



HAL
open science

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

Jebrane Bouaoud, Guillaume Beinse, Nicolas Epailard, Melika Amor-Sehlil, François Bidault, Isabelle Brocheriou, Geneviève Hervé, Jean-Philippe Spano, François Janot, Pascaline Boudou-Rouquette, et al.

► To cite this version:

Jebrane Bouaoud, Guillaume Beinse, Nicolas Epailard, Melika Amor-Sehlil, François Bidault, et al.. Lack of efficacy of neoadjuvant chemotherapy in adult patients with maxillo-facial high-grade osteosarcomas: A French experience in two reference centers. *Oral Oncology*, 2019, 95, pp.79 - 86. 10.1016/j.oraloncology.2019.06.011 . hal-03487032

HAL Id: hal-03487032

<https://hal.science/hal-03487032>

Submitted on 20 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

TITLE PAGE

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

Author names and affiliations:

Jebrane Bouaoud ^{a†}, Guillaume Beinse ^{b†}, Nicolas Epailard ^{b†}, Melika Amor-Sehlil ^c, François Bidault ^d, Isabelle Brocheriou ^e, Geneviève Hervé ^e, Jean-Philippe Spano ^b, François Janot ^f, Pascaline Boudou-Rouquette ^g, Mourad Benassarou ^a, Thomas Schouman ^a, Patrick Goudot ^a, Gabriel Malouf ^{b‡}, François Goldwasser ^{g‡}, Chloe Bertolus ^{a‡}

a. Department of Maxillo-facial Surgery and Stomatology, Pitié-Salpêtrière Hospital, Pierre et Marie Curie University Paris 6, Sorbonne Paris Cite University, AP-HP, RESAP, Paris, 75013, France.

b. Department of Medical Oncology, Pitié-Salpêtrière Hospital, Pierre et Marie Curie University Paris 6, Sorbonne Paris Cite University, AP-HP, RESAP, Paris, 75013, France.

c. Department of Radiology, Pitié-Salpêtrière Hospital, Pierre et Marie Curie University Paris 6, Sorbonne Paris Cite University, AP-HP, RESAP, Paris, 75013, France.

d. Department of Radiology, Gustave Roussy Cancer Campus, 114 Rue Edouard Vaillant, Villejuif 94800, France.

e. Department of Pathology, Pitié-Salpêtrière Hospital, Pierre et Marie Curie University Paris 6, Sorbonne Paris Cite University, AP-HP, Paris, 75013, France.

f. Unit of Head and Neck Surgery, Gustave Roussy Cancer Campus, 114 Rue Edouard Vaillant, Villejuif 94800, France.

g. Department of Medical Oncology, Cochin Hospital, Paris Descartes University, CARPEM Paris, AP-HP, RESAP, Paris, 75014, France.

† These authors contributed equally to the work. ‡ These authors contributed equally to the work

Corresponding author:

Jebrane Bouaoud, M.D

Department of Maxillo-facial Surgery and Stomatology, Pitié-Salpêtrière Hospital, Pierre et Marie

Curie University Paris 6, Sorbonne Paris Cite University, AP-HP, RESAP, Paris, 75013, France

E-mail jebrane.bouaoud@gmail.com

Phone# +33142161049

Word count: 2638

Conflict of interest statement: none declared

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

1 **ABSTRACT**

2 Introduction

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

6

7 Patients and Methods

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

14

15 Results

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

21

22 Conclusion

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

26 **Key word (MeSH):** head and neck cancer; osteosarcoma; neoadjuvant chemotherapy.

27 INTRODUCTION

28 Osteosarcomas (OS) are malignant neoplasms, locally aggressive and usually affecting long extremity
29 bones of adolescents and young adults [1,2]. Maxillo-facial OS (MFOS) are rare, representing less
30 than ten percent of all OS [3] and typically occur in the third or fourth decade of life [4]. In this
31 localization, metastases occur less frequently than in long bones osteosarcomas [5]. Indeed,
32 recurrence and evolution are mainly localized to the primary site [6]. Because of its scarcity and
33 subsequent lack of data [7], MFOS management is mostly based on long extremity OS guidelines.
34 Multimodal management is recognized as the standard of care and has been demonstrated to
35 improve outcomes in long extremity OS [8,9]. Indeed, compared to surgery alone, overall survival
36 was increased with adjuvant multi-agent chemotherapy in long extremity OS [10].

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

48 In MFOS, less than 30% of patients achieve good histological response after neo-CT [21]. Moreover,
49 no significant benefit on overall survival was found in large series [22,23]. On the other hand,
50 because of surgical constrains relative to maxillo-facial anatomy [24], the achievement of complete
51 resection is a critical therapeutic parameter in this field [4,22,25–27]. Therefore, neo-CT appears as a
52 potentially detrimental strategy, because of the potential lack of efficacy, as well as the delay to

53 surgical resection. Indeed, the risk of local evolution during neo-CT, whose effectiveness is not
54 proven, is not consistent with the therapeutic challenges of MFOS.

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

58 **PATIENTS and METHODS**

59 **Population included in the analysis**

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

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

65

66 **Collection of data**

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

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

75 Tumor histological response to neo-CT was collected from pathology reports, as Pathologists
76 routinely evaluate it using the Rosen's criteria to assess the percent of necrotic tumor cells in the
77 surgical specimen after neo-CT (good response if > 90% of necrosis on the surgical specimen) [11,28]

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

83

84 **Objective and end points**

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

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

90

91 **Statistical analyses**

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

103 **RESULTS**

104 **Patients and tumors characteristics**

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

108 Patient and tumor characteristics (n=35) are presented in Table 1 and were consistent with literature
109 [29]. Briefly, median age was 36.8 years old (range 18.5-84.4). All patients had good general
110 condition, 64% were male. The delay between first symptoms and diagnosis was extremely variable,
111 with a median time to diagnosis of 15 weeks (range 5-108). The first symptom was an evolving mass
112 syndrome in 83% of cases (**Table 1**). All tumors were developed from mandibular bone (60%), or
113 maxillary bone (40%). Most of tumors (75%) had local development corresponding to stage IIA/B of
114 AJCC staging system for long bone sarcoma. Four patients had metastasis at diagnosis (skin: n=1;
115 lung: n=3) and three had radiological suspicion of lymph nodes metastasis (not confirmed
116 histologically).

