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Lack of efficacy of neoadjuvant chemotherapy in adult patients with maxillo-facial high-grade osteosarcomas: A French experience in two reference centers

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ABSTRACT

Introduction: Neoadjuvant chemotherapy (neo-CT) for osteosarcomas is the standard of care. Management of maxillo-facial osteosarcomas (MFOS) is challenging. In this rare disease, we collected a large cohort of patients with the aim to report the histological and radiological local response rates to neo-CT.

Patients and Methods: All consecutive adult patients treated between 2001 and 2016 in two French sarcoma referral centers (Pitié-Salpêtrière Hospital, APHP, RESAP France and Gustave Roussy Institute France), for a histologically proved MFOS were included. Clinical, histological and radiological data were independently reviewed. Tumor response to neo-CT was assessed clinically, radiologically with independent review using RECIST v1.1 criterion and pathologically (percentage of necrosis). Multivariate analysis was done for outcomes, tumor response and disease-free survival (DFS).

Results: A total of 35 high grade MFOS were collected. The clinical tumor response was 4% (1/24 receiving neo-CT), the radiological response was 0% (0/18 with available data) and the pathological response was 5% (1/20 with available data). Three patients (12.5%) initially resectable became unresectable due to clinical and radiological progression during neo-CT. Tumor size and R0 (clear margins) surgical resections were significantly associated with DFS.

Conclusion: MFOS is a rare disease. This large retrospective cohort of MFOS indicates the lack of benefit and potentially deleterious effects of neo-CT. We suggest privileging primary surgery in initially localized resectable MFOS. The benefit of adjuvant chemotherapy should be prospectively studied.

Introduction

Osteosarcomas (OS) are malignant neoplasms, locally aggressive and usually affecting long extremity bones of adolescents and young adults [1,2]. Maxillo-facial OS (MFOS) are rare, representing less than ten percent of all OS [3] and typically occur in the third or fourth decade of life [4]. In this localization, metastases occur less frequently than in long bones osteosarcomas [5]. Indeed, recurrence and evolution are mainly localized to the primary site [6]. Because of its scarcity and subsequent lack of data [7], MFOS management is mostly based on long extremity OS guidelines. Multimodal management is recognized as the standard of care and has been demonstrated to improve outcomes in

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long extremity OS [8,9]. Indeed, compared to surgery alone, overall survival was increased with adjuvant multi-agent chemotherapy in long extremity OS [10].

Neoadjuvant chemotherapy (neo-CT) has been developed for the treatment of long bones OS for several reasons: (1) to choose post-operative adjuvant CT based on the response of the primary tumor to preoperative CT [11,12] and (2) to allow more time to design endoprosthetic devices for limb-salvage procedures [13]. A good histological response to neo-CT is defined by more than 90% of necrosis on the surgical specimen. In the neoadjuvant setting, pathological response has been reported to be significantly associated with better overall survival [14], leading to establish the threshold of > 90% as a predictive marker for good overall survival. Although there is a strong correlation between the degree of necrosis and survival [15,16], the criteria "good histological response to neo-CT" for extremity OS, is limited to 50% of large series in literature [17]. Moreover, considering multimodal management, neo-CT is not proven to add survival benefit [18,19] and thus despite intensified treatment [20].

In MFOS, less than 30% of patients achieve good histological response after neo-CT [21]. Moreover, no significant benefit on overall survival was found in large series [22,23]. On the other hand, because of surgical constrains relative to maxillo-facial anatomy [24], the achievement of complete resection is a critical therapeutic parameter in this field [4,5,22,25,26]. Therefore, neo-CT appears as a potentially detrimental strategy, because of the potential lack of efficacy, as well as the delay to surgical resection. Indeed, the risk of local evolution during neo-CT, whose effectiveness is not proven, is not consistent with the therapeutic challenges of MFOS.

In this orphan situation, the safety of neo-CT in MFOS in term of local control needs to be established. Our aim is to report the histological and radiological local response rates to neo-CT in a series of MFOS treated since 2001 in two MFOS referral centers in France.

Patients and methods

Population included in the analysis

All consecutive patients treated and followed for a MFOS between 2001 and 2016 in two referral centers in France (la Pitié-Salpêtrière Hospital, APHP, RESAP, Paris; Gustave Roussy Cancer Campus, Villejuif) were screened for inclusion in this cohort.

