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Original contribution

Parosteal osteosarcoma: a monocentric retrospective analysis of 195 patients☆,☆☆

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Summary Parosteal osteosarcoma is a low-grade malignant bone tumor that can undergo dedifferentiation. The aim of this study was to analyze clinicopathologic features associated with clinical outcome in a large cohort of patients. Patients consecutively treated for parosteal osteosarcoma at Rizzoli Orthopedic Institute from 1900 to 2018 were reviewed and analyzed. Clincopathologic data of 195 patients with parosteal osteosarcoma were analyzed. Age at diagnosis ranged from 9 to 75 years (median 31). Median follow-up time was 150 months (range, 3-720). The most common tumor locations were femur (61.5%), humerus (15.9%) and tibia (12.8%). Wide surgical margins were achieved in 125 (64.1%) patients. Medullary involvement was present in 69 (35.4%) cases. Dedifferentiation occurred in 48 (24.6%) patients. Forty-five patients developed recurrence (23.1%; median time to recurrence of 36 months). At last follow-up, 155 (79.5%) patients were alive and without evidence of disease, 8 (4.1%) were alive with active disease, 23 (11.8%) died from disease, and 9 (4.6%) from unrelated causes. Patients with dedifferentiated parosteal osteosarcoma had worse 5-year (65% versus 96%) and 10-year survival (60% versus 96%) when compared to conventional tumors ($P < .001$). Wide surgical margins had positive impact on both disease-free ($P < .001$) and overall survival ($P = .036$). Medullary involvement, age at presentation and tumor size had no impact on survival. Dedifferentiation is the most important factor that negatively impacts clinical outcome. Surgical aim is to ensure radical removal with wide surgical margins to improve disease-free survival.

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1. Introduction

Parosteal osteosarcoma is a low-grade, malignant bone tumor that usually arises on the metaphyseal surface of long bones. It accounts for about 4% of all osteosarcomas and, although rare, it is the most common type of osteosarcoma of the bone surface [1]. Approximately 8% to 25% of the cases reported in literature developed dedifferentiation, which was reported to had increase metastatic rate in comparison with conventional parosteal osteosarcoma, although other clinicopathologic features were not clearly described [1-3].

Medullary involvement is another important feature of parosteal osteosarcoma and has been reported in 7% to 65% of the cases in literature [2-8]. Data on its prognostic significance are still controversial. According to recent studies with large number of patients and long-term follow-up, its presence does not seem to have an impact on local recurrence, metastasis or survival [2-5,7].

Adequacy of surgical margins appears to be the most important prognostic factors, since inadequate margins were reported to associated with local recurrence [2-8], dedifferentiation and metastases [2,4,5] and, therefore, appeared as a negative predictor of patient survival.

However, these data should be verified on a large series of parosteal osteosarcoma with a long-term follow-up period. To date, only 2 studies appear adequate for number of cases enrolled and duration of follow-up [4,5].

Based on these premises, aim of this study was to evaluate the role of medullary involvement, status of surgical margins and presence of dedifferentiation on patient survival after surgery on a large cohort of patients.

2. Materials and methods

2.1. Patients

Clinical, radiological, treatment and follow-up information of all 225 cases of parosteal osteosarcoma treated at the Rizzoli Orthopedic Institute of Bologna, Italy, from 1900 to 2018 were retrospectively collected. Only patients with adequate material available for the histological examination, according to the criteria published by the World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone, were included in the study [1]. Twenty-nine cases had been reported in a previous study [3]. In particular, the World Health Organization endorses to use of a two-tier system designating a parosteal osteosarcoma as low-grade or high-grade/dedifferentiated [1]. Moreover, we analyzed four-titer histological grading in both conventional and dedifferentiated parosteal osteosarcoma, based on the highest grade identified in any component of the resected tumor, applying Broders grading system [9]. Surgical margins were defined according to the Enneking score system [10]. Wide surgical margins were considered as adequate (negative), whereas marginal and intralesional margins were considered as inadequate (positive). A wide surgical margin procedure was recognized when a cuff of normal tissue completely encased the tumor. In the case of intramedullary extension, a wide margin was given when the segment of bone with extension of the tumor was completely excised. A marginal margin was recognized when a free margin of normal cortex and marrow was seen microscopically between the tumor and the bone. The presence of intramedullary extension of the tumor was evaluated by analyzing the pathologic materials and was defined as extension of the tumor into the medullary cavity identified from the specimen following excision. Following the criteria reported to Okada et al [4], we adopted less than 25% of medullary canal involvement to distinguish parosteal osteosarcoma with medullary canal involvement from