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

120

121 **Therapeutic management**

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

125 Four patients (n=3 localized disease and n=1 with lung metastasis) did not undergo surgical resection
126 because of locally advanced/unresectable disease at initial diagnosis (n=1) or after neo-CT (n=3).
127 Surgical resection of tumor was performed for 31 (89%) patients (**Figure 1**). Among these, 10 (32%)
128 did not receive previous neo-CT. For the 21 patients operated after neo-CT, the median delay

129 between the first cycle of neo-CT and surgery was 14 weeks (range 5-40) and 8 (38%) had R1
130 resection margins. Overall, 27/31 (87%) patients had available data for surgical resection margins, 17
131 (63%) were clear (R0), 10 (37%) were marginal R1 and no intralesional R2 margins was observed.
132 Adjuvant CT was administered to 16/27 patients.
133 No patient received RT prior to surgery. Adjuvant RT was realized for 8 patients with positive surgical
134 margins.

135

136 **Radiological response to neo-CT**

137 Among patients who underwent surgical resection after neo-CT (n=21), responses distributions were
138 eight (44%) progressions (tumor size increase > 20%), ten (66%) stable diseases, while none had
139 significant radiological tumor shrinkage when using RECIST1.1 criterion (decrease > 30% in tumor
140 maximal diameter) (**Figure 2**). Median tumor size change from the baseline was + 4 millimeters [-10;
141 +20] representing a median of +12.8% of size increase. (**Table 2**).

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

147

148 **Histological response to neo-CT**

149 Among patients who underwent surgical resection after neo-CT, 20 had histological data available.
150 One out of 20 (5%) patient experienced a 100% tumor necrosis and was the only one responder
151 (necrosis >90%) to neo-CT (**Figure 3**). Regarding others, tumor necrosis was $\leq 30\%$ for 14 patients
152 (70%), 31-60% for three patients (15%) and 61-90% for two patients (10%).

153

154 **Survival and prognostic factors**

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

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

164 R0 resections were significantly associated with a better DFS compare to R1 resections (log-rank test,
165 $p=0.004$) (**Figure 4**), with a 3-years DFS of 100% versus 37.5% respectively. Other factors significantly
166 associated with poorer DFS were the median initial and pre-operative tumor sizes (**Table 3**).

167 Higher initial and post neo-CT tumor size were significantly associated with R1 margins
168 (**supplementary table 1**).

169 **DISCUSSION**

170 This study is the first to report the radiological and pathological response rates after neo-CT for a
171 recent cohort of MFOS. During fifteen years period, 35 patients with a confirmed diagnosis of MFOS
172 were treated in two reference centers. Among this cohort of patients, 11 patients were operated
173 before any CT and 24 received neo-CT followed by surgery for 21 of them. The clinical tumor
174 response rate was 4% (1/24 receiving neo-CT) and three patients (12.5%) initially resectable became
175 unresectable due to clinical tumor progression (n=2 maxillary and n=1 mandible MFOS). The
176 radiological response was 0% (RECIST v1.1 criterion). Radiological/clinical reviews revealed that
177 66.7% of patients experienced a tumor size increase during neo-CT. The pathological response was
178 5% (1/20 with available data) and necrosis rates were $\leq 30\%$ for 14 (70%) patients. These data are
179 particularly important given that tumor size and R0 surgical resection were significantly associated
180 with DFS.

181

182 MFOS represents fewer than ten percent of all osteosarcomas and have a predominantly local
183 development [30,31]. The scarcity of these tumors, the lack of knowledge and the heterogeneity of
184 reported cohorts explain the lack of evidence-based treatment guidelines for the optimal
185 management of these tumors [32,33].

186 The benefit of neo-CT in the treatment of MFOS is not widely accepted in literature [34]. Non-
187 significant or contradictory results [22,27,35–37] are issues from retrospective studies that included
188 heterogeneous patients before 2000, with few of them receiving neo-CT [26,33]. A recent large series
189 has reported a limited pathological response rate to neo-CT (27%) [7].

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

195 plans and that primary surgery alone vs. primary surgery and chemotherapy group showed
196 borderline significance [38,39].

197 The role of surgery, and particularly the achievement of R0 resection margins, has been largely
198 reviewed and reported to be associated with better outcomes [4,25,26,35,40–43]. Local failures are
199 the main causes of death in MFOS compared to other sites [7]. The therapeutic issues and the
200 operability of MFOS depend on tumor parameters such as size and volume [44,45]. It is particularly
201 true for posterior tumors, close to the skull base. Thus, the delay until surgery and the subsequent
202 increase in tumors size could be detrimental as suggested by the death of two patients with clinical
203 progression during neo-CT (which were initially resectable), and by the correlation between tumor
204 size and R1 resection. As per routine practice in our centers, some teams focused on early tumor
205 response evaluation to discontinue neo-CT, in order to perform radical tumor resection (R0) during
206 the window of therapeutic opportunity for surgery [46].

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

210

211 Why MFOS appeared so resistant to neo-CT and different from other locations remained a partially
212 unsettled question [47]. Some large series clearly underlined biologic differences between MFOS and
213 OS of other localization [34] reflecting the molecular heterogeneity of human osteosarcoma [48]. For
214 example, recent molecular characterization study allowed the identification of a new-subtype of
215 mandibular osteosarcoma with *RASAL1/MDM2* amplification [49].

216 More generally the chemoresistance in OS appears to be mediated by numerous molecular
217 mechanisms which include decreased intracellular drug accumulation, drug inactivation, enhanced
218 DNA repair, perturbations in signal transduction pathways, apoptosis- and autophagy-related
219 chemoresistance, microRNA (miRNA) dysregulation, cancer stem cell (CSC)-mediated drug resistance
220 and Interaction of OS cells and the micro-environment [50–54] (**Supplementary Table 3**).

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

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

228 Furthermore, recent studies have highlighted the importance of OS-CSCs, which have been
229 associated with chemoresistance, relapse, and metastasis events [52]. However, almost all the
230 current studies on the mechanisms of OS-CSCs related chemoresistance are in their infancy and
231 better understanding would help provide better targets for therapies.

232 Some studies have highlighted other biological processes which have been already reported as
233 implicated in the chemoresistance of other cancers as the epithelial-mesenchymal transition (EMT)
234 biological process (Visfatin, an EMT-related transcription factors, is involved in the cisplatin
235 resistance of osteosarcoma cells via upregulation of Snail and Zeb1 and cPLA2a, cytosolic
236 phospholipase A2, could promote OS cell invasion) [55,56]. More recently Bhuvaneshwar et al., have
237 reported intronic and intergenic hotspot regions from 26 genes significantly associated with
238 resistance to cisplatin, doxorubicin, and methotrexate, in children with osteosarcoma [54]. Among
239 significant results were mutations in genes belonging to AKR enzyme family (AKRD1), the cell-cell
240 adhesion biological process (genes of the cadherin family CDH13, CDH9 and PKHD1 resulting in a
241 phenotype called “cell adhesion-mediated drug resistance,” or CAM-DR) and the PI3K pathways.

