC (n = 154)	Metastatic DDC (n = 51)	p value
Current status				0.005
Alive	55 (26.8)	49 (31.8)	6 (11.8)	
Dead	150 (73.2)	105 (68.2)	45 (88.2)	
History of previous malignancy				0.266
No	166 (81)	122 (79.2)	44 (86.3)	
Yes	39 (19)	32 (20.8)	7 (13.7)	
Cause of death (n = 186)				0.041
Disease-related	126 (84)	84 (80)	42 (93.3)	
Other cause	24 (16)	21 (20)	3 (6.7)	

*Data displayed in Age, Follow-up and Overall survival refers to the median and data between brackets refers to the interquartile range. For the remaining variables, data between brackets refers to the percentage of patients.

Table 2

Associated metastases at the time of diagnosis in patients with dedifferentiated chondrosarcoma.

	Total patients (n = 205)
Lymph node	
Yes	1 (0.5)
No	204 (99.5)
Bone	
Yes	6 (2.9)
No	199 (97.1)
Lung	
Yes	30 (14.6)
No	175 (85.4)
Brain	
Yes	1 (0.5)
No	204 (99.5)
Liver	
Yes	4 (1.95)
No	201 (98.1)
Other sites*	
Yes	17 (8.3)
No	188 (91.7)

*Other sites include any location other than distant lymph node (s), bone, lung, brain and/or liver.

patients (9.8 %, 5/51) than in non-metastatic ones (2.6 %, 4/154). Patients with and without metastases underwent radiotherapy in 17.7 % (9/51) and 17.5 % (27/154) of cases, respectively. Finally, about 37.3 % (19/51) patients with metastatic disease underwent chemotherapy, compared to 29.2 % (45/154) for those without metastases.

3.3. Risk factors for metastases

We conducted a crude and multivariate analysis to determine the risk factors for presenting metastases at diagnosis. Metastasis was defined as the involvement of the distant LN, brain, lung, liver, or bone in any combination. Unfortunately, the SEER database only considers metastases that were detected at the moment of diagnosis; it does not factor in those that developed in the course of the disease. Therefore, we could

Table 3
Treatment characteristics of patients with dedifferentiated chondrosarcoma (DDC) according to metastatic status. Qx: surgery, LN: lymph node(s).

	Total (n = 205)	Non-metastatic DDC (n = 154)	Metastatic DDC (n = 51)	p
Qx to primary site				0.006
None	18 (9.8)	8 (5.8)	10 (21.7)	
Limb-salvage procedure	126 (68.5)	100 (72.5)	26 (56.5)	
Amputation	40 (21.7)	30 (21.7)	10 (21.7)	
LN surgery				0.090
No	190 (92.7)	140 (90.9)	50 (98.04)	
Yes	15 (7.3)	14 (9.1)	1 (1.96)	
Qx to another distant site⁺				0.029
No	196 (95.6)	150 (97.4)	46 (90.2)	
Yes	9 (4.4)	4 (2.6)	5 (9.8)	
Radiotherapy				0.985
No	169 (82.4)	127 (82.5)	42 (82.4)	
Yes	36 (17.6)	27 (17.5)	9 (17.7)	
Chemotherapy				0.283
No	141 (68.8)	109 (70.8)	32 (62.8)	
Yes	64 (31.2)	45 (29.2)	19 (37.3)	

⁺ In the case of metastatic DDC, it usually indirectly indicates surgery to the metastasis.

not assess if certain treatment modalities such as surgery, chemotherapy and/or radiotherapy modified the risk of developing metastases. Instead of identifying risk factors, the odds ratios of these categories indicated

Table 4
Univariate and multivariate analysis for risk factors for metastases at diagnosis in patients with dedifferentiated chondrosarcoma. Dx: diagnosis, Qx: surgery, LN: lymph node(s).