Table 1 Main clinicopathologic patient data (n = 195)

Features	Patients, n (%)
Gender	
Male	80 (41.0%)
Female	115 (59.0%)
Median age, years (range)	31 (9-75)
Site, lower extremities	
Total	155 (79.5%)
Femur	120 (61.5%)
Tibia	25 (12.8%)
Fibula	9 (4.6%)
Metatarsal bone	1 (0.5%)
Site, upper extremities	
Total	39 (20.0%)
Humerus	31 (15.9%)
Radial	3 (1.5%)
Ulnar	3 (1.5%)
Ribs	1 (0.5%)
Scapula	1 (0.5%)
Site, Pelvis (iliac wing)	1 (0.5%)
Mean tumor size, cm (range)	7.6 (1.2-29)
Surgical margin	
Wide	125 (64.1%)
Marginal	41 (21.0%)
Intralesional	29 (14.9%)
Histological grading according Broders' system	
Grade 1	119 (61%)
Grade 2	28 (14.4%)
Grade 3	0 (0%)
Grade 4	48 (24.6%)
Medullary involvement	
Yes	69 (35.4%)
No	126 (64.6%)
Recurrence	
No. of recurrences	45 (23.1%)
Median time to relapse, months (Range)	36 (4-360)
Metastasis	
No. of metastases	37 (19.0%)
Median time to metastasis, months (Range)	20 (3-240)

central conventional osteosarcoma with extracortical extension. All the patients that received neoadjuvant chemotherapy followed the MAP regimen (methotrexate, doxorubicin and cisplatin with the addition of ifosfamide in poor-responder patients).

All procedures were performed in accordance with the ethical standards of the Helsinki Declaration. The study was approved by the ethical institutional committee on November 12, 2018 (study code: AVEC 618/2018/Oss/IOR).

2.2. Immunohistochemical analysis

Immunohistochemical analysis was performed using MDM2 (Mouse monoclonal antibody clone IF2, Invitrogen, Carlsbad, CA, USA 1:50 dilution) and CDK4 (Mouse monoclonal antibody clone DCS-31, Invitrogen, Carlsbad, CA, USA 1:200 dilution) antibodies following a previously reported technique and using the same score [11]. Briefly, appropriate positive and negative controls were included in each run. Only nuclear stains of neoplastic cells were considered as positive results. CDK4 usually stained both the nuclei and cytoplasm.

2.3. Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) was performed using the SPEC MDM2/CEN 12 Dual Color Probe (ZytoVision GmbH, Bremerhaven, Germany) according to the manufacturer's protocol as previously reported [11]. Cases were scored by counting a minimum of 100 tumor cell nuclei at 100× of magnification with a DAPI/green/red triple band pass filter. The number of MDM2 and CEP12 signals was determined and a MDM2/CEP12 ratio was calculated for each nuclei. A ratio >2.0 in at least 10% of nuclei, was considered amplified for the *MDM2* gene.

2.4. Statistical analysis

Patient clinical and demographic characteristics were compared using χ^2 or t test whenever appropriate; $P \leq .05$ was considered significant. The median time to recurrence and to metastasis were compared between groups using the Mann-Whitney U test. In survival analysis, subgroups of patients were compared by estimating Kaplan-Meier survival functions, and using log-rank tests and the likelihood test of homogeneity.