242 Molecular studies could help to anticipate the chemoresistance. Indeed, a molecular classification of
243 OS had identified a 45-gene signature that could predict with 100% accuracy the chemoresponse of
244 osteosarcoma patients prior to the initiation of treatment [57]. This support the fact that neo-CT
245 should not be generalized but prescribed in a subset of patients with high level of expected

246 chemosensitivity. This could explain why the only patient of our cohort who experienced a tumor
247 response after neo-CT had no any viable tumor cell on the surgical specimen.

248 The identification of biomarkers could allow to detect tumor onset, progression and response to
249 therapy for OS [46,58]. By predicting response to therapy, these biomarkers, as well as the
250 immunohistochemical analysis of the microenvironment may represent novel tools for therapeutic
251 stratification [59].

252

253 To identify new molecular targets and develop new drugs, further studies are required to a better
254 understanding of the molecular pathogenesis Osteosarcoma [60]. Recent genome-wide sequencing
255 analyzes have demonstrated that Osteosarcomas are genetically complex and heterogeneous (intra-
256 and intertumoral) [34]. Structural and numerical alterations (somatic copy number alterations) are
257 much more common than recurrent point mutations. Regarding Cancer-causing genes, also called
258 driver genes or drivers, numerous somatic mutations have been identified by next-generation
259 sequencing of Osteosarcomas [61] (**Supplementary Table 4**). The most common driver genes
260 associated with osteosarcomas development are TP53 and RB1. TP53 and RB1 mutations have been
261 identified as causative driver genes in almost 50% of cases. Frequent alterations in PTEN and
262 PI3K/mTOR signaling pathways have also been reported. Furthermore, about 90% of all
263 osteosarcomas appear to have mutations in BRCA-associated genes and genomically show a striking
264 similarity to BRCA1 / 2-mutated tumors (so-called 'BRCAness')[34,61]. It suggests that a high
265 percentage of OS tumors may be HRR-deficient (homologous recombination repair defect) and
266 therefore be vulnerable to additional DNA damage caused by double- strand breaks.

267 At all, like a double-edged sword, all these alterations confer a growth advantage, but also creates
268 vulnerabilities in osteosarcoma cells. This give us opportunities to test targeted therapies targeting
269 the different genes and pathways involved [62,63] (**Supplementary table 5**).

270 Some recent studies support for the potential uses of immunotherapy, including monoclonal
271 antibodies, immunomodulators, Adoptive T-cell therapy, vaccine therapy, Immunologic checkpoint

272 blockade and oncolytic virotherapy for the eradication of OS cells[63,64] (**Supplementary table 5 and**
273 **6**).

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

280

281 Despite the inherent limitations due to our retrospective data collection, and the relatively limited
282 number of patients analyzed, which precluded further analysis of overall survival, our results were
283 consistent with other series [34]. Indeed, our results suggest that MFOS should not be managed as
284 OS of other localization. The natural history of MFOS is distinctive from other sites [65]. Regarding
285 demographic pattern, the mean age of diagnosis of MFOS is 30 years of age while children and
286 adolescents are most often affected for other sites [38]. Regarding embryologic development, head
287 and neck bones are structurally quite different in origin from the body. Furthermore, when
288 compared to long bones OS, MFOS showed no clinical, radiological and histological chemosensitivity
289 [66]. Finally, this disease seems to harbor a different evolution, characterized by a local invasion
290 more than lung metastasis, which suggest the need to a better local control rather than to eradicate
291 micrometastasis.

292 **Conclusion**

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

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

300 **REFERENCES**

- 301 [1] Luetke A, Meyers PA, Lewis I, Juergens H. Osteosarcoma treatment - where do we stand? A
302 state of the art review. *Cancer Treat Rev* 2014;40:523–32. doi:10.1016/j.ctrv.2013.11.006.
- 303 [2] Bielack SS, Hecker-Nolting S, Blattmann C, Kager L. Advances in the management of
304 osteosarcoma. *F1000Research* 2016;5. doi:10.12688/f1000research.9465.1.
- 305 [3] Guadagnolo BA, Zagars GK, Raymond AK, Benjamin RS, Sturgis EM. Osteosarcoma of the
306 jaw/craniofacial region: outcomes after multimodality treatment. *Cancer* 2009;115:3262–70.
307 doi:10.1002/cncr.24297.
- 308 [4] Jasnau S, Meyer U, Potratz J, Jundt G, Kevric M, Joos UK, et al. Craniofacial osteosarcoma
309 Experience of the cooperative German-Austrian-Swiss osteosarcoma study group. *Oral Oncol*
310 2008;44:286–94. doi:10.1016/j.oraloncology.2007.03.001.
- 311 [5] Laskar S, Basu A, Muckaden MA, D’Cruz A, Pai S, Jambhekar N, et al. Osteosarcoma of the
312 head and neck region: lessons learned from a single-institution experience of 50 patients. *Head Neck*
313 2008;30:1020–6. doi:10.1002/hed.20820.
- 314 [6] Ketabchi A, Kalavrezos N, Newman L. Sarcomas of the head and neck: a 10-year
315 retrospective of 25 patients to evaluate treatment modalities, function and survival. *Br J Oral*
316 *Maxillofac Surg* 2011;49:116–20. doi:10.1016/j.bjoms.2010.02.012.
- 317 [7] Thariat J, Julieron M, Brouchet A, Italiano A, Schouman T, Marcy P-Y, et al. Osteosarcomas
318 of the mandible: are they different from other tumor sites? *Crit Rev Oncol Hematol* 2012;82:280–95.
319 doi:10.1016/j.critrevonc.2011.07.001.
- 320 [8] Durfee RA, Mohammed M, Luu HH. Review of Osteosarcoma and Current Management.
321 *Rheumatol Ther* 2016;3:221–43. doi:10.1007/s40744-016-0046-y.
- 322 [9] Whelan JS, Jinks RC, McTiernan A, Sydes MR, Hook JM, Trani L, et al. Survival from high-
323 grade localised extremity osteosarcoma: combined results and prognostic factors from three European
324 Osteosarcoma Intergroup randomised controlled trials. *Ann Oncol Off J Eur Soc Med Oncol*
325 2012;23:1607–16. doi:10.1093/annonc/mdr491.
- 326 [10] The ESMO. Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and
327 follow-up. *Ann Oncol* 2014;25:iii113–23. doi:10.1093/annonc/mdu256.
- 328 [11] Rosen G, Caparros B, Huvos AG, Kosloff C, Nirenberg A, Cacavio A, et al. Preoperative
329 chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the
330 response of the primary tumor to preoperative chemotherapy. *Cancer* 1982;49:1221–30.
- 331 [12] Link MP, Goorin AM, Miser AW, Green AA, Pratt CB, Belasco JB, et al. The effect of
332 adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl*
333 *J Med* 1986;314:1600–6. doi:10.1056/NEJM198606193142502.
- 334 [13] Isakoff MS, Bielack SS, Meltzer P, Gorlick R. Osteosarcoma: Current Treatment and a
335 Collaborative Pathway to Success. *J Clin Oncol Off J Am Soc Clin Oncol* 2015;33:3029–35.
336 doi:10.1200/JCO.2014.59.4895.
- 337 [14] Marina N, Gebhardt M, Teot L, Gorlick R. Biology and therapeutic advances for pediatric