We included all adult patients treated for a histologically proven MFOS, with at least surgery and/or chemotherapy (with or without metastasis).

Collection of data

Collected data included: baseline patient (clinical and demographic data) and tumor characteristics (pathological and radiological data), chemotherapy regimens, surgical characteristics, outcomes (first date of relapse or progression, date of death or date of last news). Resection margins were considered as clear (R0) or not (microscopically involved (R1) or macroscopically intralesional (R2)).

All available radiological exams (CT-scan, Magnetic resonance imaging (MRI)) in each center were independently reviewed by two expert radiologists in order to collect tumor size before and after neo-CT. Radiological responses were assessed according to change in maximal tumor diameter (Recist v1.1 criterion).

Tumor histological response to neo-CT was collected from pathology reports, as Pathologists routinely evaluate it using the Rosen's criteria to assess the percent of necrotic tumor cells in the surgical specimen after neo-CT (good response if > 90% of necrosis on the surgical specimen) [11,27].

This study was approved by Institutional review board and done in accordance with the Helsinki declaration. Written consent was not required from patients because of the retrospective non-interventional design, consistently with French standard regulations. Collection of data and analysis was in accordance with guidelines of the French national committee for protection of personal data (CNIL).

Objective and end points

The primary objective of this study was to describe the pathological and radiological responses to neo-CT.

Secondary outcomes of interest were disease free survival (DFS), defined by the duration between surgery and first relapse (or death) or censoring by the date of last news alive, and correlation between tumor responses and surgical margins.

Statistical analyses

The retrospective design of this study and the scarcity of the disease prevented us to calculate a population to confirm statistical hypotheses. Binary data were described by ratios. Quantitative data were described using median and range. Correlations between binary variables were assessed using Fisher exact test. Because of the limited number of patients included, correlations between binary and quantitative variables were assessed using non-parametric Wilcoxon test. Follow-up was estimated using the reverse Kaplan-Meier estimation method (1-KM). Survival curves were performed using the Kaplan-Meier method and analyzed using two-sided log-rank test. Exploratory survival analysis was performed with Cox logistic regression model. Proportional hazards assumption was tested for each analysis. Survivals are considered from the date of first treatment (surgery, or first neo-CT infusion), to the date of event of interest, censored by the date of last news. Significance was defined by $p < 0.05$. All analyses were performed using R software version 3.3.3.

Results

Patients and tumors characteristics

Forty patients were screened for the inclusion (Fig. 1). Thirty-five high grade MFOS were included for the final analysis (n = 5 excluded: other diagnosis (n = 4) and missing data (n = 1; histological report unavailable).

Patient and tumor characteristics (n = 35) are presented in Table 1 and were consistent with literature [28]. Briefly, median age was 36.8 years old (range 18.5–84.4). All patients had good general condition, 64% were male. The delay between first symptoms and diagnosis was extremely variable, with a median time to diagnosis of 15 weeks (range 5–108). The first symptom was an evolving mass syndrome in 83% of cases (Table 1). All tumors were developed from mandibular bone (60%), or maxillary bone (40%). Most of tumors (75%) had local development corresponding to stage IIA/B of AJCC staging system for long bone sarcoma. Four patients had metastasis at diagnosis (skin: n = 1; lung: n = 3) and three had radiological suspicion of lymph nodes metastasis (not confirmed histologically).

Median initial tumor size was 40 mm (range 15–99). All MFOS were high grade tumors. The main histological subtypes were chondroblastic (37%), osteoblastic (31%) or undifferentiated (14%). Twenty-nine percent of tumors had a mixed histological type.

Therapeutic management

Twenty-four (77.4%) patients received neo-CT. Regimens were based on Adriamycine, Platine Ifosfamide and high-dose methotrexate. Regimens heterogeneity prevented any further analyses for correlations with resection margins or survival.

Four patients (n = 3 localized disease and n = 1 with lung metastasis) did not undergo surgical resection because of locally advanced/unresectable disease at initial diagnosis (n = 1) or after neo-CT (n = 3).

