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ORIGINAL ARTICLE

Multimodal treatment of craniofacial osteosarcoma with high-grade histology. A single-center experience over 35 years

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Abstract High-grade craniofacial osteosarcoma (CFOS) is an aggressive malignancy with a poor prognosis. Our goals were to evaluate treatment outcomes in those treated at a single referral institution over 35 years and to compare our results to the available literature. A retrospective analysis of all 42 patients treated between 1980 and 2015 at Oslo University Hospital, Norway, identified in a prospectively collected database, was conducted. Mean follow-up was 79.6 months. Overall survival at 2 and 5 years was 70.5 and 44.7%, respectively. The corresponding disease-specific survival rates were 73.0 and 49.8%. Treatment was surgery only in eight cases. Additional therapy was administered in 34 patients: chemotherapy in nine, radiotherapy in seven, and a combination of these in 18 cases. Stratified analysis by resection margins demonstrated significantly better survival at 2 and 5 years after radical surgical treatment. Neoadjuvant chemotherapy and subsequent adequate surgery resulted in better survival than surgery alone. Half of the patients either had a primary or familial cancer predisposition. This is the largest single-center study conducted on high-grade CFOS to date. Our experience indicates that neoadjuvant chemotherapy with complete surgical resection significantly improved survival, compared to surgery alone.

Keywords Osteosarcoma · Surgical resection · Craniofacial bones · Multidisciplinary approach · Multimodal treatment · Survival

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Introduction

Osteosarcoma (OS) is the most commonly occurring primary malignant bone tumor worldwide [1–3]. The incidence of all OS subtypes is approximately 3.3 per one million persons per year in Norway [4] and is most common during the second decade of life (during natural bone growth) [1]. Approximately 97% of all OSs are high-grade lesions [3].

Craniofacial osteosarcoma (CFOS) represents only 10% of all OS and less than 1% of all head and neck cancers [2, 4, 5]. CFOS is generally diagnosed two decades later than its long-bone counterparts [4, 6] and shows clinical behavior that is different to OS of the trunk and extremity. In this regard, CFOS has less propensity to metastasize, but higher mortality due to the difficulty of obtaining tumor control [4–8].

Radical surgery, with the aim of achieving complete resection with negative histological margins, is the mainstay of curative OS management. The role of multimodal treatment in patients with OS in long bones is well established, and combination chemotherapy (ChT) has been shown to improve survival [9]. In contrast, the role of ChT is less clear in CFOS [4–8].

The goals of this study were to evaluate the management of patients with CFOS with high-grade tumors on histological

examination undergoing surgical resection at Oslo University Hospital (OUH) in Norway from 1980 to 2015 and to compare our results with other outcomes reported in the literature.

Materials and method

Patient cohort

We conducted an analysis of all patients with CFOS (defined as OS arising in the mandible, maxilla, or any of the extragnathic bones of the head) treated at OUH from 1980 to 2015. The catchment area of this institution covers approximately 56% of the entire Norwegian population. In addition, our institution accepts referrals involving challenging clinical cases from other health regions in Norway. Patient information was retrieved from a prospective database of all patients treated for OS in our health region.

Inclusion criteria were histologically verified high-grade CFOS [World Health Organization (WHO) grades III–IV] and primary surgical resection at OUH from 1980 to 2015, with or without radiotherapy (XRT) and/or ChT. The medical records of patients were also reviewed retrospectively to identify the study parameters not included in the database records.

Tumor-related variables

A histopathological diagnosis of OS was made by a consultant pathologist at presentation. All cases were formally re-examined by two dedicated sarcoma pathologists. Tumors were assessed for type, grade, determination of soft tissue infiltration, and chemotherapy response grade [10, 11]. The tumor site was classified according to the region of presumed origin in tumors affecting several craniofacial bones. Tumor size was determined from the surgical specimens and/or radiographical images at diagnosis and categorized depending on the maximum length of the tumor in centimeters. The quality of the surgical margins was also retrospectively scrutinized.

