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Pediatrics Surface Osteosarcomas: A French Multicenter Study (SURFOS), Which is the Most Appropriate Treatment?

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Abstract

Background: Most of osteosarcomas (OS) originate on the medullary canal, and only a small proportion arises from the surface of bone. Surface OS can be divided into three distinct histologic subtypes: parosteal OS, periosteal OS and high-grade surface OS. This national retrospective study was conducted to review the treatment and clinical outcome of children surface' OS in order to upgrade and homogenize practices.

Methods: Data of 28 pediatric patients with surface OS treated in 11 French Cancer Centers (SFCE) between 1990 and 2010 were reviewed.

Results: Eleven patients had parosteal, sixteen patients had periosteal and one patient had high-grade surface OS. The median age at the diagnosis was 14.3 years (range, 5.8 –17.9 years). Seven patients were male. None had metastatic disease at diagnosis. All 28 patients were treated with surgery, of whom 21 (7 parosteal, 13 periosteal and 1 high-grade tumors) received chemotherapy (adjuvant or neo-adjuvant). Three patients relapsed (local relapse for 1 patient with parosteal OS and distant relapses for two patients with periosteal OS) and four patients with periosteal OS developed a second cancer (three out of four died). The 11-year overall survival rate was 100% for parosteal OS and 63 ± 18% for periosteal OS.

Conclusion: The histologic grade determines the clinical behavior and prognosis in pediatric surface OS. Complete resection is the treatment of choice regardless of pathology. Regarding prognosis, our study argues for the use of adjuvant chemotherapy in periosteal OS, as well as for oncogenetic counseling.

Keywords: Surface osteosarcoma; Children; Parosteal; Periosteal; High grade surface; Chemotherapy; Metastatic disease; Cancer center

Introduction

Malignant bone tumors account for 4-6% of all cancers occurring among children aged 0-14 years in most European countries [1]. Osteosarcomas (OS) mostly arises from intra medullar canal, but a small proportion originates from the surface of bone. The last World Health Organization (WHO) classification of bone tumors revised in 2012 defines three main subtypes of surface OS: parosteal, periosteal, and high-grade surface OS [2].

The most common histologic subtype of surface osteosarcoma is parosteal, a low-grade OS which usually arises from the distal femur's posterior side and has an excellent prognosis. Periosteal OS, the second most common surface OS, is a malignant tumor which mainly occurs in the diaphysis of long bones and harbors a metastatic and relapse

potential, although associated with a better prognosis than conventional OS or high-grade surface OS. The least common and most aggressive subtype is high-grade surface OS [3].

The rarity of surface OS and the fact that they are usually not included in national first-line therapeutic trials design for OS, have limited the information about their clinical features, their management and outcome, especially in children. In addition, most reported series present small numbers of patients and did not distinguish pediatric and adult patients [4-6].

The objective of this study was to review the therapeutic management of these tumors in children to homogenize treatment practices of surface OS in this population.

Materials and Methods

Study design

We conducted a retrospective multicenter national study on pediatric surface OS (SURFOS). The present study was conducted in accordance with the Declaration of Helsinki and approved by the national institutional review board and ethical committee (CCTIRS - Comate Consultative sur le Treatment de l 'Information an matière de Recherche dans le domain de la Santé).

Study population

The inclusion criteria were as follows: patients aged under 18 years old at diagnosis, treated for a histopathologically proven diagnosis of surface OS (parosteal, periosteal or high-grade surface OS), between 01/01/1990 and 01/01/2011 in metropolitan France. Exclusion criteria were: initial diagnosis over the age of 18 years old, conventional osteosarcomas. We use the WHO 2012 definition of these entities based on radiological and histological features [2].

Data collection

Due to the non-inclusion of patients with surface OS in French protocols, we asked clinicians and pathologists of the pediatric and bone sarcoma group (GROUPOS) to report their cases. Information about the clinical characteristics, treatment and outcome of the patients were obtained from their medical records: patient characteristics (age at diagnosis, gender), tumor characteristics (anatomic location, size, grade and histological type, stage of disease), treatment modalities (chemotherapy, surgery, radiotherapy), evolution under treatment (Histological response to neo-adjuvant chemotherapy defined by Huvos and Rosen grading: more 90% necrosis as "good" responders and <90% necrosis as "poor" responders, and outcomes (relapses, second malignancies, death and causes) were collected.