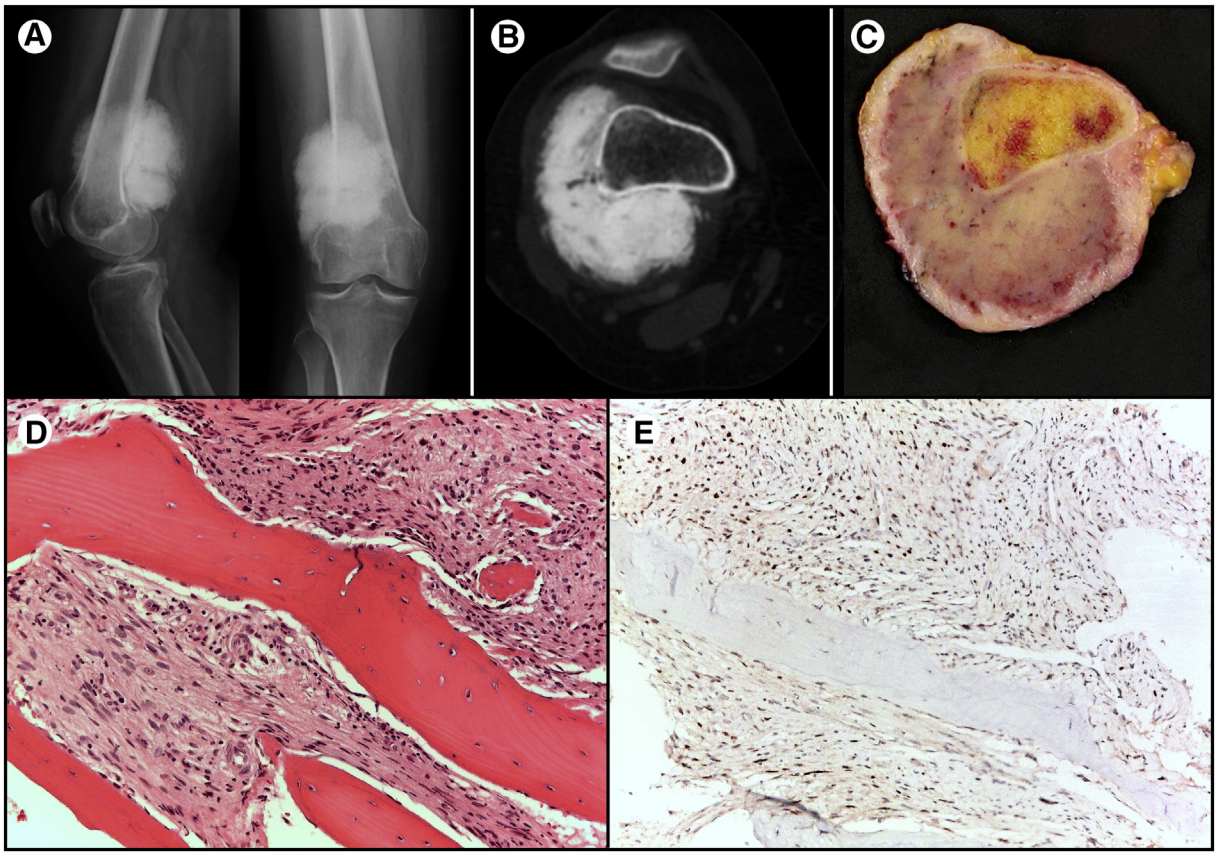

Figure 1 A and B, Conventional parosteal osteosarcoma. Computed tomography scan of distal tibia shows exophytic tumor with extensive mineralization wrapped around the tibial surface. C, Macroscopically, tumor appears as gray-white, hard, lobulated mass. D, Tumor is composed of deceptively bland-looking spindle cell admixed with well-formed trabecular bone embedded on dense collagenous stroma (H&E, original magnification ×200). E, Neoplastic cells show positivity for MDM2 immunohistochemistry (original magnification ×200).