Treatment variables

Surgical treatment was deemed adequate if resection margins were negative according to a surgeon and pathologist joint assessment. ChT was defined adequate if the patient had received at least six chemotherapy courses containing a minimum of two drugs [high-dose methotrexate (at least 8 g/m^2), doxorubicin, cisplatin, or ifosfamide], according to previous publications [8, 12]. ChT was defined inadequate if only one drug or less than 6 cycles of therapy was administered.

Statistical analysis

The main endpoints of this study were overall and disease-specific survivals. Follow-up time was calculated from the date of surgery to either death, with or without disease, or last known status. Event time distributions were approximated using the Kaplan-Meier estimator [13], and the log rank test was used to test for any significant differences between the survival curves [14]. Prognostic factors for overall survival were identified using the Cox proportional hazard regression model [15]. Whether or not the observed proportions for a categorical variable differed from the hypothesized proportions was determined using the chi-square test or Fisher's exact test, as appropriate [16]. The level of statistical significance was set at p value = 0.050. Descriptive statistics were reported as a mean, range, 95% confidence interval (CI), and median, if appropriate. Statistical analysis was conducted using SPSS® version 22 (SPSS Inc., Chicago, USA).

Results

Clinical findings

The medical records of 49 patients were reviewed. Seven patients were excluded due to primary treatment prior to 1980 (three cases), the absence of surgical treatment due to locally advanced disease (two cases), primary treatment at another hospital (one case), and low-grade CFOS (one case), leaving 42 patients eligible for inclusion. Patient characteristics are summarized in Table 1. The sex distribution was nearly equal, comprising 22 male (52%) and 20 female (48%) patients. All of the patients were of Caucasian descent, with 41 of European (98%) and one of Arabic origin (2%). The mean age at diagnosis was 41.6 years (range 6–86 years, 95% CI 35.2–48.1 years). The peak incidence of disease in our cohort occurred from the age of 30–39 years.

Painless swelling was the most common presenting symptom, observed in 50% of all cases. Presenting symptoms were predating primary diagnosis with a mean of 4.7 months (range 0–29 months, 95% CI 2.8–6.5). Painless swelling as presenting symptom has led to significantly longer latency of diagnosis, compared to other, more nocuous symptoms [6.2 months (range 0.0–29.0 months, 95% CI 2.7–9.8) vs. 3.1 months (range 0.0–8.0 months, 95% CI 2.1–4.1), p value = 0.042].

Predisposing factors

A total of 21 (50%) patients in our cohort had either primary or familial cancer predisposition. Six of the patients with a primary predisposition to cancer had at least two first-grade relatives with cancer also (Table 1). Predisposition to cancer was