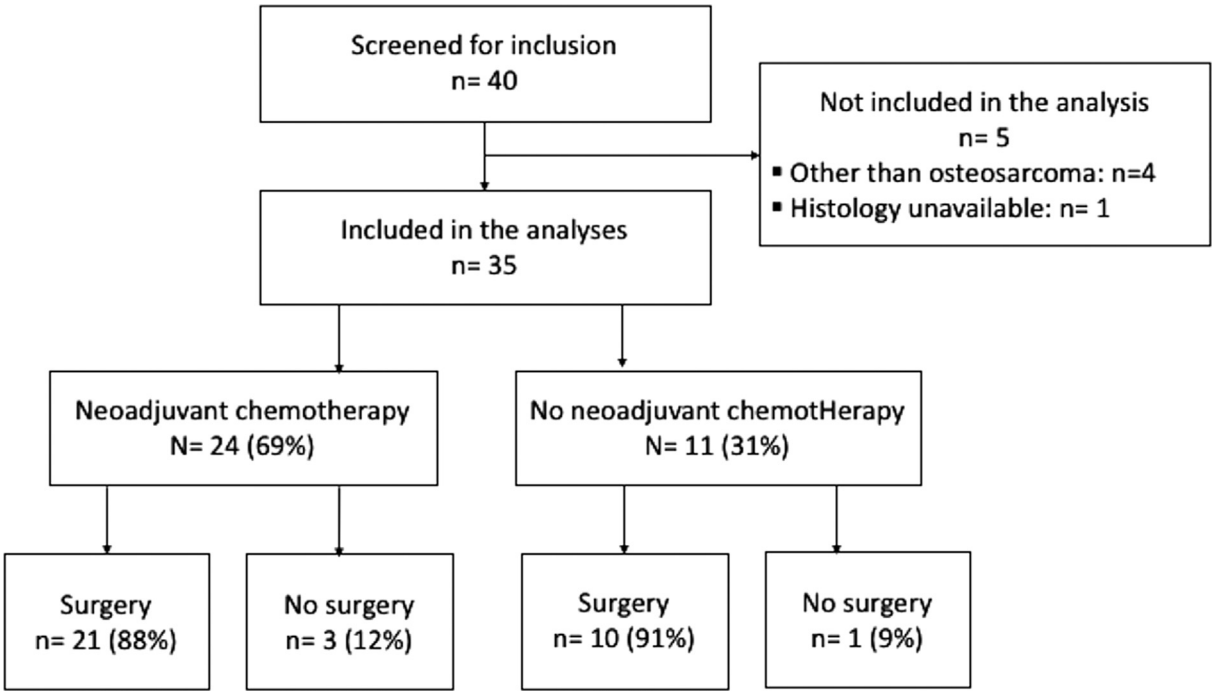

Fig. 1. Flow-chart: patient selection and treatments.

Table 1
Patients' baseline characteristics and initial therapeutic management (n = 35).

Variables	Overall population	
Age (Median, range)	36.8	18.5–84.4
Gender (N, %)		
Male	23	64%
Female	12	36%
ECOG-PS at diagnostic (N, %)		
0	33	94%
1	1	3%
Missing data	1	3%
Histological (N, %)		
Osteoblastic	11	31%
Chondroblastic	13	37%
Fibroblastic	1	3%
Undifferentiated	5	14%
Not specified	5	30%
Mixed histology	10	29%
Primary tumor site (N, %)		
Maxillary bone	14	40%
Mandibular bone	21	60%
First symptom (N, %)		
Evolving mass syndrome	29	83%
Pain	6	17%
AJCC stages (N, %)		
IIA	24	69%
IIB	2	6%
IVA	4	11%
IVB	3	9%
Missing data (n)	2	
Tumor size[a] (mm: median, range)	40	15.0–99.0
Missing data	4	
Neoadjuvant chemotherapy (N, %)	24	69%
Carcinologic resection (N, %)	31	89%
Total (N, %)	35	100%

AJCC: American Joint Committee on Cancer classification for osteosarcoma.
mm: millimeter.
[a] Tumor size according to the largest dimension.

Surgical resection of tumor was performed for 31 (89%) patients (Fig. 1). Among these, 10 (32%) did not receive previous neo-CT. For the 21 patients operated after neo-CT, the median delay between the first cycle of neo-CT and surgery was 14 weeks (range 5–40) and 8 (38%) had R1 resection margins. Overall, 27/31 (87%) patients had available data for surgical resection margins, 17 (63%) were clear (R0), 10 (37%) were marginal R1 and no intralesional R2 margins was observed. Adjuvant CT was administered to 16/27 patients.