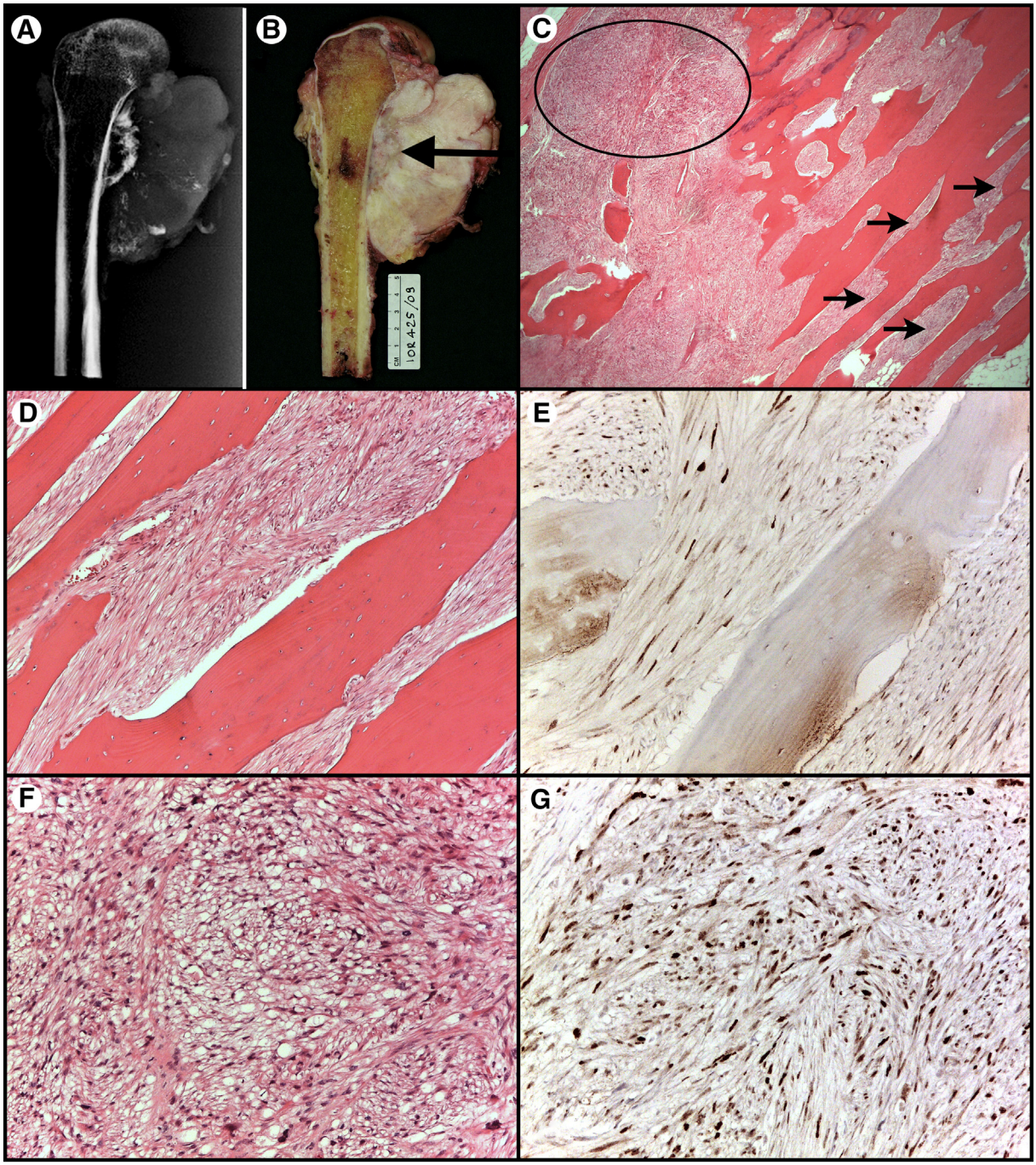

Figure 2 A, Dedifferentiated parosteal osteosarcoma. Deep radiolucent area within otherwise heavily mineralized tumor is suggestive of dedifferentiation. B, On gross examination, dedifferentiated part, correspond to radiolucent area, appears as soft myxoid area (arrow) compared to solid area of conventional tumor. C, Histologically, dedifferentiation is characterized by sharp demarcation between low-grade spindle cells area (arrows) and high-grade, more cellular areas (circle) (H&E, original magnification ×50). Low-grade area (D) shows deceptively bland-looking spindle cells between well-formed bony trabeculae (H&E, original magnification ×200). High-grade area (F) shows more increased cellularity with more nuclear hyperchromasia and pleomorphism (H&E, original magnification ×200). Both components (E and G) show nuclear positivity for MDM2 immunohistochemistry (MDM2, original magnification ×200).