Table 1 Patient, treatment, and survival characteristics

Pt No	Sex	Predisposing factors	Age at dg	Presenting symptom	Localization	Tumor size (cm)	Treatment strategy	Surgical treatment	ChT	Follow-up time (months)	Survival status
1	F	FCP	36	Painful swelling	Os frontale	9	S + ChT + XRT	Inadequate	Adequate	32	DOD
2	F	MM	65	Painless swelling	Mandibula	8	S	Adequate	–	164	NED
3	F	–	38	Localized pain	Mandibula	10	S + ChT + XRT	Inadequate	Inadequate	11	DOD
4	F	–	61	Local bleeding	Os temporale	Unknown	S + XRT	Inadequate	–	3	DOD
5	M	Fibrous dysplasia	25	Local bleeding	Maxilla	Unknown	S + ChT + XRT	Adequate	Inadequate	28	DOD
6	M	–	33	Reduced sensation	Maxilla	Unknown	S	Inadequate	–	343	NED
7	M	–	19	Painless swelling	Os parietale	9	S + ChT + XRT	Inadequate	Adequate	41	DOD
8	F	–	27	Painless swelling	Maxilla	Unknown	S	Adequate	–	57	NED
9	M	–	72	Painless swelling	Maxilla	4	S + XRT[a]	Inadequate	–	32	DOD
10	F	–	65	Painless swelling	Mandibula	Unknown	S + ChT	Adequate	Inadequate	27	DOD
11	F	–	87	Painless swelling	Mandibula	6	XRT + S	Adequate	–	12	DOD
12	F	FCP	38	Painless swelling	Os ethmoidale	Unknown	S + XRT	Adequate	–	281	NED
13	F	–	31	Unknown	Mandibula	9	S + ChT + XRT	Inadequate	Inadequate	55	DOD
14	M	–	73	Painless swelling	Mandibula	6	S + XRT	Adequate	–	24	DOD
15	F	-	13	Painless swelling	Mandibula	7.5	ChT + XRT + S + XRT	Inadequate	Inadequate	13	DOD
16	M	FCP	38	Localized pain	Mandibula	5	ChT + S + ChT + XRT	Adequate	Adequate	149	NED
17	M	FCP	30	Painless swelling	Maxilla	4.5	ChT + S + ChT	Adequate	Adequate	245	NED
18	M	FCP + astrocytoma, BCC	41	Reduced sensation	Mandibula	4	ChT + S + ChT + XRT	Inadequate	Adequate	79	DOD
19	F	–	26	Painless swelling	Maxilla	Unknown	S	Inadequate	–	248	NED
20	M	FCP + BCC	45	Localized pain	Maxilla	6.4	ChT + XRT + S	Inadequate	Inadequate	3	DOD
21	M	–	54	Painless swelling	Maxilla	Unknown	S	Inadequate	–	223	NED
22	M	von Hippel-Lindau disease	26	Painless swelling	Os occipitale	5	S + ChT + XRT	Inadequate	Adequate	21	DOD
23	M	FCP	63	Localized pain	Maxilla	4.5	S + ChT + XRT	Inadequate	Inadequate	25	DOD
24	F	Rhabdomyosarcoma	10	Asymptomatic	Mandibula	3.8	ChT + S + ChT[a]	Inadequate	Inadequate	178	DOD
25	F	–	15	Painless swelling	Maxilla	4	S + XRT	Inadequate	–	10	DOD
26	F	Liposarcoma	45	Reduced sensation	Mandibula	4	ChT + S + ChT + XRT	Adequate	Adequate	41	NED
27	M	–	38	Painless swelling	Os parietale	11	ChT + S + ChT + XRT	Inadequate	Adequate	19	DOD
28	M	FCP + RB	45	Nasal obstruction	Maxilla	4.4	ChT + S + ChT + XRT[a]	Inadequate	Adequate	85	DOD
29	F	–	11	Painless swelling	Mandibula	1.2	S	Inadequate	–	166	NED
30	F	FCP	77	Painful swelling	Maxilla	3	S + XRT	Adequate	–	148	NED
31	M	SCC	59	Painless swelling	Mandibula	8	ChT + S + ChT + XRT[a]	Inadequate	Inadequate	9	DOD
32	M	–	60	Painless swelling	Mandibula	2.2	S	Adequate	–	18	DOD
33	M	–	18	Localized pain	Os parietale	3.4	S + ChT	Inadequate	Inadequate	110	NED
34	F	FCP + BCC	61	Painless swelling	Mandibula	3.6	ChT + S + ChT	Adequate	Inadequate	99	NED
35	M	Li-Fraumeni syndrome	28	Painless swelling	Mandibula	4.5	ChT + S + ChT + XRT	Adequate	Adequate	99	NED
36	F	FCP + RB	7	Localized pain	Os frontale	1.8	ChT + S + ChT[a]	Adequate	Adequate	88	NED
37	F	–	33	Gingival fistula	Mandibula	2	ChT + S + ChT	Inadequate	Adequate	76	NED
38	F	Astrocytoma	45	Painless swelling	Os temporale	4.2	S + ChT + XRT[a]	Inadequate	Adequate	30	DOD
39	M	SCC	77	Localized pain	Mandibula	6	S[a]	Inadequate	–	4	DOD
40	M	Non-Hodgkin's lymphoma	59	Reduced Sensation	Mandibula	3.8	S + ChT[a]	Inadequate	Adequate	31	AWD
41	M	–	46	Reduced sensation	Os parietale	5	S + ChT + XRT	Inadequate	Adequate	18	NED
42	M	–	33	Localized pain	Mandibula	2	ChT + S + ChT	Inadequate	Adequate	2	NED