		Crude			Adjusted*		
		OR	95 % CI	p	OR	95 % CI	p
Gender	Male	–	–	–	–	–	–
	Female	1.54	0.82–2.91	0.183	1.97	0.93–4.14	0.075
Age at Dx		0.99	0.97–1.02	0.514	0.99	0.96–1.02	0.653
Primary location	Upper limb	–	–	–	–	–	–
	Lower limb	1.43	0.69–2.97	0.341	1.25	0.55–2.84	0.601
T score	T1	–	–	–	–	–	–
	T2	2.38	1.02–5.56	0.045	2.54	1.03–6.24	0.043
	T3	7.05	1.7–28.7	0.006	7.46	1.69–32.77	0.008
N score	N0	–	–	–	–	–	–
	N1	0.75	0.08–6.87	0.799	0.5	0.05–5.16	0.560
Qx to primary site	No	–	–	–	–	–	–
	Yes	0.22	0.08–0.61	0.003	0.07	0.02–0.28	<0.001
Type of Qx	None	–	–	–	–	–	–
	Limb-salvage procedure	0.21	0.07–0.58	0.003	0.04	0.01–0.22	<0.001
	Amputation	0.27	0.08–0.86	0.027	0.05	0.01–0.32	0.001
LN Qx	No	–	–	–	–	–	–
	Yes	0.2	0.03–1.56	0.125	0.13	0.01–1.29	0.081
Chemotherapy	No	–	–	–	–	–	–
	Yes	1.44	0.74–2.8	0.284	1.28	0.54–3	0.575
Radiotherapy	No	–	–	–	–	–	–
	Yes	1.01	0.44–2.31	0.985	1.33	0.53–3.31	0.543
Previous malignancy	No	–	–	–	–	–	–
	Yes	0.61	0.25–1.47	0.269	0.81	0.29–2.22	0.678

*Adjusted for gender, age, marital status, race, primary location, T score, N score and previous malignancy.

the likelihood of these treatments occurring in patients with metastatic disease.

Crude analysis showed that a high T score (T2 and T3) significantly modified the rate of metastatic disease (Table 4). On multivariate analysis, patients with a tumor > 8 cm (T2) were 2.54 times more likely to present metastatic disease at diagnosis (OR = 2.54, p = 0.043); for those with discontinuous tumor in the bone (T3), the risk was 7 times higher (OR = 7.46, p = 0.008). Surgery to the primary site was less likely to occur when metastatic disease was present (OR = 0.07, p < 0.001); the same pattern was found on LN surgery (OR = 0.13, p = 0.081).

3.4. Risk factors for overall death

We additionally reviewed what factors directly affected patient survival, specifically overall death as the sample was too small to assess disease-specific death. In order to assess correctly if any treatment modality modified the risk of death, we analyzed these variables on metastatic and non-metastatic DDC separately.

On crude analysis, we found that age at diagnosis and metastatic status (M score) significantly impacted overall death rates (Table 5). Our adjusted analysis showed that the female gender was a protective factor for overall death (OR = 0.33, p = 0.019). Patients with metastatic disease (M1) were 18.2 times more likely to die (OR = 18.2, p < 0.009). We also performed a sub-analysis of the M1 status, to determine if having an M1a or M1b score significantly affected overall death rates. Patients with M1b score were 49 times more likely to die (OR = 49, p = 0.01), compared to 15.81 times in the case of M1a score (OR = 15.81, p = 0.081).

When we analyzed treatment modalities as modifiers of the risk of death, we only found radiotherapy to be statistically significant in patients with non-metastatic DDC (OR = 6.04, p = 0.008). This does not indicate that radiotherapy increases the risk of dying; rather, it states that radiotherapy was utilized more frequently in patients with advanced disease, who had a higher risk of death due to the intrinsic progression of the tumor.

Table 5

Univariate and multivariate analysis for risk factors for overall death among patients with dedifferentiated chondrosarcoma. Dx: diagnosis, Qx: surgery, LN: lymph node(s).