- 338 osteosarcoma. *The Oncologist* 2004;9:422–41.
- 339 [15] Provisor AJ, Ettinger LJ, Nachman JB, Krailo MD, Makley JT, Yunis EJ, et al. Treatment of
340 nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: a
341 report from the Children’s Cancer Group. *J Clin Oncol Off J Am Soc Clin Oncol* 1997;15:76–84.
342 doi:10.1200/JCO.1997.15.1.76.
- 343 [16] Bacci G, Longhi A, Ferrari S, Briccoli A, Donati D, De Paolis M, et al. Prognostic
344 significance of serum lactate dehydrogenase in osteosarcoma of the extremity: experience at Rizzoli
345 on 1421 patients treated over the last 30 years. *Tumori* 2004;90:478–84.
- 346 [17] Friebele JC, Peck J, Pan X, Abdel-Rasoul M, Mayerson JL. Osteosarcoma: A Meta-Analysis
347 and Review of the Literature. *Am J Orthop Belle Mead NJ* 2015;44:547–53.
- 348 [18] Gerrand C, Athanasou N, Brennan B, Grimer R, Judson I, Morland B, et al. UK guidelines for
349 the management of bone sarcomas. *Clin Sarcoma Res* 2016;6. doi:10.1186/s13569-016-0047-1.
- 350 [19] Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to
351 2004: Data from the Surveillance, Epidemiology, and End Results Program. *Cancer* 2009;115:1531–
352 43. doi:10.1002/cncr.24121.
- 353 [20] Meyers PA, Gorlick R, Heller G, Casper E, Lane J, Huvos AG, et al. Intensification of
354 preoperative chemotherapy for osteogenic sarcoma: results of the Memorial Sloan-Kettering (T12)
355 protocol. *J Clin Oncol Off J Am Soc Clin Oncol* 1998;16:2452–8. doi:10.1200/JCO.1998.16.7.2452.
- 356 [21] Boon E, van der Graaf WTA, Gelderblom H, Tesselaaar MET, van Es RJJ, Oosting SF, et al.
357 Impact of chemotherapy on the outcome of osteosarcoma of the head and neck in adults. *Head Neck*
358 2017;39:140–6. doi:10.1002/hed.24556.
- 359 [22] Thariat J, Schouman T, Brouchet A, Sarini J, Miller RC, Reyckler H, et al. Osteosarcomas of
360 the mandible: multidisciplinary management of a rare tumor of the young adult a cooperative study of
361 the GSF-GETO, Rare Cancer Network, GETTEC/REFCOR and SFCE. *Ann Oncol Off J Eur Soc Med*
362 *Oncol* 2013;24:824–31. doi:10.1093/annonc/mds507.
- 363 [23] Canadian Society of Otolaryngology-Head and Neck Surgery Oncology Study Group.
364 Osteogenic sarcoma of the mandible and maxilla: a Canadian review (1980-2000). *J Otolaryngol*
365 2004;33:139–44.
- 366 [24] Nthumba PM. Osteosarcoma of the jaws: a review of literature and a case report on
367 synchronous multicentric osteosarcomas. *World J Surg Oncol* 2012;10:240. doi:10.1186/1477-7819-
368 10-240.
- 369 [25] Laskar S, Basu A, Muckaden MA, D’Cruz A, Pai S, Jambhekar N, et al. Osteosarcoma of the
370 head and neck region: lessons learned from a single-institution experience of 50 patients. *Head Neck*
371 2008;30:1020–6. doi:10.1002/hed.20820.
- 372 [26] Granados-Garcia M, Luna-Ortiz K, Castillo-Oliva HA, Villavicencio-Valencia V, Herrera-
373 Gómez A, Mosqueda-Taylor A, et al. Free osseous and soft tissue surgical margins as prognostic
374 factors in mandibular osteosarcoma. *Oral Oncol* 2006;42:172–6.
375 doi:10.1016/j.oraloncology.2005.06.027.
- 376 [27] Patel SG, Meyers P, Huvos AG, Wolden S, Singh B, Shaha AR, et al. Improved outcomes in

377 patients with osteogenic sarcoma of the head and neck. *Cancer* 2002;95:1495–503.
378 doi:10.1002/cncr.10849.

379 [28] Huvos AG, Rosen G, Marcove RC. Primary osteogenic sarcoma: pathologic aspects in 20
380 patients after treatment with chemotherapy en bloc resection, and prosthetic bone replacement. *Arch*
381 *Pathol Lab Med* 1977;101:14–8.

382 [29] van den Berg H, Schreuder WH, de Lange J. Osteosarcoma: A Comparison of Jaw versus
383 Nonjaw Localizations and Review of the Literature. *Sarcoma* 2013;2013. doi:10.1155/2013/316123.

384 [30] O’Neill JP, Bilsky MH, Kraus D. Head and neck sarcomas: epidemiology, pathology, and
385 management. *Neurosurg Clin N Am* 2013;24:67–78. doi:10.1016/j.nec.2012.08.010.

386 [31] Sarkar R. Pathological and clinical features of primary osseous tumours of the jaw. *J Bone*
387 *Oncol* 2014;3:90–5. doi:10.1016/j.jbo.2014.06.001.

388 [32] Tudor-Green B, Fonseca FP, Gomez RS, Brennan PA. Current update on the diagnosis and
389 management of head and neck hard tissue sarcomas. *J Oral Pathol Med Off Publ Int Assoc Oral Pathol*
390 *Am Acad Oral Pathol* 2017;46:667–73. doi:10.1111/jop.12573.

391 [33] Thiele OC, Freier K, Bacon C, Egerer G, Hofele CM. Interdisciplinary combined treatment of
392 craniofacial osteosarcoma with neoadjuvant and adjuvant chemotherapy and excision of the tumour: a
393 retrospective study. *Br J Oral Maxillofac Surg* 2008;46:533–6. doi:10.1016/j.bjoms.2008.03.010.

394 [34] Baumhoer D, Brunner P, Eppenberger-Castori S, Smida J, Nathrath M, Jundt G.
395 Osteosarcomas of the jaws differ from their peripheral counterparts and require a distinct treatment
396 approach. Experiences from the DOESAK Registry. *Oral Oncol* 2014;50:147–53.
397 doi:10.1016/j.oraloncology.2013.10.017.

398 [35] Kassir RR, Rassekh CH, Kinsella JB, Segas J, Carrau RL, Hokanson JA. Osteosarcoma of the
399 head and neck: meta-analysis of nonrandomized studies. *The Laryngoscope* 1997;107:56–61.