Cases are numbered in chronological order

FCP familial cancer predisposition, *BCC* basal cell carcinoma, *RB* retinoblastoma, *SCC* squamous cell carcinoma, *MM* malignant melanoma, *S* surgery, *ChT* chemotherapy, *XRT* radiotherapy, *NED* no evidence of disease, *AWD* alive with disease, *DOD* died of disease

[a] XRT-induced OS

present in 16 patients (38%). Eight patients (19%) had previously been diagnosed with either bilateral retinoblastoma (two patients), squamous cell carcinoma of the nasal and oral cavity (one and two patients, respectively), embryonal rhabdomyosarcoma (one patient), non-Hodgkin's lymphoma (one patient), and low-grade glioma (one patient). All of them had previously undergone surgical treatment and XRT before developing CFOS. The mean time between XRT and the CFOS diagnosis was 186.7 months (range 70–448 months, 95% CI 50.2–323.3). Eight patients (19%) had fibrous dysplasia, low-grade glioma, malignant melanoma, basal cell carcinoma, von Hippel-Lindau disease, liposarcoma or Li-Fraumeni syndrome prior to the diagnosis of CFOS. In addition, malignant disease was present in the first-degree relatives of 14 of the patients (33%). At least two first-degree relatives of nine of these 14 patients (21%) had cancer.

Tumor characteristics

All of the patients had high-grade CFOS [WHO grade IV in 34 (81.0%) cases]. Histologically, chondroblastic tumors were the most common, observed in 20 cases (48%). The mean tumor size was 5.2 cm (a median of 4.5 cm, 95% CI 4.3–6.0). The jaws were affected in 32 (76%) patients, while the tumor was extragnathic in 10 (24%) patients.

Treatment

Treatment constituted surgery alone for eight cases (19%). Multimodal therapy was given in 34 patients (80%), including ChT in 9 (21%), XRT in 7 (17%), and a combination of ChT and XRT in 18 (43%). Fourteen patients (33%) underwent both neoadjuvant and adjuvant treatments, in addition to surgery. The mean time between diagnosis and primary treatment was 0.5 months (a range of 0.0–4.0 months, 95% CI 0.2–0.7). Treatment characteristics are summarized in Table 1.

Surgical resection

Mandibular resection was the most common procedure (18 cases, 43%). Eleven patients (26%) underwent maxillary resection (combined with craniectomy in four cases). Craniotomy was performed in ten cases (24%). Orbital exenteration had to be undertaken in four cases (10%). One patient had both mandibular and maxillary resections, combined with craniectomy, owing to the presence of a large and highly invasive tumor. Fourteen patients (33%) underwent surgical reconstruction as a part of the primary surgical treatment, using free skin graft in six, fibula graft in five, Vitallium implant in two, and myocutaneous flap in one case.

Adequate surgical resection was achieved in 15 cases (36%). Seven of the 15 patients underwent neoadjuvant therapy, including ChT in six and XRT in one case. Malignant cells were found in, or very close to, the resection margins in 21 cases (50%), while the status of the surgical margins remained unknown in 6 cases (14%).

Complications relating directly to surgical treatment were registered in seven cases (17%), including cerebrospinal fluid leak and localized infection in two cases and submental fistula, localized hematoma, and acute myocardial infarction in one case each.