Table 2 Clinical-pathological comparison between conventional and dedifferentiated parosteal osteosarcoma

Features	Conventional POS (n = 147)	Dedifferentiated POS (n = 48)	Test, *P*-value
Gender, n (%)			
Male	60 (40.8%)	20 (41.7%)	$\chi^2 = 0.01$, $P = .917$
Female	87 (59.2%)	28 (58.3%)	
Median age, years (range)	31 (9-75)	33 (13-65)	$t = -1.03$, $P = .306$
Site, n (%)			
Lower extremities	122 (83.6)	33 (68.7)	$\chi^2 = 4.93$, $P = .026$
Upper extremities	24 (16.4)	15 (31.3)	
Mean tumor size, cm (range)	6.6 (1.2-25)	10.7 (3-29)	$t = -5.47$, $P < .001$
Surgical margin, n (%)			
Wide	99 (67.3%)	26 (54.2%)	$\chi^2 = 3.86$, $P = .145$
Marginal	30 (20.4%)	11 (22.9%)	
Intralesional	18 (12.3%)	11 (22.9%)	
Medullary involvement, n (%)			
Yes	40 (27.2%)	29 (60.4%)	$\chi^2 = 17.45$, $P < .001$
No	107 (72.8%)	19 (39.6%)	
Metastasis			
No. of metastases	7 (4.8%)	30 (62.5%)	$\chi^2 = 78.46$, $P < .001$
Median time to metastasis, months (Range)	36 (4-198)	15.5 (0-240)	
Chemotherapy, n (%)			
Yes	4 (2.7%)	38 (79.2%)	$P < .001$ [a]
No	143 (97.3%)	10 (20.8%)	
Overall survival, % (95% CI)			
5-year OS	96.3% (91.3-98.4)	65.2% (49.6-77.0)	$\chi^2 = 36.58$, $P < .001$
10-year OS	96.3% (91.3-98.4)	60.1% (44.3-72.8)	

Abbreviation: POS, parosteal osteosarcoma.
[a] Fisher's exact test.

3. Results

3.1. Clinical-pathological data

Thirty (13.3%) of the 225 cases collected were excluded due to incomplete clinicopathologic data. The most important data of the 195 remaining cases are summarized in Table 1. In particular, 115 (59.0%) patients were females and 80 (41.0%) were males; mean age at presentation was 31 years (range, 9-75 years). Sixteen (8.2%) patients were younger than 17 years old. Mean tumor size was 7.6 cm (range, 1.2-29 cm). The most common tumor location was the femur (n = 120, 61.5%) followed by humerus (n = 31, 15.9%) and tibia (n = 25, 12.8%); fibula, radius, ulna, ribs, scapula and metatarsal bone accounted for less than 5% of the cases. Medullary involvement was detected in 69 (35.4%) cases. Wide surgical margins were achieved in 125 (64.1%) cases, while 41 (21.0%) and 29 (14.9%) patients had marginal and intralesional surgical margins, respectively. Of 147 conventional parosteal osteosarcoma, 119 (87.8%) were grade 1 and 28 (12.2%) were grade 2 according to Broder's grading system. Forty-eight (24.6%) cases were dedifferentiated parosteal osteosarcoma. All these 48 cases were grade 4 according to Broder's grading system associated with an area of grade 1 conventional parosteal osteosarcoma in 41 cases, and with a grade 2 area in 7 cases. Dedifferentiation was presented at first diagnosis in 32 (16.4%) cases, while it developed after recurrence in 16 (8.2%) cases. Cartilaginous component was identified in 49 cases (25.1%). Thirty-six of them had cartilaginous component at the periphery of the conventional parosteal osteosarcoma, simulating the appearance of an osteochondroma. The remaining 13 cases were dedifferentiated component of parosteal osteosarcoma that showed foci of chondroblastic differentiation.