400 [36] Granowski-LeCornu M, Chuang S-K, Kaban LB, August M. Osteosarcoma of the jaws:
401 factors influencing prognosis. *J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg*
402 2011;69:2368–75. doi:10.1016/j.joms.2010.10.023.

403 [37] Mücke T, Mitchell DA, Tannapfel A, Wolff K-D, Loeffelbein DJ, Kanatas A. Effect of
404 neoadjuvant treatment in the management of osteosarcomas of the head and neck. *J Cancer Res Clin*
405 *Oncol* 2014;140:127–31. doi:10.1007/s00432-013-1550-x.

406 [38] Chen Y, Shen Q, Gokavarapu S, Lin C, Yahiya null, Cao W, et al. Osteosarcoma of head and
407 neck: A retrospective study on prognostic factors from a single institute database. *Oral Oncol*
408 2016;58:1–7. doi:10.1016/j.oraloncology.2016.04.008.

409 [39] Chen Y, Gokavarapu S, Shen Q, Liu F, Cao W, Ling Y, et al. Chemotherapy in head and neck
410 osteosarcoma: Adjuvant chemotherapy improves overall survival. *Oral Oncol* 2017;73:124–31.
411 doi:10.1016/j.oraloncology.2017.08.017.

412 [40] Mücke T, Mitchell DA, Tannapfel A, Hölzle F, Kesting MR, Wolff K-D, et al. Outcome in
413 adult patients with head and neck sarcomas--a 10-year analysis. *J Surg Oncol* 2010;102:170–4.
414 doi:10.1002/jso.21595.

- 415 [41] Kämmerer PW, Shabazfar N, Vorkhshori Makoie N, Moergel M, Al-Nawas B. Clinical,
416 therapeutic and prognostic features of osteosarcoma of the jaws - experience of 36 cases. *J Cranio-*
417 *Maxillo-Fac Surg Off Publ Eur Assoc Cranio-Maxillo-Fac Surg* 2012;40:541–8.
418 doi:10.1016/j.jcms.2011.10.001.
- 419 [42] Chen YM, Shen QC, Gokavarapu S, Ong HS, Cao W, Ji T. Osteosarcoma of the Mandible: A
420 Site-Specific Study on Survival and Prognostic Factors. *J Craniofac Surg* 2016;27:1929–33.
421 doi:10.1097/SCS.0000000000002968.
- 422 [43] Jeong H-I, Lee MJ, Nam W, Cha I-H, Kim HJ. Osteosarcoma of the jaws in Koreans: analysis
423 of 26 cases. *J Korean Assoc Oral Maxillofac Surg* 2017;43:312–7. doi:10.5125/jkaoms.2017.43.5.312.
- 424 [44] Lee RJ, Arshi A, Schwartz HC, Christensen RE. Characteristics and prognostic factors of
425 osteosarcoma of the jaws: a retrospective cohort study. *JAMA Otolaryngol-- Head Neck Surg*
426 2015;141:470–7. doi:10.1001/jamaoto.2015.0340.
- 427 [45] Gadwal SR, Gannon FH, Fanburg-Smith JC, Becoskie EM, Thompson LD. Primary
428 osteosarcoma of the head and neck in pediatric patients: a clinicopathologic study of 22 cases with a
429 review of the literature. *Cancer* 2001;91:598–605.
- 430 [46] Kimura Y, Tomihara K, Tachinami H, Imaue S, Nakamori K, Fujiwara K, et al. Conventional
431 osteosarcoma of the mandible successfully treated with radical surgery and adjuvant chemotherapy
432 after responding poorly to neoadjuvant chemotherapy: a case report. *J Med Case Reports* 2017;11.
433 doi:10.1186/s13256-017-1386-0.
- 434 [47] Ferrari D, Moneghini L, Allevi F, Biglioli GB and F. Osteosarcoma of the Jaw: Classification,
435 Diagnosis and Treatment 2017. doi:10.5772/67564.
- 436 [48] Penel N, Coindre J-M, Giraud A, Terrier P, Ranchere-Vince D, Collin F, et al. Presentation
437 and outcome of frequent and rare sarcoma histologic subtypes: A study of 10,262 patients with
438 localized visceral/soft tissue sarcoma managed in reference centers. *Cancer* 2017.
439 doi:10.1002/cncr.31176.
- 440 [49] Guérin M, Thariat J, Ouali M, Bouvier C, Decouvelaere A-V, Cassagnau E, et al. A new
441 subtype of high-grade mandibular osteosarcoma with RASAL1/MDM2 amplification. *Hum Pathol*
442 2016;50:70–8. doi:10.1016/j.humpath.2015.11.012.
- 443 [50] HE H, NI J, HUANG J. Molecular mechanisms of chemoresistance in osteosarcoma (Review).
444 *Oncol Lett* 2014;7:1352–62. doi:10.3892/ol.2014.1935.
- 445 [51] Li J, Yang Z, Li Y, Xia J, Li D, Li H, et al. Cell apoptosis, autophagy and necroptosis in
446 osteosarcoma treatment. *Oncotarget* 2016;7:44763–78. doi:10.18632/oncotarget.8206.
- 447 [52] Abarrategi A, Tornin J, Martinez-Cruzado L, Hamilton A, Martinez-Campos E, Rodrigo JP, et
448 al. Osteosarcoma: Cells-of-Origin, Cancer Stem Cells, and Targeted Therapies. *Stem Cells Int*
449 2016;2016. doi:10.1155/2016/3631764.
- 450 [53] Lindsey BA, Markel JE, Kleinerman ES. Osteosarcoma Overview. *Rheumatol Ther*
451 2016;4:25–43. doi:10.1007/s40744-016-0050-2.
- 452 [54] Bhuvaneshwar K, Harris M, Gusev Y, Madhavan S, Iyer R, Vilboux T, et al. Genome
453 sequencing analysis of blood cells identifies germline haplotypes strongly associated with drug