Chemotherapy

ChT regimens were not well defined prior to 1990. Thereafter, protocols established by the Scandinavian Sarcoma Group—primarily designed for OS of the extremities—were followed, adjusted for age and toxicity in patients unable to receive all of the cycles according to the predefined protocol [17].

The treatment strategy in our study constituted ChT in 27 patients (64%). Adequate ChT—as defined previously—was administered to 16 of these 27 patients. Fifteen patients (36%) received neoadjuvant ChT prior to surgery, and it was deemed to be adequate in 12. The histological response to neoadjuvant ChT could be evaluated in 13 patients. A response rate of >90% was observed in only three cases.

The number of patients receiving adequate ChT has increased over the last three decades. Forty percent of all patients treated with ChT received adequate treatment between 1980 and 1989, 44% between 1990 and 1999, and 77% between 2000 and 2015.

Radiotherapy

Twenty-five patients (60%) received XRT, mainly administered postoperatively (22 cases). It was used as an adjunct to suboptimal surgical resection (16 cases) or against recurrence and metastasis (six cases) in the majority of cases. XRT was boosted with brachytherapy (192-Iridium) or bone-targeted radionuclide therapy with samarium-153-ethylenediaminetetramethylene phosphonate in five patients. The mean dose of XRT administered postoperatively was 59 Gy (a median of 60 Gy, 95% CI 50.0–68.1).

Outcomes

Fourteen (33%) patients in our cohort were still alive, 13 without evidence of disease on completion of the study. Twenty-three patients (67%) had deceased due to their CFOS, and five deaths were due to other diseases. We obtained 100% follow-up. The mean follow-up time was 79.6 months (range 2–343 months, median 36.5 months, 95% CI 52.6–106.7) as of October 1, 2015 (the final follow-up). The mean follow-up time of patients with no evidence of disease was 141.9 months (range 0–343 months, median 129 months, 95% CI 94.6–

189.3). Importantly, none of the patients were lost to follow-up.

The overall survival rate (OS) of the cohort was calculated to be 70.5% at 2 years and 44.7% at 5 years postoperatively (Fig. 1). The corresponding disease-specific survival (DSS) rates were 73 and 49.8% (Fig. 2).

Tumor size at diagnosis of <5 cm correlated significantly with better DSS (88.9 vs. 45.0% at 2 years, 71.8 vs. 15.0% at 5 years, p value = 0.003) (Fig. 3). There was a significant correlation (p value = 0.017) between positive surgical margins and subsequent death from the disease (odds ratio of 2.3). Stratified DSS was 86.7 and 66.7% at 2 and 5 years, respectively, where adequate surgery had been performed, compared to 65.0 and 39.3% for cases of non-radical surgery (p value = 0.042) (Fig. 4).

We found no significant correlations between outcome measures and age, sex, presenting symptoms, histological type, previous XRT, and primary or familial cancer predisposition. Tumor location did not impact survival significantly either. However, it is intuitively convincing that complete resection of a tumor in the mandible should be performed more easily than at other locations of the head. Failure to detect a difference may be the result of a type II statistical error, because of the low number of patients included in the study or a de facto lack of an effect. DSS stratified by tumor location showed best survival for patients with CFOS located to the maxilla in our cohort (83.3 and 58.3% at 2 and 5 years vs. 68.4 and 51.5% with tumor located to the mandibula and 67.5 and 33.8% with tumor located to the extragnathic bones of the head).

Seventeen patients (40.5%) experienced recurrence of disease after a mean time of 19 months postoperatively (median 12 months, range 1–120 months, 95% CI 5.3–33.2). The mean recurrence-free survival (RFS) rate was 62.9% at 2 years and 56.8% at 5 years of follow-up (Fig. 5). Stratified RFS was 78.8% 2 years and 70.9% 5 years postoperatively in cases where adequate surgery was performed, compared to 53.3 and 48.5% at 2 and 5 years of follow-up, respectively, in cases of non-radical surgery (Fig. 6).

Distant metastases affecting the lungs and the skeleton developed in 11 patients (26%), with a mean time of 29 months (range 5–83 months, 95% CI 13.8–44.2).