		Crude			Adjusted*		
		OR	95 % CI	p	OR	95 % CI	p
Gender	Male	–	–	–	–	–	–
	Female	0.87	0.48–1.57	0.644	0.33	0.13–0.84	0.019
Age at Dx		1.03	1.01–1.05	0.007	1.05	1.01–1.09	0.018
Primary location	Upper limb	–	–	–	–	–	–
	Lower limb	0.81	0.42–1.58	0.540	0.95	0.36–2.46	0.912
T score	T1	–	–	–	–	–	–
	T2	1.33	0.65–2.62	0.449	1.2	0.46–3.08	0.710
	T3	0.97	0.26–3.66	0.968	0.97	0.13–7.26	0.978
N score	N0	–	–	–	–	–	–
	N1	0.56	0.09–3.43	0.528	2.95	0.13–65.14	0.493
M score	M0	–	–	–	–	–	–
	M1	3.5	1.4–8.75	0.007	18.2	2.04–162.5	0.009
M score sub-analysis (M1a/b)	M0	–	–	–	–	–	–
	M1a	2.68	0.88–8.18	0.083	15.81	0.71–350.62	0.081
	M1b	9.8	1.28–74.96	0.028	49	2.56–938.65	0.010
Previous malignancy	No	–	–	–	–	–	–
	Yes	1.97	0.83–4.69	0.124	1.15	0.35–3.71	0.821
Non-metastatic DDC							
Qx to primary site ⁺	No	–	–	–	–	–	–
	Yes	0.29	0.03–2.44	0.255	0.48	0.05–4.31	0.512
Type of Qx ⁺	None	–	–	–	–	–	–
	Limb-salvage procedure	0.29	0.03–2.46	0.256	0.55	0.06–5.16	0.602
LN Qx ⁺	Amputation	0.29	0.03–2.65	0.271	0.58	0.06–5.98	0.648
	No	–	–	–	–	–	–
Qx to other distant sites ⁺	Yes	1.18	0.35–3.98	0.785	1.56	0.44–5.49	0.488
	No	–	–	–	–	–	–
Chemotherapy ⁺	Yes	1.41	0.14–13.93	0.768	1.5	0.13–17.56	0.747
	No	–	–	–	–	–	–
Radiotherapy ⁺	Yes	0.68	0.33–1.42	0.309	1.01	0.44–2.35	0.981
	No	–	–	–	–	–	–
	Yes	4.54	1.3–15.91	0.018	6.04	1.59–22.98	0.008
	No	–	–	–	–	–	–
Metastatic DDC							
Qx to primary site ⁺	No	–	–	–	–	–	–
	Yes	0.8	0.08–7.73	0.847	0.67	0.06–7.17	0.738
Type of Qx ⁺	None	–	–	–	–	–	–
	Limb-salvage procedure	0.85	0.08–9.3	0.895	0.69	0.05–8.86	0.777
LN Qx ⁺	Amputation	1	0.05–18.57	1.00	0.7	0.03–14.76	0.817
	No	–	–	–	–	–	–
Qx to other distant sites ⁺	Yes	–	–	–	–	–	–
	No	–	–	–	–	–	–
Chemotherapy ⁺	Yes	0.14	0.02–1.12	0.064	0.16	0.01–1.84	0.140
	No	–	–	–	–	–	–
Radiotherapy ⁺	Yes	0.55	0.1–3.06	0.496	0.74	0.09–5.85	0.776
	No	–	–	–	–	–	–
	Yes	–	–	–	–	–	–
	No	–	–	–	–	–	–

*Adjusted to all variables included, with the exception of ⁺variables which were adjusted for gender, primary location, previous malignancy.

3.5. Overall survival according to AJCC stage and treatment approach

We additionally described the overall survival of patients with DDC according to AJCC stage and treatment modality (Table 6). On Kaplan-Meier survival estimates, there was a tendency towards higher overall survival in patients that received a combination of surgery and chemotherapy in the non-metastatic group (Fig. 1A and B). Due to the small sample size included in our analyses, this tendency was not significant. In the metastatic group, we did not see any difference in survival patterns according to treatment modalities.