No patient received RT prior to surgery. Adjuvant RT was realized for 8 patients with positive surgical margins.

Radiological response to neo-CT

Among patients who underwent surgical resection after neo-CT (n = 21), responses distributions were eight (44%) progressions (tumor size increase > 20%), ten (66%) stable diseases, while none had significant radiological tumor shrinkage when using RECIST1.1 criterion (decrease > 30% in tumor maximal diameter) (Fig. 2). Median tumor size change from the baseline was +4 mm [−10; +20] representing a median of +12.8% of size increase. (Table 2).

The three patients who received neo-CT (n = 1 and n = 2 having received 6 and 4 cycles respectively) but were not resected thereafter had not radiological examinations available. They were in clinical progression. They were resectable at initial diagnosis and became unresectable after neo-CT due to the large progression of the tumor. Overall, 16/24 patients (66.7%) had an increase in tumor size or were in clinical progression during the neo-CT.

Histological response to neo-CT

Among patients who underwent surgical resection after neo-CT, 20 had histological data available. One out of 20 (5%) patient experienced a 100% tumor necrosis and was the only one responder (necrosis > 90%) to neo-CT (Figure 3). Regarding others, tumor necrosis was ≤30% for 14 patients (70%), 31–60% for three patients (15%) and 61–90% for two patients (10%).

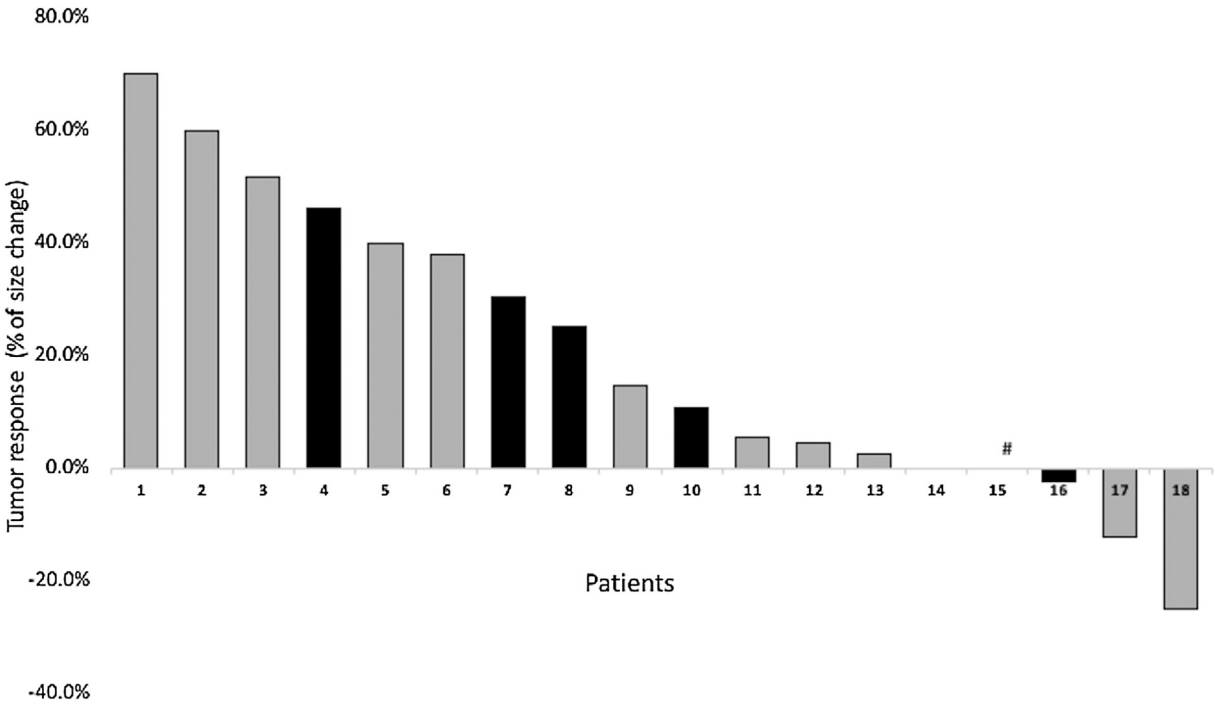

Fig. 2. Radiological response to neoadjuvant chemotherapy for patients who underwent surgery. Patients included: n = 18. (Data missing for 3 patients; Bars represent the percentage tumor size change relative to baseline; Bars in black or with # highlight patients with uncomplete resection).