The use of neoadjuvant ChT in patients who subsequently underwent adequate surgical treatment correlated significantly with better survival than adequate surgery alone (p value ≤0.001). By contrast, a statistically significant correlation between the use of neoadjuvant ChT and negative surgical margins was not observed (p value = 0.666).

Failure to administer adequate ChT correlated significantly with disease recurrence and dismal outcome (relative risk of 1.87, p value = 0.048). Furthermore, DSS in patients who received adequate ChT was superior to that in patients where ChT was inadequate (85.7 vs. 63.6% at 2 years and 62.9 vs. 27.3% at 5 years), but this correlation did not reach statistical significance because of the low cohort size (Fig. 7).

Discussion

The goals of this study were to evaluate the clinical features, management, and outcome of 42 patients with high-grade

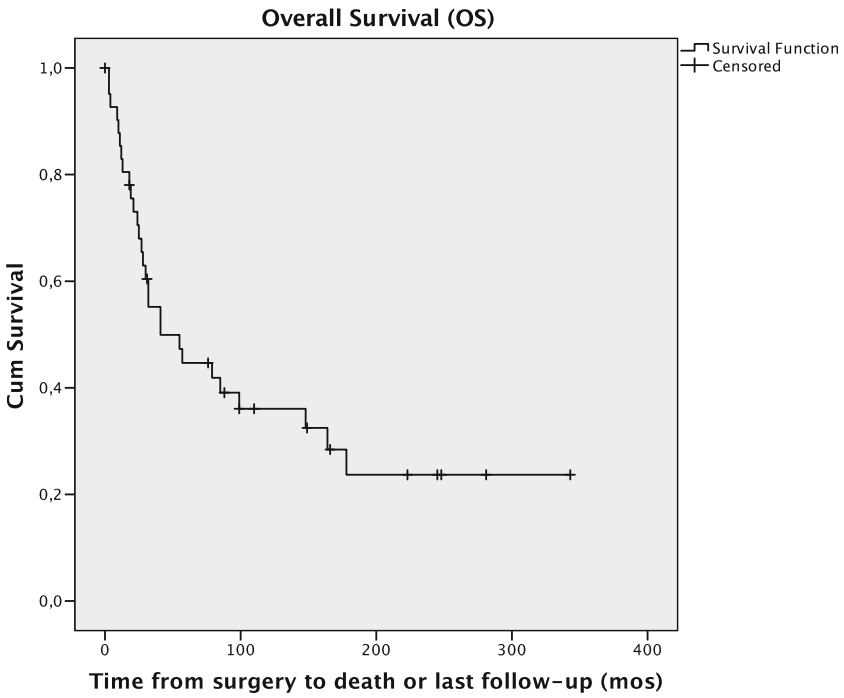

Fig. 1 Overall survival for the whole study population

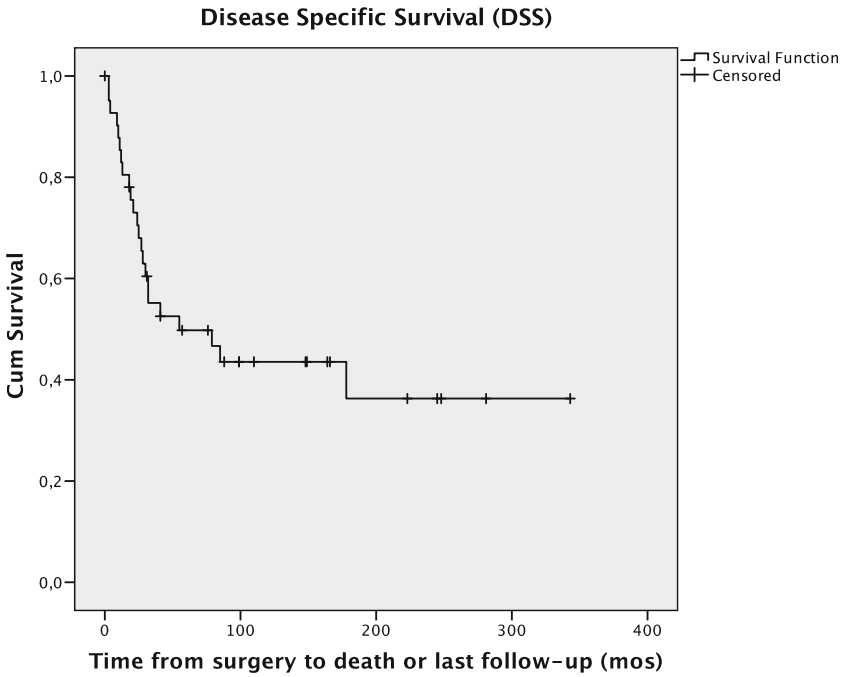

Fig. 2 Disease-specific survival for the whole study population