- 454 resistance in osteosarcoma patients. *BMC Cancer* 2019;19. doi:10.1186/s12885-019-5474-y.
- 455 [55] Wang D, Qian G, Wang J, Wang T, Zhang L, Yang P, et al. Visfatin is involved in the
456 cisplatin resistance of osteosarcoma cells via upregulation of Snail and Zeb1. *Cancer Biol Ther*
457 2019;1–8. doi:10.1080/15384047.2019.1591675.
- 458 [56] Pang X, Yin P, Han J, Wang Z, Zheng F, Chen X. cPLA2a correlates with metastasis and poor
459 prognosis of osteosarcoma by facilitating epithelial-mesenchymal transition. *Pathol Res Pract* 2019.
460 doi:10.1016/j.prp.2019.03.026.
- 461 [57] Lau CC. Molecular classification of osteosarcoma. *Cancer Treat Res* 2009;152:459–65.
462 doi:10.1007/978-1-4419-0284-9_26.
- 463 [58] Raimondi L, De Luca A, Costa V, Amodio N, Carina V, Bellavia D, et al. Circulating
464 biomarkers in osteosarcoma: new translational tools for diagnosis and treatment. *Oncotarget*
465 2017;8:100831–51. doi:10.18632/oncotarget.19852.
- 466 [59] Gomez-Brouchet A, Illac C, Gilhodes J, Bouvier C, Aubert S, Guinebretiere J-M, et al.
467 CD163-positive tumor-associated macrophages and CD8-positive cytotoxic lymphocytes are powerful
468 diagnostic markers for the therapeutic stratification of osteosarcoma patients: An
469 immunohistochemical analysis of the biopsies from the French OS2006 phase 3 trial.
470 *Oncoimmunology* 2017;6:e1331193. doi:10.1080/2162402X.2017.1331193.
- 471 [60] Chiappetta C, Mancini M, Lessi F, Aretini P, De Gregorio V, Puggioni C, et al. Whole-exome
472 analysis in osteosarcoma to identify a personalized therapy. *Oncotarget* 2017;8:80416–28.
473 doi:10.18632/oncotarget.19010.
- 474 [61] Rickel K, Fang F, Tao J. Molecular genetics of osteosarcoma. *Bone* 2017;102:69–79.
475 doi:10.1016/j.bone.2016.10.017.
- 476 [62] Brown HK, Schiavone K, Gouin F, Heymann M-F, Heymann D. Biology of Bone Sarcomas
477 and New Therapeutic Developments. *Calcif Tissue Int* 2018;102:174–95. doi:10.1007/s00223-017-
478 0372-2.
- 479 [63] Wedekind MF, Wagner LM, Cripe TP. Immunotherapy for osteosarcoma: Where do we go
480 from here? *Pediatr Blood Cancer* 2018;65:e27227. doi:10.1002/pbc.27227.
- 481 [64] WAN J, ZHANG X, LIU T, ZHANG X. Strategies and developments of immunotherapies in
482 osteosarcoma. *Oncol Lett* 2016;11:511–20. doi:10.3892/ol.2015.3962.
- 483 [65] Peng KA, Grogan T, Wang MB. Head and neck sarcomas: analysis of the SEER database.
484 *Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg* 2014;151:627–33.
485 doi:10.1177/0194599814545747.
- 486 [66] Bacci G, Longhi A, Versari M, Mercuri M, Briccoli A, Picci P. Prognostic factors for
487 osteosarcoma of the extremity treated with neoadjuvant chemotherapy: 15-year experience in 789
488 patients treated at a single institution. *Cancer* 2006;106:1154–61. doi:10.1002/cncr.21724.

Figure legends and tables.

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

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

Figure 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 incomplete resection);

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

Table 2. Radiological and pathological response to neoadjuvant chemotherapy.

Figure 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).

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

Patients included: n=31 (in 21 patients who underwent chemotherapy - as assessed by radiological reviewing. Maximal diameter was taken into account. Pathological response as assessed by tumor necrosis on surgical specimen).

Supplementary Table 1. Patients' characteristics associated with positive surgical resection margins (n=27).

Supplementary table 2. Differences between treatments of patients with MFOS according to their metastatic status. (MFOS: maxillofacial osteosarcoma; (M-) patients with localized/non-metastatic MFOS and (M+) with metastases; CT: chemotherapy; NA: Not applicable).

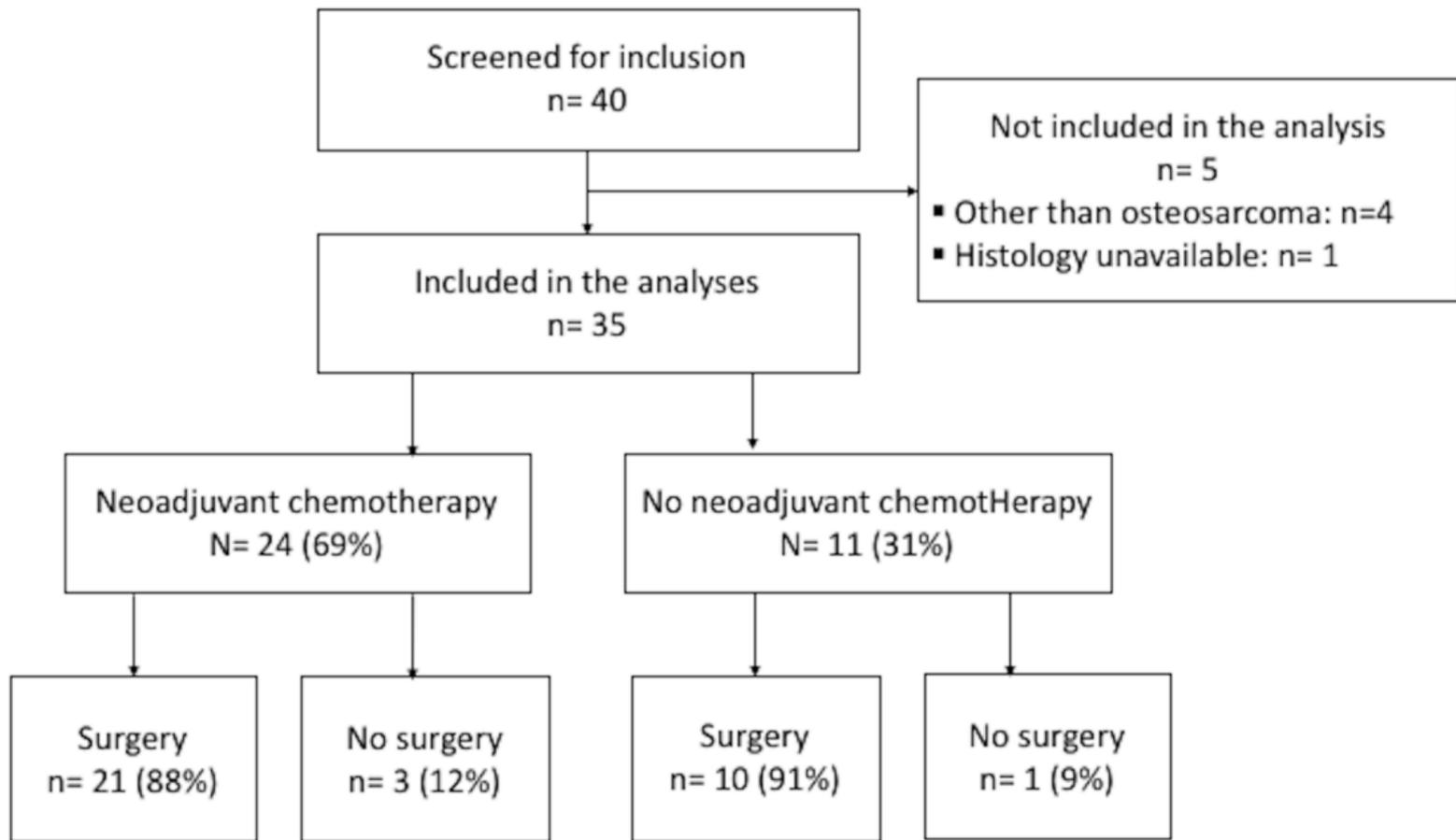
Supplementary table 3. Molecular mechanisms of chemoresistance in OS (adapted from He et al., 2014, Li et al., 2016, Abarategi et al., 2016 and Lindsey et al., 2016)