Table 2
Radiological and pathological response to neoadjuvant chemotherapy.

	Overall population (n = 24)	
Median change in tumor size (in millimeters) from baselin[a] (median [range]; % of size progression)	+4 [−10; +20]	+12.8%
Objective response[a] (N, %)		
Partial response[b]	0	0%
Stable disease	10	66%
Progressive disease	8	44%
Pathological response[c] > **90%** (N, %)	1	5%

mm: millimeter.

[a] Among 21 patients who underwent chemotherapy – as assessed by radiological reviewing.

[b] Decreasing in tumor largest dimension > 30%.

[c] Pathological response as assessed by tumor necrosis on surgical specimen.

Survival and prognostic factors

Median follow-up was 43.6 months (95%CI [32.1; 63.7]; range [1.0–160.7]). We observed 8 deaths during the period of follow-up. One patient died of tumor bleeding prior to any treatment, one patient treated by surgery alone died of pulmonary infection in the post-surgical period. The six others had received neo-CT and died after tumor relapses either locally (3) or secondary to metastatic disease progression (3).

Among patients who were resected for the primary tumor (n = 31/35), 8 (26%) relapsed, with a 3-years DFS of 76% (95% confidence interval [60%; 95%]). Among the 8 patients who relapsed, 5 have died at the date of last news. The 3 other patients were still alive after long follow-up (34 months, 40 months, 160 months)

R0 resections were significantly associated with a better DFS compare to R1 resections (log-rank test, p = 0.004) (Fig. 4), with a 3-years DFS of 100% versus 37.5% respectively. Other factors significantly associated with poorer DFS were the median initial and pre-operative tumor sizes (Table 3).

Higher initial and post neo-CT tumor size were significantly associated with R1 margins (Supplementary Table 1).

Discussion

This study is the first to report the radiological and pathological response rates after neo-CT for a recent cohort of MFOS. During fifteen years period, 35 patients with a confirmed diagnosis of MFOS were treated in two reference centers. Among this cohort of patients, 11 patients were operated before any CT and 24 received neo-CT followed by surgery for 21 of them. The clinical tumor response rate was 4% (1/24 receiving neo-CT) and three patients (12.5%) initially resectable became unresectable due to clinical tumor progression (n = 2 maxillary and n = 1 mandible MFOS). The radiological response was 0% (RECIST v1.1 criterion). Radiological/clinical reviews revealed that 66.7% of patients experienced a tumor size increase during neo-CT. The pathological response was 5% (1/20 with available data) and necrosis rates were ≤30% for 14 (70%) patients. These data are particularly important given that tumor size and R0 surgical resection were significantly associated with DFS.

MFOS represents fewer than ten percent of all osteosarcomas and have a predominantly local development [29,30]. The scarcity of these tumors, the lack of knowledge and the heterogeneity of reported cohorts explain the lack of evidence-based treatment guidelines for the optimal management of these tumors [31,32].

The benefit of neo-CT in the treatment of MFOS is not widely accepted in literature [33]. Non-significant or contradictory results [22,26,34–36] are issues from retrospective studies that included heterogeneous patients before 2000, with few of them receiving neo-CT [25,32]. A recent large series has reported a limited pathological response rate to neo-CT (27%) [7].

Regarding adjuvant chemotherapy, the limited number of patients in our cohort precluded relevant statistical analyses comparing patients who received adjuvant chemotherapy versus patients who did not. In 2016 and 2017, Chen et al., have reported a series of n = 160 head and neck osteosarcoma and affirmed that adjuvant chemotherapy improves overall survival. They found that the overall survival was significantly