Statistical analysis

Descriptive statistics were reported as absolute frequencies and percentages for qualitative variables, while median and range were used for continuous variables. Differences between groups were evaluated by the Chi square test and Wilcoxon test. For all analyses, $p<0.05$ was considered as significant. The following parameters were analyzed: complete remission rate, event-free survival (EFS), overall survival (OS). Complete remission was defined as the disappearance of all signs of cancer in response to treatment. EFS was defined as the time from diagnosis to treatment failure, secondary neoplasm, or death, whichever came first. OS was measured from the date of diagnosis to death from any cause. OS and EFS curves were calculated using the Kaplan Meier method. All the analyses were performed using the SAS software (version 9.4, Cary, NC, USA).

Results

Between 01/01/1990 and 01/01/2011, 28 patients with surface osteosarcoma were identified from 11 French oncological centers. Twenty-one were females (75%) and seven males (25%). Patients' ages ranged from 5.8 to 17.9 years (median age 14.3 years). Sixteen patients had parosteal OS (57.1%), 11 had periosteal OS (39.3%) and one had high-grade surface OS (3.6%). Primary tumors were located to the: femur (n=14), tibia (n=6), humerus (n=3), fibula (n=2), radius (n=2), acromion (n=1). All 28 patients had localized disease at the time of diagnosis. The chemotherapy regimens used were those of the high-grade conventional OS and varied overtime according to national protocol available: OS 87 [7], OS94 randomising Methotrexate-Adriamycin vs Metotrexate-Etoposide-Ifosfamide (M-EI) [8], OS 2006 based on M-EI regimen [9]. Patient characteristics are summarized in Table 1. We separately analyzed the management and results of the 3 histopathological types.

Sex	Age at diag	Bone	Primary surgical treatment	Anatomo-pathology	Neo-adjuvant chemo-therapy	Surgical resection	Histo-logical response	Adjuvant chemo-therapy	Status at the end of treatment	Relapse	Secondary malignancy	Status at latest news	Particularities
F	16,5	Femur	Biopsy	Parosteal	yes	complete	PR	yes	CR			CR	
F	10,1	Femur	Biopsy	Parosteal	no	complete		yes	CR			CR	Anapath (2): POS + dediff. foci
M	10,4	Acromion	Biopsy	Parosteal	yes	complete	PR	yes	CR			CR	Anapath (2): POS + dediff. foci
M	17,5	Femur	Biopsy	Parosteal	yes	complete	PR	yes	CR			CR	
F	17,1	Femur	Biopsy	Parosteal	yes	incomplete	PR	yes	CR			CR	Radiotherapy

F	13,5	Femur	Biopsy	Parosteal	no	complete		no	CR			CR	
F	17,9	Humerus	Complete resection	Parosteal	no			no	CR			CR	
M	11,6	Femur	Incomplete resection	Parosteal	yes	complete	PR	yes	CR			CR	
F	16,3	Humerus	Biopsy	Parosteal	no	complete		no	CR			CR	
F	15,5	Radius	Incomplete resection	Parosteal	no	complete		no	CR			CR	
F	17,9	Femur	Incomplete resection	Parosteal	yes	complete	PR	yes	CR	Local relapse ? surgical treatment		CR	
Sex	**Age at diag**	**Bone**	**Primary surgical treatment**	**Anatomo-pathology**	**Neo-adjuvant chemo-therapy**	**Surgical resection**	**Histo-logical response**	**Adjuvant chemo-therapy**	**Status at the end of treatment**	**Relapse**	**Secondary malignancy**	**Status at latest news**	**Particularities**
F	16,3	Femur	Biopsy	Periosteal	yes	complete	GR	yes	CR			CR	
F	5,9	Fibula	Complete resection	Periosteal	no			no	CR			CR	
F	15,5	Femur	Biopsy	Periosteal	yes	complete	GR	yes	CR			CR	
F	14,5	Tibia	Biopsy	Periosteal	no	complete		no	CR			CR	
M	15,7	Tibia	Biopsy	Periosteal	yes	complete	GR	yes	CR			CR	
M	15,9	Femur	Biopsy	Periosteal	yes	complete	GR	yes	CR			CR	
F	14	Femur	Biopsy	Periosteal	yes	complete	GR	yes	CR		Breast cancer	CR	OS on irradiated area (thigh RMS)
M	9,8	Tibia	Biopsy	Periosteal	yes	complete	GR	yes	CR	2nd loc (rib, femur, tibia) ? surgical treatment	Thigh liposarcoma + metastases	Dead	
F	7,9	Tibia	Biopsy	Periosteal	yes	complete	GR	yes	CR		Brain tumor	Dead	Li Fraumeni
F	12,4	Radius	Biopsy	Periosteal	yes	complete	GR	yes	CR			CR	
F	12,6	Femur	Biopsy	Periosteal	yes	complete	GR	yes	CR			CR	History of nephroblastoma
F	8,9	Femur	Biopsy	Periosteal	yes	complete	PR	yes	CR			CR	Li Fraumeni
F	14,2	Humerus	Biopsy	Periosteal	yes	complete	GR	yes	CR	2nd loc (bone and lung)	Brain tumor	Dead	History of corticosurrenaloma and RMS