4. Discussion:

4.1. Patient demographics and clinical characteristics

We reported a median age of diagnosis of 70 years and a slight male predominance. In comparison, the European Musculo Skeletal Oncology Society (EMSOS) found that DDC affected younger men, with a median

age of presentation of 59 years [7]. Out of the 205 patients included in this study, 24.9 % presented with metastases at the time of diagnosis, similar to the 21 % reported by the European group and lower than the 36 % reported by a Norwegian national cohort [3,7]. Median follow up periods were shorter in metastatic patients than in non-metastatic ones (6 and 10 months, respectively). This is consistent with previous studies and is probably secondary to referrals to palliative facilities and less overall survival [7].

Regarding the tumor primary location, our study only included tumors in the upper or lower limb, excluding those located in the spine or pelvis. Retrospective studies of pelvic chondrosarcoma (including DDC) have reported worse survival outcomes for axial tumors (pelvis and spine) compared to those located in the limbs [7,10,11]. In a multicenter study of 337 patients with DDC, Grimer *et al* found axial location of the tumor as a significant risk factor for death (p = 0.016) [7]. This is explained occurs due to the complexity of the pelvis and close proximity to neurovascular structures, which makes it more difficult to achieve adequate margins, this leading to higher rates of recurrence and

Table 6

Overall survival in patients with dedifferentiated chondrosarcoma according to AJCC stage 8th Edition and treatment modality. QT: chemotherapy, RT: radiotherapy. Data displayed between brackets refers to the 95% confidence interval (CI).

	Median (months)	1-year	2-year	5-year
AJCC stage				
Stage I	10 (5–20)	50 % (27.1–69.2)	23.1 % (7.8–43)	21.1 % (6.6–41)
Stage II	14 (7–)	58.8 % (48.5–67.7)	38.2 % (28.5–47.8)	30.8 % (21.7–40.3)
Stage III	–	66.7 % (5.4–94.5)	60 % (2.5–93.2)	50 % (0.6–91)
Stage IV	7 (3–14)	28.9 % (17.3–41.4)	14.6 % (6.6–25.5)	8.9 % (3.1–18.7)
Treatment				
Surgery only	9 (4–39)	44.4 % (35.5–52.8)	28.3 % (20.6–36.6)	20.9 % (14.1–28.6)
Surgery + QT	14 (8–)	63.1 % (48.5–74.6)	38.6 % (25.4–51.7)	29.2 % (17.2–42.3)
Surgery + RT	10 (5–25)	48.7 % (25.8–68.3)	28.2 % (10.9–48.5)	12.8 % (2.7–31.1)
Surgery + QT + RT	13 (6–22)	60 % (31.8–79.7)	20 % (4.9–42.4)	13.3 % (2.2–34.6)