Immunohistochemical analysis was available in 43 cases and showed a focal nuclear expression of MDM2 in all 43 cases, of these 25 cases of conventional parosteal osteosarcoma and 18 cases of dedifferentiated parosteal osteosarcoma. FISH analysis obtained with a readable signal in 10 out of these 43 cases, confirmed the presence of *MDM2* gene amplification in all 10 cases (5 conventional and 5 dedifferentiated parosteal osteosarcoma). CDK4 immunohistochemical analysis showed a nuclear and cytoplasmic expression in all but one of 43 cases evaluated. The negative case was a conventional parosteal osteosarcoma that was positive for MDM2 expression. The non-informative cases were because of excessive decalcification to process a very heavily ossified, hard mass or of the scant tissue quality (very old tissue blocks).

Recurrences occurred in 45 (23.1%) patients. Median time from treatment to recurrence was 36 months (range,

Table 3 Comparative survival analysis in patients with and without tumor dedifferentiation

	Disease-free survival			Overall survival		
	All patients (n = 195)	C-POS (n = 147)	D-POS (n = 48)	All patients (n = 195)	C-POS (n = 147)	D-POS (n = 48)
Presence of dedifferentiation	$\chi^2 = 7.24$; $P = .007$			$\chi^2 = 45.46$; $P < .001$		
Age ≥ 17 years	$\chi^2 = 2.80$; $P = .094$	$\chi^2 = 3.91$; $P = .048$	$\chi^2 = 1.34$; $P = .247$	$\chi^2 = 1.34$; $P = .247$	$\chi^2 = 1.26$; $P = .262$	$\chi^2 = 0.69$; $P = .407$
Medullary involvement	$\chi^2 = 1.30$; $P = .255$	$\chi^2 = 0.66$; $P = .415$	$\chi^2 = 0.12$; $P = .724$	$\chi^2 = 0.70$; $P = .402$	$\chi^2 = 1.15$; $P = .283$	$\chi^2 = 1.11$; $P = .292$
Tumor size >6 cm	$\chi^2 = 0.02$; $P = .885$	$\chi^2 = 0.01$; $P = .922$	$\chi^2 = 2.74$; $P = .098$	$\chi^2 = 2.11$; $P = .146$	$\chi^2 = 1.24$; $P = .266$	$\chi^2 = 0.07$; $P = .798$
Surgical margin	$\chi^2 = 72.02$; $P < .001$	$\chi^2 = 51.73$; $P < .001$	$\chi^2 = 16.79$; $P < .001$	$\chi^2 = 6.65$; $P = .036$	$\chi^2 = 3.82$; $P = .148$	$\chi^2 = 1.55$; $P = .461$

Abbreviations: C-POS, conventional parosteal osteosarcoma; D-POS, dedifferentiated parosteal osteosarcoma.

4-360 months). Thirty-seven (19%) patients had lung metastases: they were present at first diagnosis in 3 cases, while in 34 developed during the follow-up, with a median time of 20 months (range, 3-240 months). At the last follow-up, 155 (79.5%) patients were alive and disease free, 8 (4.1%) were alive with active disease, 23 (11.8%) had died from disease and 9 (4.6%) had died from unrelated causes.

3.2. Comparison between conventional and dedifferentiated parosteal osteosarcoma

Main differences observed in the comparisons between conventional (Fig. 1) and dedifferentiated parosteal osteosarcoma (Fig. 2) are summarized in Table 2. Dedifferentiated tumor had a predilection for the upper extremities (P =.026), was significantly larger (10.7 versus 6.6 cm, $P < .001$), more frequently involved the medullary canal (60.4% versus