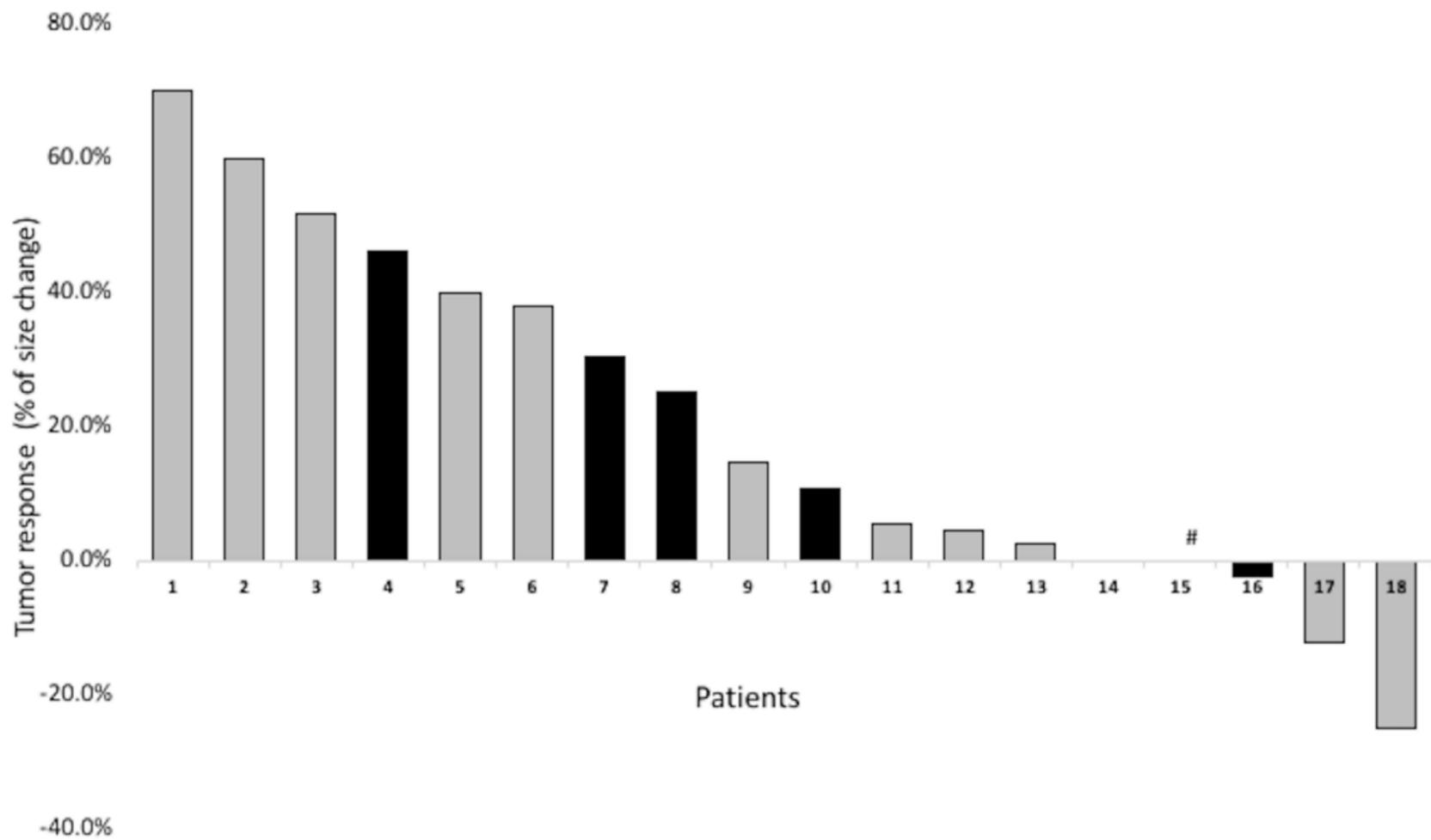
Supplementary table 4. Validated somatic mutations in candidate cancer genes identified by next-generation sequencing for Osteosarcoma. Specifically, Tumor Suppressor genes including p53, Rb,