										? surgery + high dose chemotherapy			Li Fraumeni
M	14,6	Tibia	Biopsy	Periosteal	yes	complete	GR	yes	CR			CR	
F	5,8	Fibula	Biopsy	Periosteal	no	complete		no	CR			CR	
F	14,1	Femur	Biopsy	Periosteal	yes	complete	PR	yes	CR			CR	
F	16,4	Tibia	Complete resection	High-grade surface				yes	CR			CR	
CR: Complete Remission, F: Female, GR: Good Response, Loc.: Localization, M: Male, PR: Poor Response, RMS: Rhabdomyosarcoma													

Table 1: Patients characteristics.

Parosteal OS

Of the 11 patients with parosteal OS, seven (63.6%) were diagnosed by an initial biopsy, while four patients (36.4%) had a primary surgical resection of the lesion without previous biopsy (Figures 1A and 1B).

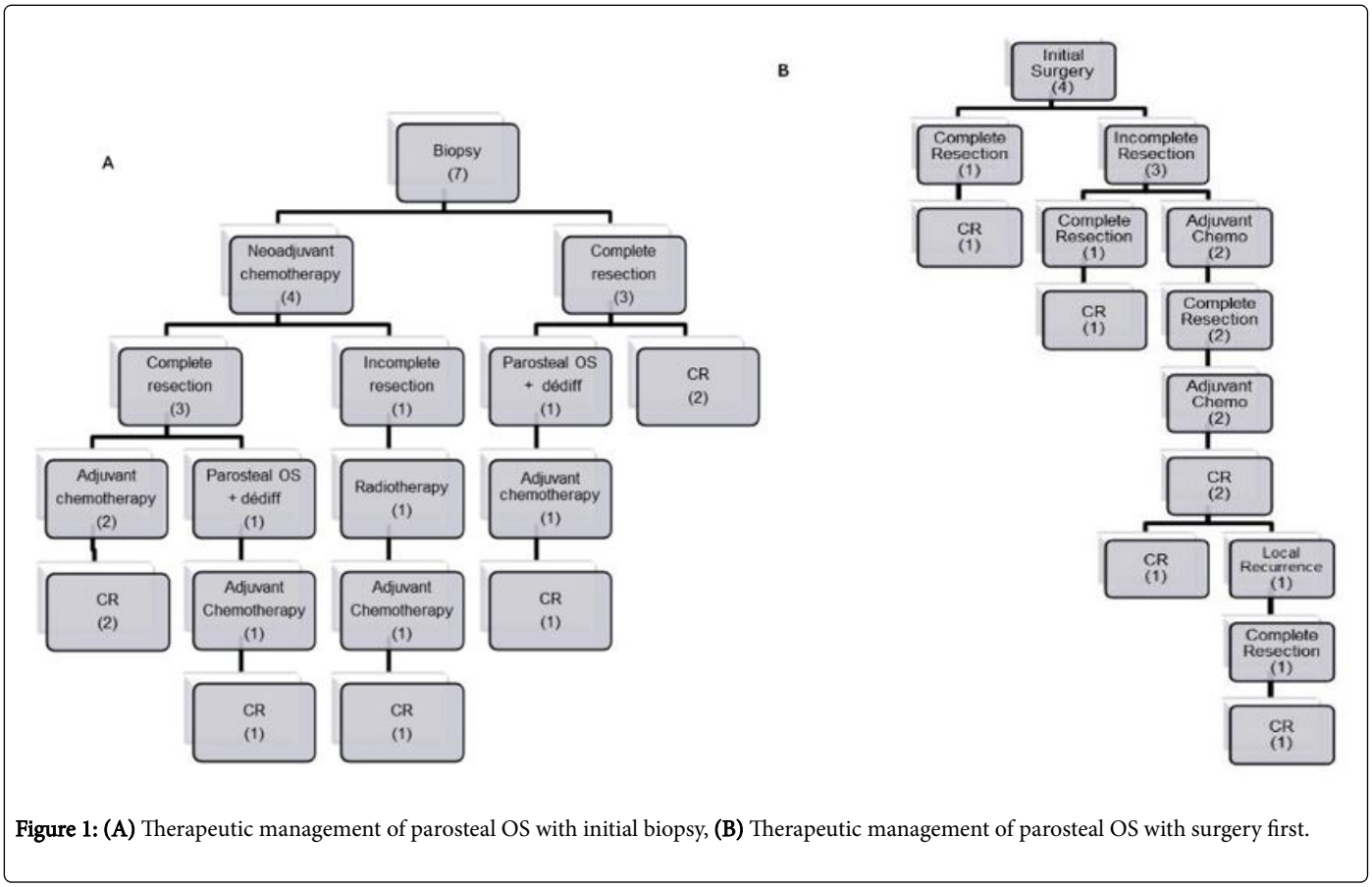

Figure 1: (A) Therapeutic management of parosteal OS with initial biopsy, **(B)** Therapeutic management of parosteal OS with surgery first.

Of the seven patients with initial biopsy, four patients received both neo-adjuvant and post-operative chemotherapy. For three of them, surgical resection complete and the last patient with incomplete surgical resection also received radiotherapy. These four patients had a poor histologic tumor response. Three other patients had only a wide surgical excision. Of the four patients with initial surgical procedure, only one had a complete resection, and resection was incomplete for the three other patients. One underwent a re-excision and two received chemotherapy followed by a re-excision (Figure 2).