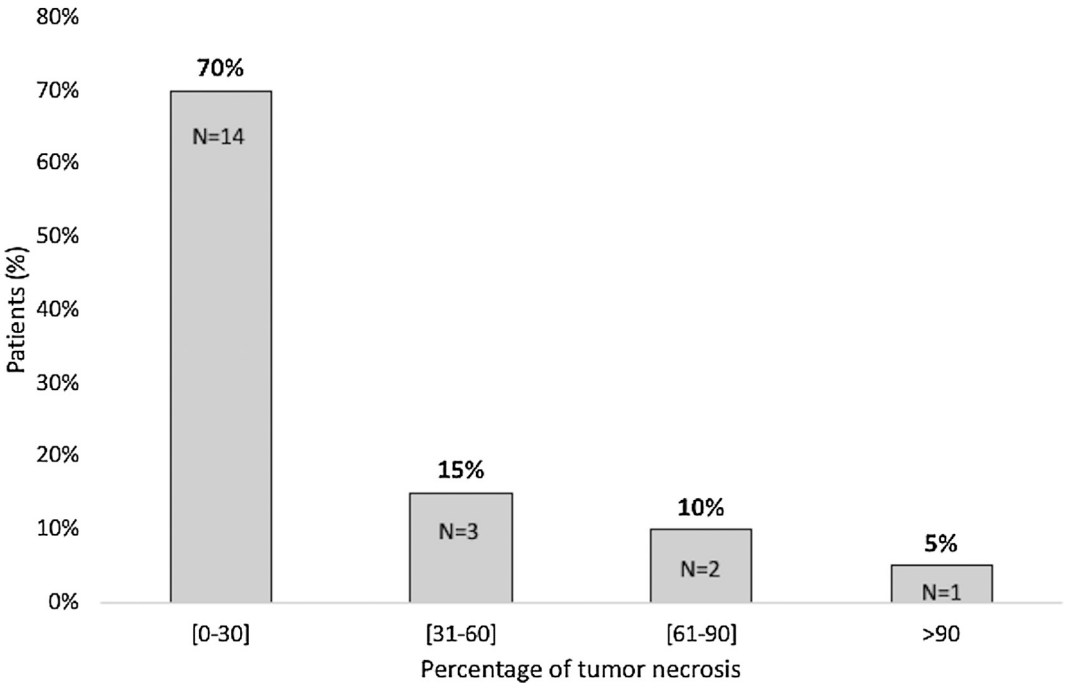

Fig. 3. Histological response to neoadjuvant chemotherapy for the n = 18 patients who underwent surgery with available data.

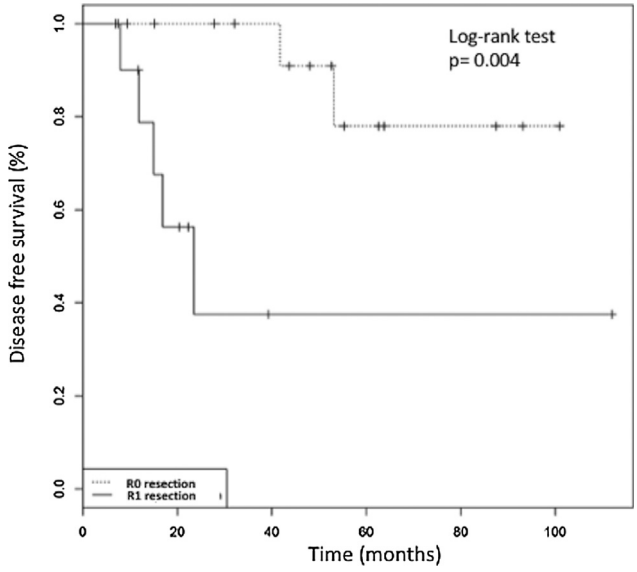

Fig. 4. Disease free survival according to surgical margins. Patients included: n = 31 (n = 4 NA, n = 17 complete resection R0, n = 20 incomplete resection either R1 or R2).

better with adjuvant chemotherapy among various treatment plans and that primary surgery alone vs. primary surgery and chemotherapy group showed borderline significance [37,38].

The role of surgery, and particularly the achievement of R0 resection margins, has been largely reviewed and reported to be associated with better outcomes [4,5,25,34,39–42]. Local failures are the main causes of death in MFOS compared to other sites [7]. The therapeutic issues and the operability of MFOS depend on tumor parameters such as size and volume [43,44]. It is particularly true for posterior tumors, close to the skull base. Thus, the delay until surgery and the subsequent increase in tumors size could be detrimental as suggested by the death of two patients with clinical progression during neo-CT (which were initially resectable), and by the correlation between tumor size and R1 resection. As per routine practice in our centers, some teams focused on early tumor response evaluation to discontinue neo-CT, in order to perform radical tumor resection (R0) during the window of therapeutic opportunity for surgery [45].