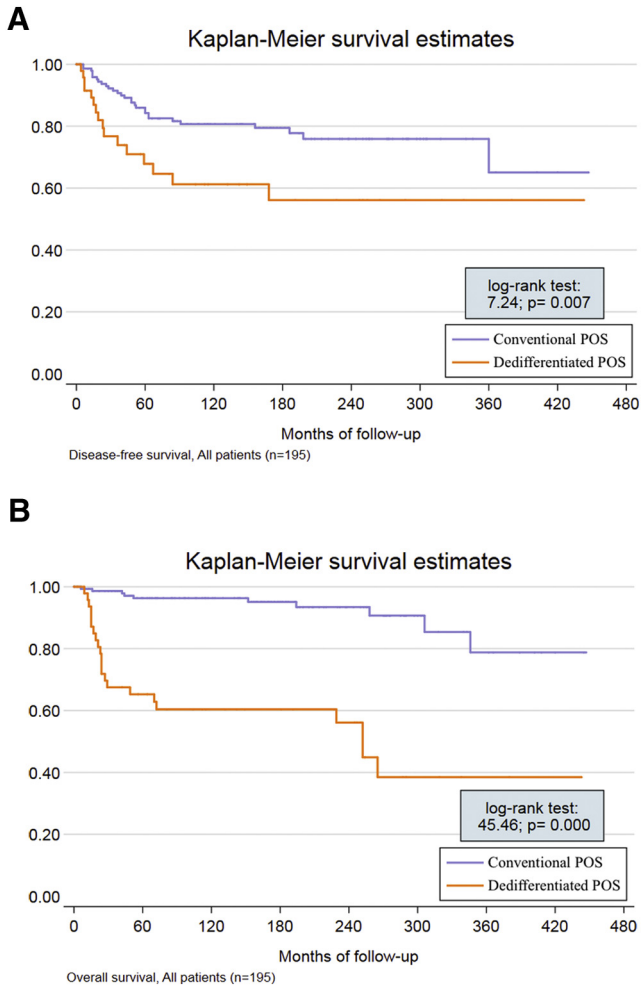

Figure 3 Kaplan-Meier estimate of survival in parosteal osteosarcoma. Difference between disease-free survival and overall survival between conventional and dedifferentiated parosteal sarcoma is shown in panels A and B, respectively.

27.2%, $P < .001$), and had higher metastatic rate (62.5% versus 4.8%, $P < .001$).

Thirty-eight (79.2%) patients with dedifferentiation parosteal osteosarcoma received chemotherapy. Five patients received neo-adjuvant chemotherapy; four of them showed poor treatment response (<90% of tumor necrosis, mean 50%, range 20%–65%), while one showed good treatment response (95% of tumor necrosis). Thirty-three patients received adjuvant chemotherapy after tumor excision.

3.3. Survival analysis

The mean follow-up period was 150 months (range, 3-720). Summary of survival analysis is shown in Table 3. Considering all 195 cases, dedifferentiated parosteal osteosarcoma showed worse 10-year overall survival (60.1% versus 96.3%, $P < .001$) and 10-year disease-free survival (61.6% versus 80.0%, $P = .007$) as compared to conventional tumors (Figs. 3A-B). Presence of medullary canal involvement and the distinction between grade 1 and grade 2 tumor in 147 cases of conventional parosteal osteosarcoma did not correlate with survival outcome. Our results also showed that adequate surgical margins had a positive impact both in terms of overall ($P = .036$) and disease-free survival ($P < .001$).

4. Discussion

Parosteal osteosarcoma is a low-grade malignant tumor which is capable of dedifferentiation. Of the 147 conventional parosteal osteosarcoma, 119 (87.8%) were grade 1 and 28 (12.2%) were grade 2 according to Broder's grading system. We found no difference in survival outcome between grade 1 and grade 2 tumor in conventional parosteal osteosarcoma, confirming the data reported in literature [1-8]. Dedifferentiation has been reported to negatively affect the outcome of parosteal osteosarcoma [5]. In our series of 195 patients, 48 cases (24,6%) developed dedifferentiation. The incidence of dedifferentiation in our series was higher than that reported by a study performed at Mayo Clinic (24.6% versus 16%) and by the majority of the studies [4-6]. Our data confirmed that dedifferentiation is the most important feature associated with worse 5-year (65% versus 96%, $P < .001$) and 10-year survival (60% versus 96%, $P < .001$, as compared to conventional tumors. Conventional parosteal osteosarcoma has a better 10-year overall and disease-free survival than periosteal and high-grade surface osteosarcoma [12-17]. Dedifferentiated parosteal osteosarcoma behaves similarly to conventional osteosarcoma in terms of survival (65% versus 60%-70%) [16], and has better overall 5-year survival rate than high-grade surface osteosarcoma (65% versus 46%) [12].