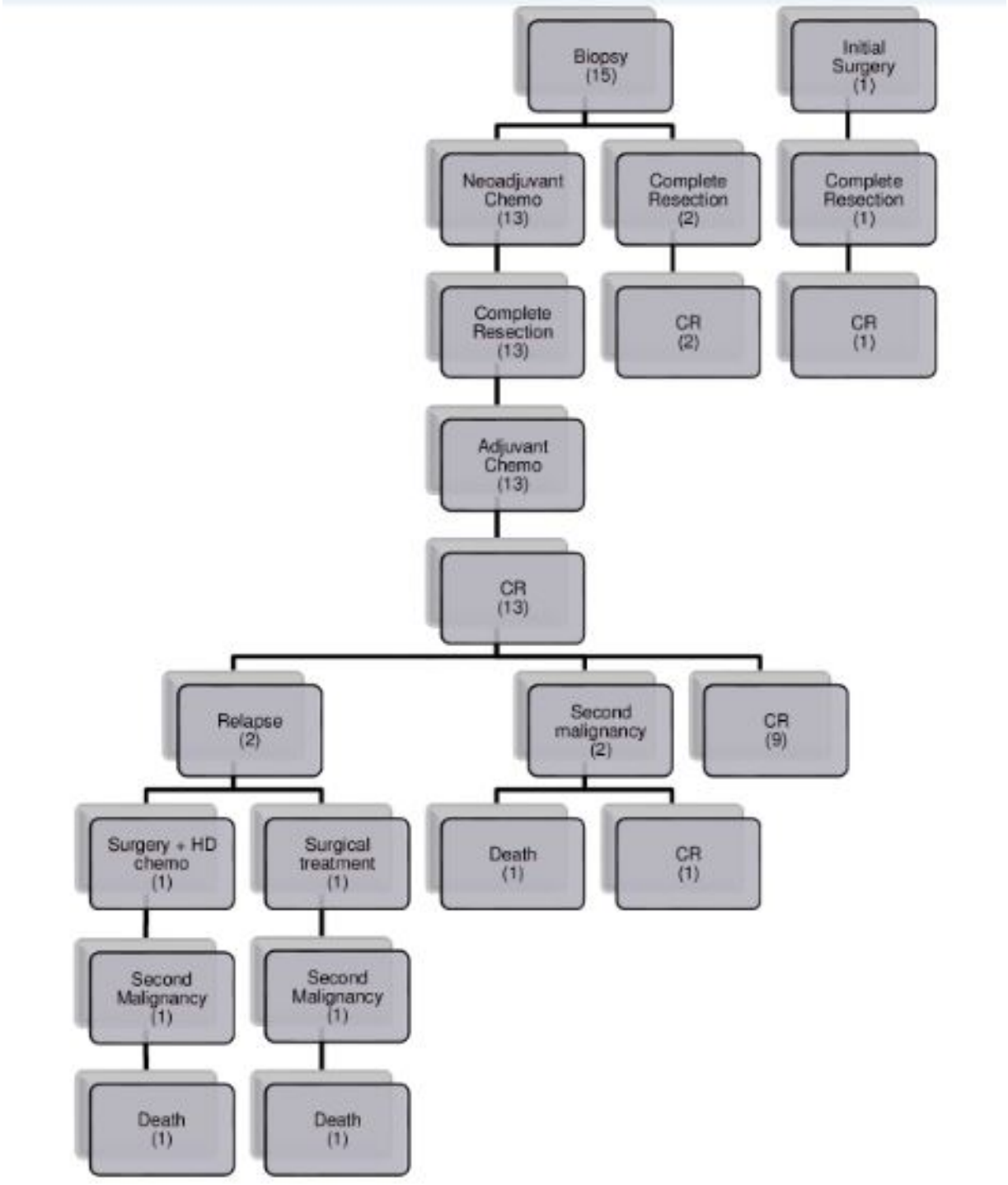

Figure 2: Therapeutic management of periosteal OS.

Two of the 11 parosteal OS experimented malignant evolution to a high-grade surface OS. Whereas initial biopsy confirmed the parosteal OS, pathological analysis of the surgical specimen detected dedifferentiation foci and conclude to high-grade surface OS. These two cases were then treated with chemotherapy as conventional OS. Only one patient had local relapse surgically treated, 3.6 years after end of treatment. All 11 patients remained alive and disease-free with a median follow-up of 7.6 years (range 1.4 - 15.6). Event free survival was 100% at 5 years and 87% (± 12%) at 10 years (Figure 3A). Overall survival was 100% at 10 years (Figure 3B).

Intermediate or high-grade periosteal OS

Fifteen (93.5%) of the 16 patients with periosteal OS were confirmed by initial biopsy. Thirteen received a standard osteosarcoma treatment with neo-adjuvant chemotherapy, adequate surgical resection and adjuvant chemotherapy; which resulted in complete remission (CR) at the end of treatment. Three patients were treated by surgery alone included one without previous biopsy (Figure 2).