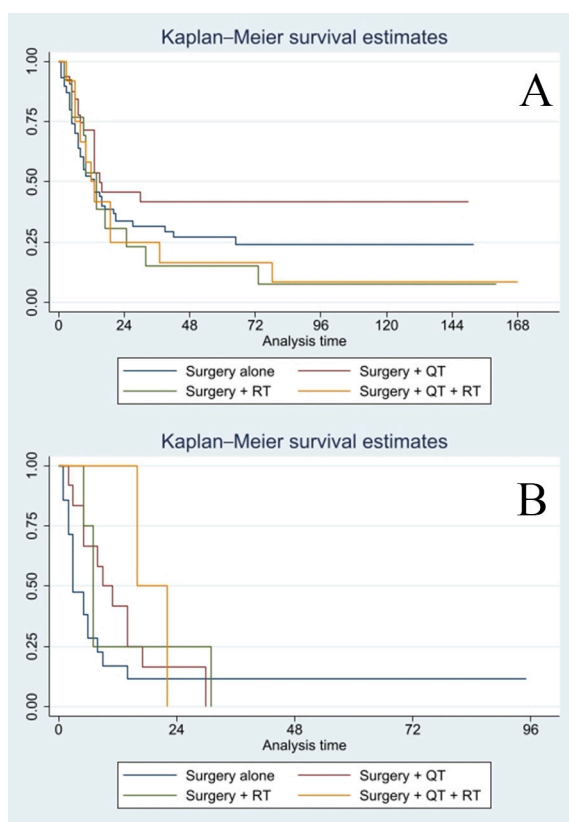


Fig. 1. Kaplan-Meier overall survival estimated for patients dedifferentiated chondrosarcoma according to treatment modality with (A) non-metastatic and (B) metastatic dedifferentiated chondrosarcoma according to treatment modality. In both cases, differences were not significant when performing the Log-rank test*. QT: chemotherapy, RT: radiotherapy. *Log-rank analysis non-metastatic: (a) For the entire sample: $p = 0.2283$, (b) For Surgery alone vs Surgery + QT: $p = 0.1069$. *Log-rank analysis metastatic: (a) For the entire sample: $p = 0.3845$, (b) For Surgery alone vs Surgery + QT: $p = 0.1703$.

metastatic disease [12]. However, a recent study based on the SEER database found axial location as a protective factor for disease-specific death [6]. We corroborated the findings reported by Strotman *et al* on their study running an independent statistical analysis of our included sample. In light of this findings, we concluded that the improved survival found in pelvic DDC in the SEER database is misleading and in disagreement with the ample literature published on the topics, probably due to confounding factors not displayed in the database. We decided to restrict our analysis to extremity DDC to avoid potential confusions on the topic.

Lower limb tumors were the most frequent in both metastatic and non-metastatic disease, affecting the right and left side equally. Appendicular tumors have been described more frequently than axial ones (87 % and 13 %, respectively) [3]. Studies have indicated that the femur is the most common location (46 %), followed by the pelvis (28 %) and the humerus (11 %). Other locations have also been described but their frequencies are much lower [7].

Regarding tumor size, patients with metastatic disease presented a higher frequency of T2 (>8cm) tumors than non-metastatic patients (68 % and 54.4 %, respectively). Similarly, Kozawa *et al* reported that T2 score was the most common among primary DDC tumors [13]. It has already been reported that DDC have a statistically significant larger average size than other classes of bone sarcomas (108.2 mm) [14]. In comparison, the European group described tumor size without TNM score and found a median size of 12.6 cm (range of 4–25 cm) [7].

We found that metastasis most commonly occurred in the lung (14.6 %), followed by other sites (8.3 %) and bone (2.9 %). These results agree with previous studies that also reported a predominance of lung metastases (61 %), followed by skeletal system metastases (17 %) and other sites (22 %) [15].

Although it could not be assessed in our study, determining the high-grade component of DDC and the area of the tissue it involves can affect the patient’s prognosis. The high-grade component most frequently has the aspect of an osteosarcoma, followed in frequency by fibrosarcoma, malignant fibrous histiocytoma (MFH) and anaplastic spindle cell sarcoma [16]. In addition, a classical bimorphic histological appearance with the presence of low-grade chondrosarcoma next to high-grade sarcoma is expected [7].

4.2. Treatment modalities for DDC

Overall, surgery to the primary site was more frequently performed in non-metastatic (94.2 %) than in metastatic patients (78.3 %). This probably occurred due to the tumor being classified as unresectable, poor patients prognosis or severe medical comorbidities in metastatic patients [6].

Limb-salvage procedures were preferred over amputations, the latter being performed with similar rates metastatic and non-metastatic patients. At the moment, there is no evidence showing a certain surgery type may have an impact in survival, although clear surgical margins are associated with better local control. According to the principles of sarcoma surgery, wide margins are mandatory in patients with DDC [16]. Patients with axial DDCs achieve adequate surgical margins less commonly than those with appendicular tumors. Despite amputation traditionally achieved better surgical margins than limb salvage procedures, this data remains controversial in the context of chondrosarcoma [7].