In line with the aforementioned therapeutic issues, our results highlight a major concern: the overall lack of efficacy of neo-CT could lead to a delay until surgery, during which tumor can grow beyond the theoretical limits of complete resection.

Why MFOS appeared so resistant to neo-CT and different from other locations remained a partially unsettled question [46]. Some large series clearly underlined biologic differences between MFOS and OS of other localization [33] reflecting the molecular heterogeneity of human osteosarcoma [47]. For example, recent molecular characterization study allowed the identification of a new-subtype of mandibular osteosarcoma with *RASAL1/MDM2* amplification [48].

More generally the chemoresistance in OS appears to be mediated by numerous molecular mechanisms which include decreased intracellular drug accumulation, drug inactivation, enhanced DNA repair, perturbations in signal transduction pathways, apoptosis- and autophagy-related chemoresistance, microRNA (miRNA) dysregulation, cancer stem cell (CSC)-mediated drug resistance and Interaction of OS cells and the micro-environment [49–53] (Supplementary Table 3).

Although identified, the precise role of each of these mechanisms of chemoresistance remains unclear.

To illustrate it, we can mention the autophagy and apoptosis processes, which have been already referred to as a double-edged sword. On one hand, they promote osteosarcoma cells survival, while in other circumstances, they can lead to tumor cell death. Furthermore, there is a close interplay between autophagy and apoptosis during OS cells development, progression and response to therapy (role of the PI3K and Akt regulators).

Furthermore, recent studies have highlighted the importance of OS-CSCs, which have been associated with chemoresistance, relapse, and metastasis events [51]. However, almost all the current studies on the mechanisms of OS-CSCs related chemoresistance are in their infancy and better understanding would help provide better targets for therapies.

Some studies have highlighted other biological processes which have been already reported as implicated in the chemoresistance of

Table 3
Disease free survival following surgical resection according to patients' characteristics.

Variables	Recurrence (%)	3-years DFS [95%CI]	HR [95%CI][a]	p-Value[a]
Age (year)				
> Median	3/16 (18.8%)	93% [80%;100%]	–	
< Median	5/15 (33.3%)	52% [29%;97%]	3.45 [0.79; 15.10]	0.1
Primary tumor site				
Mandibular bone	3/19 (15.8%)	84% [66%; 100%]	0.47 [0.11; 1.99]	0.308
Maxillary bone	5/12 (41.7%)	67% [45%; 99%]	–	
Median initial tumor size (mm)[b,c]	7/27 (25.9%)	–	1.05 [1.01; 1.10]	0.026
Median tumor size before surgery (including patients treated with neoCT) (mm)[c]	7/26 (26.9%)	–	1.04 [1.00; 1.08]	0.031
Neo adjuvant chemotherapy				
Yes	5/21 (23.8%)	79% [62%; 100%]	0.56 [0.13; 2.38]	0.438
No	3/10 (30%)	67% [36%; 100%]	–	
Surgical resection				
R0	2/17 (11.8%)	100% [100%; 100%]	–	
R1	5/10 (50%)	38% [14%; 100%]	8.96 [1.58; 50.68]	0.004

DFS: Disease free survival.
HR: hazard ratio.
95%CI: 95% confidence interval.
mm: millimeter.
[a] Estimated using Cox regression model.
[b] Assessed by radiological reviewing. Largest dimension was taken into account.
[c] These variables were considered as continuous variables.

other cancers as the epithelial-mesenchymal transition (EMT) biological process (Visfatin, an EMT-related transcription factors, is involved in the cisplatin resistance of osteosarcoma cells via upregulation of Snail and Zeb1 and cPLA2a, cytosolic phospholipase A2, could promote OS cell invasion) [54,55]. More recently Bhuvaneshwar et al., have reported intronic and intergenic hotspot regions from 26 genes significantly associated with resistance to cisplatin, doxorubicin, and methotrexate, in children with osteosarcoma [53]. Among significant results were mutations in genes belonging to AKR enzyme family (AKRD1), the cell-cell adhesion biological process (genes of the cadherin family CDH13, CDH9 and PKHD1 resulting in a phenotype called "cell adhesion-mediated drug resistance," or CAM-DR) and the PI3K pathways.