Two patients with periosteal OS had a local relapse 11 and 23 months after initial diagnosis, treated respectively by surgery alone and surgery associated with high-dose chemotherapy. Both developed a second malignant neoplasm (thigh liposarcoma, brain tumor) 9.5 and 7 years after the initial diagnosis of surface OS and both died due to this secondary malignancy. Two other patients (12.5%) developed a second malignant neoplasm without previous relapse of OS, 10 and one year after initial diagnosis (one breast cancer and one brain tumor). The second patient died of its brain tumor. Germ line mutations of TP53 were found in three of these patients, but not for the fourth patient. There was no other genetic exploration available in the medical records.

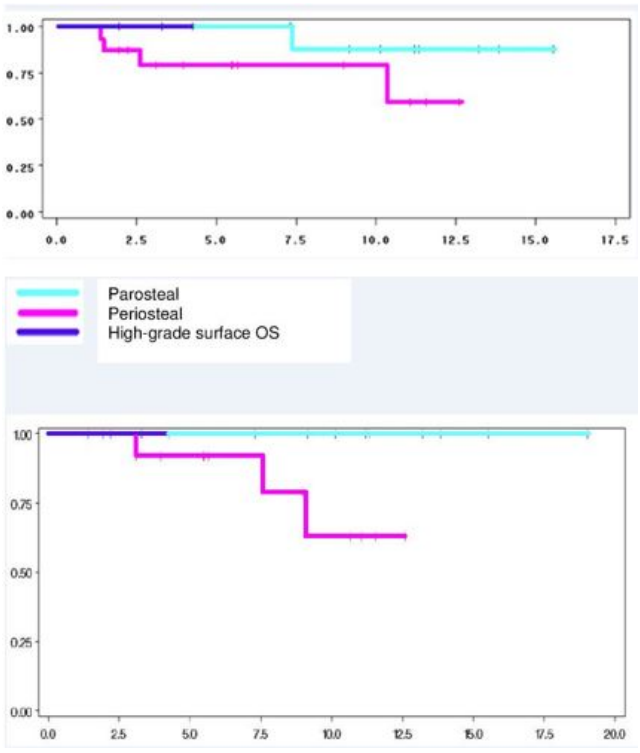

Figure 3: (A) Event Free Survival (EFS) depending on the histological subtype, **(B)** Overall Survival (OS) depending on histological subtype.