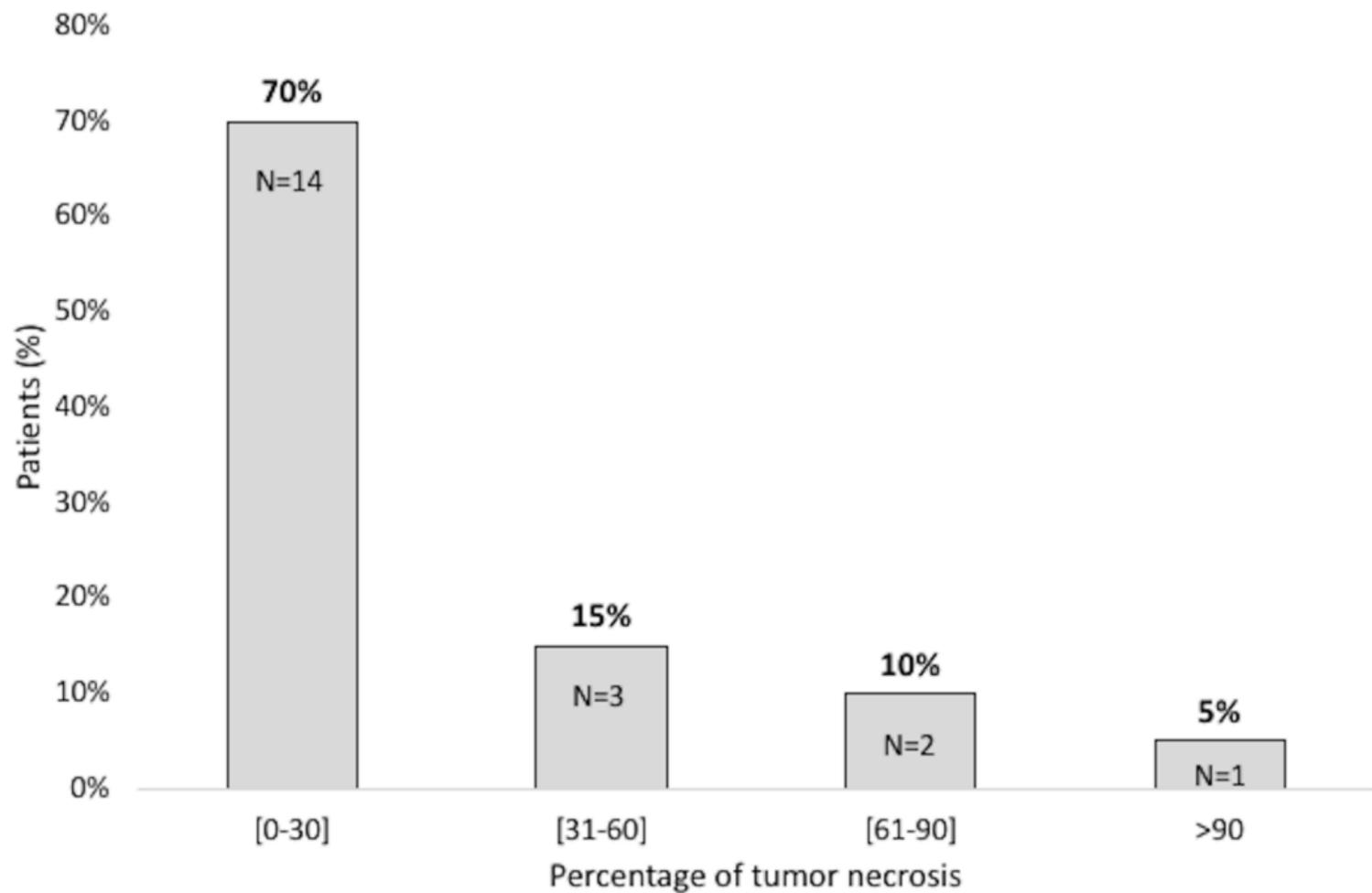
RECQL4, BLM, and WRN play a critical role in the development of osteosarcoma in patients with inherited familial syndromes that predisposed to this condition: Li-Fraumeni, hereditary retinoblastoma, Rothmund-Thomson, Bloom or Werner syndromes, respectively (adapted from Baumhoer 2018 and Rickel et al., 2017).

Supplementary table 5. Recent clinical trials for targeted therapies, immunotherapies and immunomodulators. (more details, see: <https://clinicaltrials.gov/ct2/search/advanced/osteosarcoma>; adapted from Wan et al., 2016 and Wedekind et al., 2018)

Supplementary table 6. Different type of targeted therapies using Monoclonal antibodies (mab) and immunotherapies for osteosarcoma treatment. (For more details, see: Wan et al., 2016, Wedekind et al., 2018)







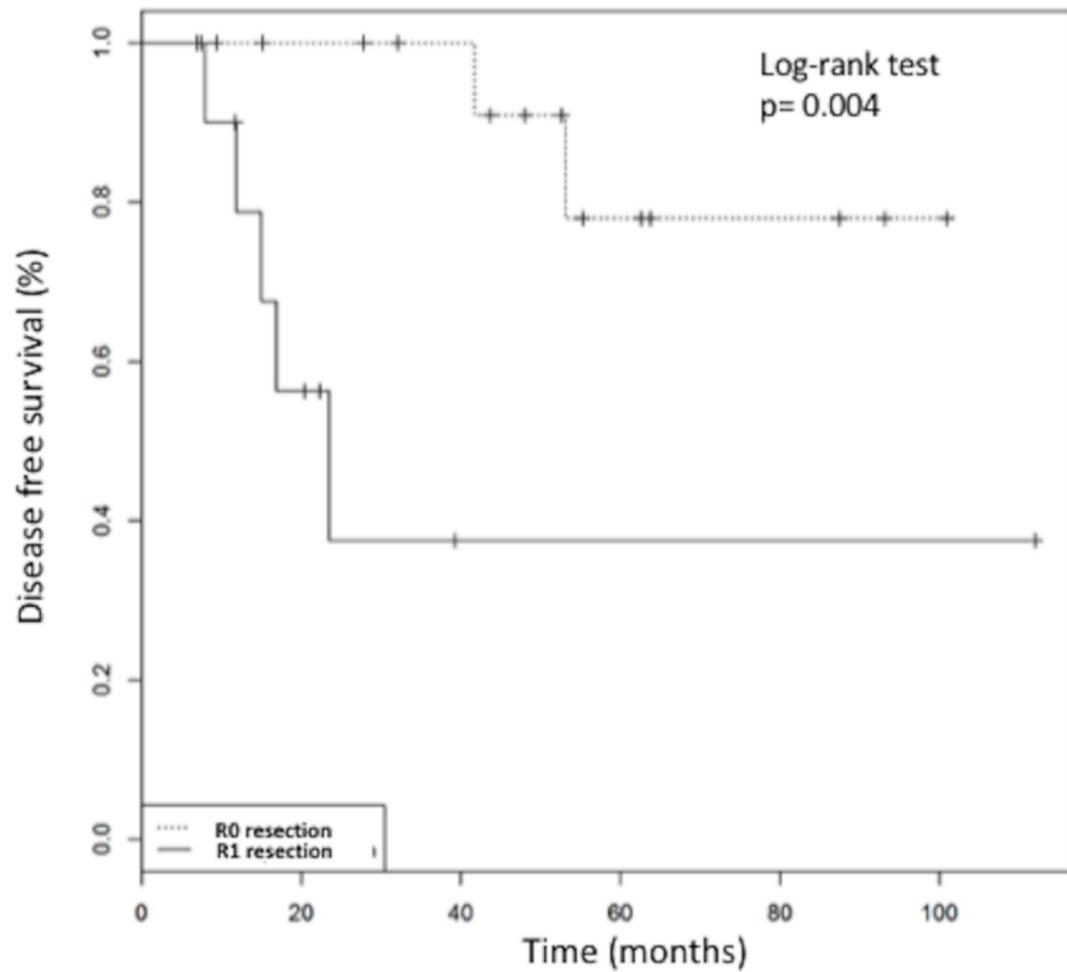


Table 1

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

^atumor size according to the largest dimension;

mm: millimeter;

Table 2

Table 2. Radiological and pathological response to neoadjuvant chemotherapy.

	Overall population (n=24)	
Median change in tumor size (in millimeters) from baseline^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.

Table 3

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]	
Maxillary bone	5/12 (41.7%)	67% [45%;99%]	-	0.308
Median initial tumor size (mm)^{bc}	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]	
No	3/10 (30%)	67% [36%;100%]	-	0.438
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