Molecular studies could help to anticipate the chemoresistance. Indeed, a molecular classification of OS had identified a 45-gene signature that could predict with 100% accuracy the chemoresponse of osteosarcoma patients prior to the initiation of treatment [56]. This support the fact that neo-CT should not be generalized but prescribed in a subset of patients with high level of expected chemosensitivity. This could explain why the only patient of our cohort who experienced a tumor response after neo-CT had no any viable tumor cell on the surgical specimen.

The identification of biomarkers could allow to detect tumor onset, progression and response to therapy for OS [45,57]. By predicting response to therapy, these biomarkers, as well as the immunohistochemical analysis of the microenvironment may represent novel tools for therapeutic stratification [58].

To identify new molecular targets and develop new drugs, further studies are required to a better understanding of the molecular pathogenesis Osteosarcoma [59]. Recent genome-wide sequencing analyzes have demonstrated that Osteosarcomas are genetically complex and heterogeneous (intra- and intertumoral) [33]. Structural and numerical alterations (somatic copy number alterations) are much more common than recurrent point mutations. Regarding Cancer-causing genes, also called driver genes or drivers, numerous somatic mutations have been identified by next-generation sequencing of Osteosarcomas [60] (Supplementary Table 4). The most common driver genes associated with osteosarcomas development are TP53 and RB1. TP53 and RB1 mutations have been identified as causative driver genes in almost 50% of cases. Frequent alterations in PTEN and PI3K/mTOR signaling pathways have also been reported. Furthermore, about 90% of all osteosarcomas appear to have mutations in BRCA-associated genes and genomically show a striking similarity to BRCA1 / 2-mutated tumors (so-called 'BRCAness') [33,60]. It suggests that a high percentage of OS tumors may be HRR-deficient (homologous recombination repair defect) and therefore be vulnerable to additional DNA damage caused by double- strand breaks.

At all, like a double-edged sword, all these alterations confer a growth advantage, but also creates vulnerabilities in osteosarcoma cells. This give us opportunities to test targeted therapies targeting the different genes and pathways involved [61,62] (Supplementary Table 5).

Some recent studies support for the potential uses of immunotherapy, including monoclonal antibodies, immunomodulators, Adoptive T-cell therapy, vaccine therapy, Immunologic checkpoint blockade and oncolytic virotherapy for the eradication of OS cells [62,63] (Supplementary Tables 5 and 6).

At all, combination strategies are probably necessary to achieve meaningful and durable responses to therapies for osteosarcoma, especially immunotherapies. Indeed, as seen with conventional CT, tumors development involves multiple pathways to resist to therapies. The recent development developments in genomics, therapeutics and imaging technologies will allow the early detection of the genomic risk of sarcomas for each patient and may participate to better personalized management.

Despite the inherent limitations due to our retrospective data collection, and the relatively limited number of patients analyzed, which precluded further analysis of overall survival, our results were consistent with other series [33]. Indeed, our results suggest that MFOS should not be managed as OS of other localization. The natural history of MFOS is distinctive from other sites [64]. Regarding demographic pattern, the mean age of diagnosis of MFOS is 30 years of age while children and adolescents are most often affected for other sites [37]. Regarding embryologic development, head and neck bones are structurally quite different in origin from the body. Furthermore, when compared to long bones OS, MFOS showed no clinical, radiological and histological chemosensitivity [65]. Finally, this disease seems to harbor a different evolution, characterized by a local invasion more than lung metastasis, which suggest the need to a better local control rather than to eradicate micrometastasis.

Conclusion

MFOS is a rare disease. This large retrospective cohort of MFOS indicates the lack of benefit and potentially deleterious effects of neo-CT. We suggest privileging primary surgery in initially localized resectable MFOS. The benefit of adjuvant chemotherapy should be prospectively studied.

Neo-CT could benefit only for a limited group of patients with high predisposition of chemosensitivity, on the basis of molecular analysis. Collaborative and large high-throughput genomic analysis are warranted to better characterize MFOS, and to allow the emergence of predictive biomarkers, as well as the development of targeted therapies.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.06.011.

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