Patients with periosteal OS had a significant better response to chemotherapy than patients with parosteal OS (77% good response to neo-adjuvant chemotherapy in the periosteal group versus 0% in the parosteal group; p=0.003). But there was no significant difference in relapse rate between patients who had a good or a poor response to chemotherapy.

Event free survival was 79% (± 11%) at 5 years and 59% (± 19%) at 10 years (Figure 3A). Overall survival was 92% (± 7%) at 5 years and 63% (± 18%) at 10 years (Figure 3B).

High grade surface OS

Only one patient in our study presented this histological subtype. This patient had initial ultra-sound-guided micro-biopsy, which did not permit to conclude on a reliable diagnosis; then a wide surgical excision which confirmed the diagnosis of high-grade surface OS. Treatment was completed by adjuvant chemotherapy of conventional OS. The patient did not relapse and remained alive at five years from the diagnosis (Figures 3A and 3B).

Discussion

We have described the therapeutic management of 28 pediatric cases of surface OS. We found an excellent survival of parosteal OS despite their chemoresistance. Periosteal OS appeared chemo sensitive but associated with a risk of metastatic relapse and a high risk of second malignancies. High-grade surface osteosarcoma is very rare.

The strength of our study is that, to our knowledge, this is the largest pediatric study of these rare diseases of surface OS at a national level. We acknowledge some limitations of our study due to its retrospective nature, the small number of patients explained by the rarity of these entities, and the treatments variations over the long 20-year study period.

Sex ratio was in favor of girls, although previous studies reported a sex ratio of 1:1 with a slight predominance of female for parosteal OS [10] and male for periosteal OS [6,11]. The main entity observed was periosteal OS (57.1%) while predominance of parosteal OS is usually describe in the literature [3,4,10,12], maybe due to recruitment biases. Indeed, therapeutic management of parosteal OS is mostly only surgical and patients are unknown from Pediatric Oncology units.

Parosteal OS presented a good prognosis with 100% overall survival at 10 years in our pediatric population, while larger adults' population studies, report long-term survival rate of only 80%, due to late recurrence. This point emphasizes the importance of the long-term follow up of these patients [13,14]. In this low-grade lesion, the absence of relapse in our study, especially in patients treated by complete surgical resection alone and the histological chemoresistance that we observed after neo-adjuvant chemotherapy, argue for exclusive surgery as unique treatment in parosteal OS.

The low metastatic potential of these tumor has also participated to this recommendation by mixt pediatric and adult series [15-18]. However, the risk of indolent local recurrence in case of intralesional surgical procedure should not be underestimated and surgery properly planned. The potential of these tumors to "dedifferentiate" (two out of 11 patients in our study), previously reported in 16% to 27% of the cases [15,19,20], might be more common in adult than in pediatric population [21]. They might develop foci of high-grade spindle cell sarcoma, increased aggressiveness, and increased risk of metastasis [15,16,22]. Thus, they should be surgically treated when diagnose.

Periosteal OS presented a different clinical behavior with lower survival than in parosteal OS. The 63% 10-years overall survival of our serie was also lower than the 80% overall survival reported in previous studies [6,11,23,24] and was due to relapses and high rate of secondary malignancy in our cohort.

In our study, metastatic (n=2/11) recurrences were observed. The risk of metastatic relapses observed in our study and other (6), as well as the chemosensitivity demonstrated on histological response, as in previously series [11,23], plead for the use of chemotherapy. However, in the literature, adjunctive therapy had showed no overall survival improvement [25] and was not demonstrated as being a prognostic factor in the large European Musculoskeletal Oncology Society study (n=119) where two-thirds of the patients received chemotherapy [26].