Staals *et al* found that patients undergoing limb sparing surgery tended to have better outcomes, but this difference was not statistically significant [16]. In highly aggressive tumors such as DDC, achieving adequate surgical margins is extremely important to minimize the risk of local recurrence. On the other hand, no increased risk of local recurrence has been found with pathological fractures, axial tumors or limb-salvage procedures [7].

Regarding the use of chemotherapy, our study found that chemotherapy was more frequently employed in metastatic patients (37.3 %)

than in non-metastatic ones (29.2 %). Chondrosarcomas have been traditionally considered chemotherapy-insensitive, particularly high-grade dedifferentiated DDCs with a more aggressive and malignant behavior [15]. However, the utility of chemotherapy in DDC is controversial. Several old retrospective studies found no significant benefit in the rate of disease-free survival [6,7,16,17]. Additionally, the toxicity of chemotherapy regimens especially in elder patients and the lack of evidence regarding its benefits at the time made authors reluctant to recommend it as standard treatment [7].

Recent studies have described positive results when chemotherapy is added to the treatment regimen [15,16,18]. The EURO-BOSS clinical trial reported that a regimen of doxorubicin, ifosfamide and cisplatin, with a possible addition of methotrexate, achieved a 5-year overall survival of 39 %, which is significantly higher than the ones previously reported ranging 10–24 % [19]. The toxicity of this regimen was evaluated and deemed considerable but manageable, with no toxic deaths reported. Thus, the concept that DDC tumors are always associated with a poor prognosis and are chemotherapy-resistant should be reassessed. Selected patients with a complete surgical remission at all sites could achieve long term survival [15].

Seventeen percent of our patients, irrespective of their metastatic status, underwent radiotherapy. Chondrosarcomas are also considered relatively radiotherapy-resistant due to their hypoxic nature and low mitotic rate [6]. In particular, dedifferentiated, poorly differentiated, and mesenchymal chondrosarcomas have a worse prognosis and are classified as unfavorable for radiotherapy [20]. Difficulties such as the persistent radiologic defect post-irradiation and the delayed clinical regression also make follow-up and response assessment difficult. Additionally, palliative irradiation in low doses has shown to be ineffective [21].

Although some reports describe limited local benefit from irradiation, conclusions about permanent local control cannot be drawn due to rapid disease progression and early death. In the setting of surgical resection with inadequate margins, adjuvant irradiation postoperatively may be of value, especially in axial tumors where surgical tumor-control is complicated and rates of local recurrence are higher [21].

4.3. Risk factors for metastases

Our multivariate analysis identified T2 and T3 scores as risk factors for presenting metastatic disease at diagnosis (OR = 2.54, $p = 0.043$ and OR = 7.46, $p = 0.008$ respectively). This association agrees with other studies results, where a larger (T2) or discontinuous tumor (T3) occurred more commonly in metastatic patients than non-metastatic ones [7,13]. Although not described by us, pelvic tumors are also associated with higher rates of metastatic disease and can be considered a risk factor for metastasis at diagnosis. Compared to appendicular tumors, pelvic tumors are considerably larger in size and have a lower survival rate [22].

Regarding the likelihood of certain treatment modalities in patients with metastatic disease, our multivariate analysis showed metastatic disease made it less likely to undergo surgery to the primary site, both limb-salvage and amputation, and less likely to undergo lymph node surgery. These associations describe the impact that metastasis at the diagnosis have on treatment approach [6].

4.4. Risk factors for overall death

Our additional multivariate analysis showed that female gender was a protective factor for overall death. As expected, presence of metastases at diagnosis was risk factor for overall death. Additional risk factors for dying identified on previous retrospective studies include older age at diagnosis, axial location, presentation with a pathological fracture and inadequate surgical margins [7].