Unfortunately, there is no clinical or radiological features that can definitely determine the presence of dedifferentiated component. Early studies found that presence of deep intralesional radiolucencies among heavily mineralized area typically seen in parosteal osteosarcoma, with or without medullary canal involvement, is suggestive of dedifferentiated part and biopsy should be, therefore, focused on these area [18,19].

Medullary involvement is a frequent finding in parosteal osteosarcoma, ranging from 7 to 65% of the cases, depending on the study [2-8]. Definition of medullary canal involvement by parosteal osteosarcoma using radiological imaging has not been suggested and data in literatures did not reveal the method used in assessing the extent of medullary canal invasion. A study on 226 patients by Okada et al [4] reported that medullary canal involvement, when presented, is usually involved only less than 25% of the total medullary canal area. The authors also found significant association between medullary involvement and histological grade, as we have observed in our series where the medullary involvement is statistically correlated to the presence of dedifferentiation and consequently to histological grade (conventional parosteal osteosarcoma (grade 1 and grade 2 according Broder's system) versus dedifferentiated parosteal osteosarcoma (grade 4 according Broder's system) $P < .001$, see table 2); but, in agreement with many other studies [2,4-6], the presence of medullary involvement did not significantly affect the clinical outcome. Moreover, the accuracy of radiological imaging (usually include MRI and CT) in evaluating the medullary involvement is debatable in literature, as reported by Shimoyama et al [7]. These authors suggested that finding of medullary canal involvement on radiology may only reflect benign bone remodeling process on histology, so the histological evaluation of the presence of tumor cells into the medullary cavity is the gold standard to confirm the presence of medullary involvement.

Our study confirms the importance of MDM2 and CDK4 immunoexpression as diagnostic markers without any predictive or prognostic meaning, in agreement with other studies reported in literature [20,21]; in fact, these markers could be helpful to distinguish parosteal osteosarcoma from potential benign fibro-osseous mimics, particularly in small biopsies.

Conventional parosteal osteosarcoma is considered a low-grade malignancy with low metastatic potential and surgery is the first-line treatment. However, when dedifferentiation occurs, chemotherapy is indicated, as for high-grade osteosarcoma [22]. There is a long-standing agreement on the fact that adequate disease-free surgical margin positively affect clinical outcome, with lower incidence of local recurrence and metastases [2-6,8-10]. Our study also showed that tumors with wide surgical margins had better disease-free survival and, to a lesser degree, overall survival. On the other hand, we did not find significant differences regarding local recurrence between conventional and dedifferentiated tumors.

To our knowledge, there is no clear evidence on the benefits of chemotherapy in dedifferentiated parosteal osteosarcoma. Laitinen et al [5] reported 10 cases of dedifferentiated parosteal osteosarcoma treated with preoperative chemotherapy. Only two of them showed a good treatment response (>90% tumor necrosis). These results are similar to those

obtained in our series, in that only one of patients showed a good treatment response. Our study did not demonstrate any impact of neo-adjuvant therapy on survival, possibly because of the small number of cases treated.

Our data reported a higher percentage of metastasis (19% versus 5%-10%) as compared to previous studies [2,5,6]. On the other hand, metastasis occurred more frequently in dedifferentiated groups, in agreement with previously reported studies [4,5,8], that further underlines the importance of recognizing the presence of tumor dedifferentiation.

In conclusion, parosteal osteosarcoma is a low-grade malignant bone tumor with ability to dedifferentiate into high-grade tumor. In this case, prognosis becomes similar to conventional osteosarcoma. Dedifferentiation is the most important factor that negatively affect prognosis. On the contrary, medullary canal involvement has no significant impact on patient survival. Achieving adequate disease-free surgical margin is crucial for disease control and is associated with better survival outcome. The role of neo-adjuvant chemotherapy remains controversial.

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