In this study, overall survival was 89% at 5 years and 83% at 10 years and the only prognostic factor found was the appearance of local recurrence ($p<0.0001$). On the other hand, local recurrences rate, also observed in the literature up to 21% [6], are higher than for classic high-grade osteosarcomas which usually present a recurrence pattern composed mainly of metastasis [26]. These local recurrences might also be associated with a risk of subsequent distant metastasis and death as seen in two of our patients. Thus, local treatment (surgery) and the quality of the local treatment (clear margin) are crucial in the management of these tumors to prevent local recurrences but also metastatic recurrences. To further insist on this point, in 1976, Campanacci reported that 36% of patients treated at the Rizzoli Institute died of metastatic disease; a large number of these patients did not undergo adequate surgical resection [27]. Treatment guidelines for periosteal OS should therefore include both chemotherapy and surgery recommendations.

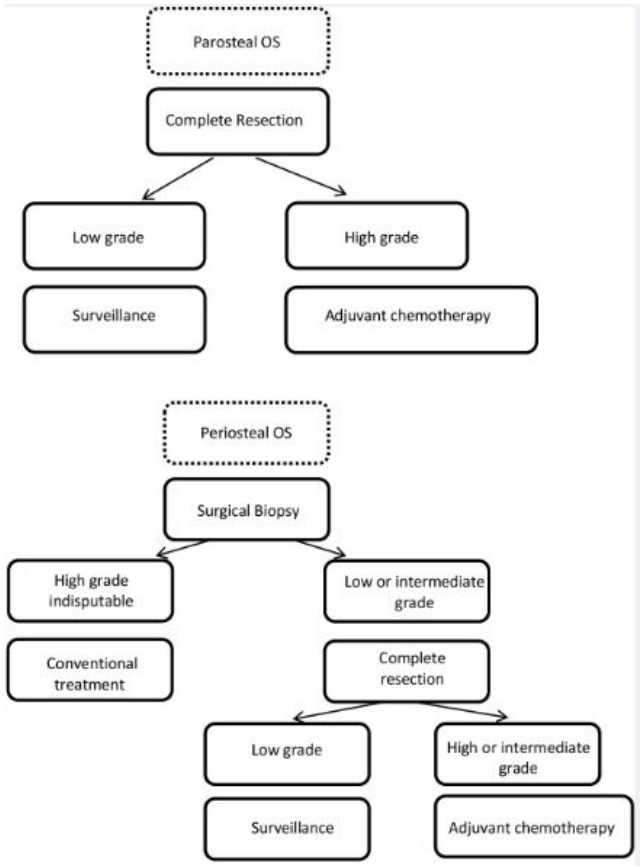

Figure 4: French national guidelines for surface osteosarcomas' therapeutic management (French Sarcoma Group).

Interestingly, we also observed a high rate of secondary malignancy, in up to 25% of the patients with periosteal OS, either as first event (n=2) or as secondary event (n=2). Previous reports analyzing such cases reported lower rates around 10% (6,11). The occurrence of multiple cancers could reveal a genetic predisposition such as Li Fraumeni Syndrome, linked to a germline TP53 mutation. Li Fraumeni families are at risk to develop conventional OS, but some cases of surface OS are also described [28,29].

In our study, molecular genetics studies were available for four patients and Li Fraumeni Syndrome was confirmed for three of them. Three other patients with multiple cancers could not have genetic counselling. A systematic proposition of oncogenetic counseling looking at least for germ line mutations of TP53, appears essential in periosteal OS and may balance the use of chemotherapy, which is also a known factor of second cancer.

Concerning high-grade surface OS, no data can be derived from our unique cases. However, data from the literature suggest a prognosis similar to that of conventional OS, and that wide excision and effective systemic chemotherapy should be associated to have better clinical results [30-32].

To conclude based on this retrospective work and the data available on the literature, the French Sarcoma group has proposed guidelines for surface osteosarcomas' therapeutic management (Figure 4).

Conclusion

The histological grade of surface OS seems to predict its clinical behavior: parosteal OS being the least aggressive, periosteal OS intermediate and high-grade surface OS the most aggressive one. Regardless of the tumor subtype, complete tumor resection remains the treatment of choice. Whereas chemotherapy is not necessary for the treatment of parosteal OS (subject to: anatomopathological review and absence of dedifferentiated areas), its necessity for the periosteal OS will depend on histological grade. Finally, in case of multiple cancers, an oncogenetic consultation has to be proposed.

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All authors of this paper have directly participated in the planning, research, writing and substantial reviewing of the draft manuscript, and have read and approved the final version submitted.

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