Unfortunately, our adjusted analysis did not include tumor grade. Staals *et al* described that patients with a high-grade component of

fibrous histiocytoma had a worse prognosis. Likewise, they performed Kaplan-Meier survival curves and found that patients with >50 % dedifferentiated component had a median survival of 8 months and that patients with ≤50 % that had a higher median survival of 23 months [16]. Both the percentage of dedifferentiation and metastatic disease at presentation are expected predictors of overall survival, considering the rapid progression of DDC. The transition from a usually low grade, slow-growing, cartilaginous tumor to a highly malignant tumor requires a rapid increase in the differentiated component causing distant metastatic disease and rapid death [16].

Even though our database did not include pathological fractures at the time of diagnosis, they have been reported to occur in 16 % of patients with DDC, with a frequency significantly higher in long bone tumors (29 %) than in axial ones (29 % and 2 %, respectively) [7,13]. Pathological fractures have been considered a poor prognostic factor due to bleeding and tumor dissemination caused by them [13].

4.5. Overall survival according to AJCC stage and treatment approach

Finally, we described overall survival according to AJCC stage and treatment modality. As expected, stage IV DDC presented lower 1, 2, and 5-year overall mortality with a median survival time of 7 months. Similarly, Grimer *et al* found a median survival of 5 months for metastatic disease and a 10 % 2-year survival [7].

Since patient outcomes differed according to metastatic status, we performed independent Kaplan-Meier analysis for non-metastatic and metastatic patients. Only in patients without metastasis did the Kaplan-Meier survival estimates show a trend towards higher overall survival in patients that received a combination of surgery and chemotherapy; this, however, was not significant. This finding highlights the possible beneficial role that chemotherapy might play in the treatment of certain patients with DDC. Although traditionally deemed chemotherapy-insensitive, newer studies have shown some benefits with the addition of chemotherapy to the treatment of a specific subset of patients with DDC [15,16,18]. In this regard, the SEER database does not specify the chemotherapy regimen that each patient underwent and it is thus not possible to conclude whether there is a survival benefit associated with it [15].

4.6. Limitations of the study

Due to the nature of the SEER database, several limitations must be noted. Our analysis of risk factors for development of metastases was restricted to metastases present at the moment of diagnosis, which limits the external validity of the analysis as many metastases develop in the course of the disease. In addition, classification of the surgical treatment was not specific enough and we resorted to only analyzing limb-salvage and amputation procedures. Likewise, in patients with multiple metastases who had surgery to the distant site, what metastatic organ was treated could not be identified. Specific information on radiation and systemic treatment schemes was not available. Finally, when analyzing the factor “previous malignancy”, we could not identify the location of that previous malignancy and whether it was in the same or a different location to the current tumor.

5. Conclusions and final considerations

DDC is a rare bone neoplasm with an extremely high metastatic rate. Patients with newly diagnosed DDC should be educated on the highly aggressive nature of the tumor and their expectations managed accordingly. Treatment consists of either a limb-salvage procedure or limb amputation, the former being more common. Despite the highly aggressive behavior of DDC, the nature of the treatment (amputation or limb-salvage surgery) did not significantly alter patient survival. However, further analysis is required in this field adjusting for variables such as the adequacy of surgical margins. Furthermore, in the setting of a

dismal prognosis, treatment approach should also consider preserving the patient functional status and quality of life. Tumor size was the most important risk factor for presenting metastasis at diagnosis. Females with DDC were less likely to die. In non-metastatic patients, combination of surgery and chemotherapy showed a trend for increased survival when compared to other treatment modalities; however, this was not statistically significant. For all disease stages, less than half the patients were alive after 5 years.

CRedit authorship contribution statement

Marcos R. Gonzalez: Methodology, Investigation, Writing – original draft, Visualization, Project administration. **Mayte Bryce-Alberti:** Investigation, Writing – original draft. **Arianna Portmann-Baracco:** Data curation, Formal analysis. **Maria L. Inchaustegui:** Writing – original draft. **Samy Castillo-Flores:** . **Juan Pretell-Mazzini:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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