CFOS undergoing multimodal treatment, including surgical resection, at OUH, Norway, over the last 35 years and to compare our results to the available literature. To our knowledge, our study represents the largest single-institution cohort of high-grade CFOS ever published.

Peak incidence of this disease was observed in the third decade, with no gender predilection. Younger patients usually had a genetic predisposition (i.e., Li-Fraumeni syndrome), had other underlying abnormalities (i.e., fibrous dysplasia), or had undergone previous radiation of the bone due to other malignancies. A remarkably high degree of primary and familial predisposition to cancer was observed in our cohort.

We investigated 57 articles from the surgical, otolaryngological, orthopedic, and oncological literature after a non-systematic review [2, 5–8, 18–70]. Fifty of these were reported on specific treatment methods and survival data for individuals with OS of the head and neck [2, 5, 7, 10, 18, 20, 23, 24, 26, 28–53, 56–70]. Only 21 of these articles were solely

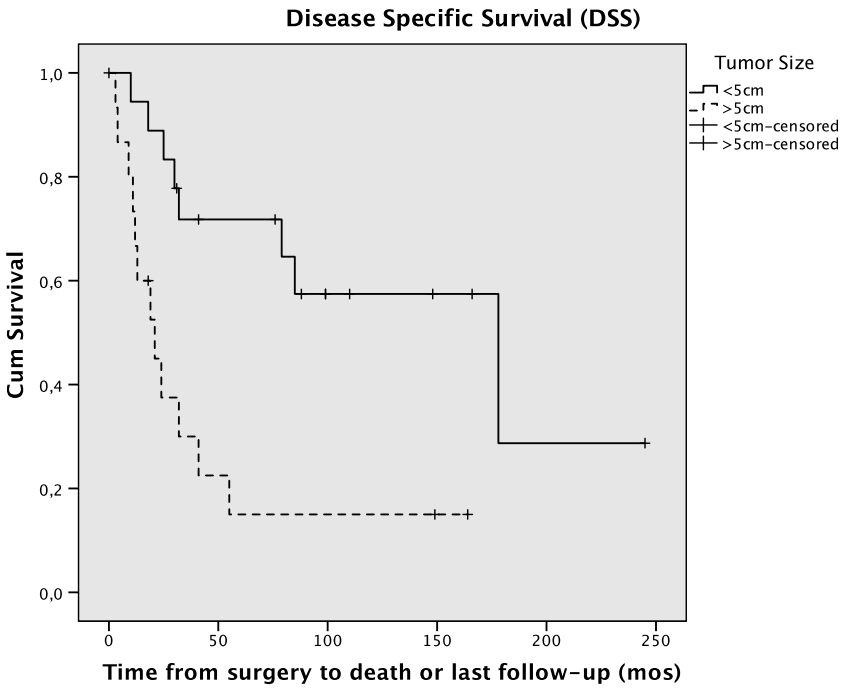

Fig. 3 Disease-specific survival for the whole study population, stratified by tumor size at diagnosis

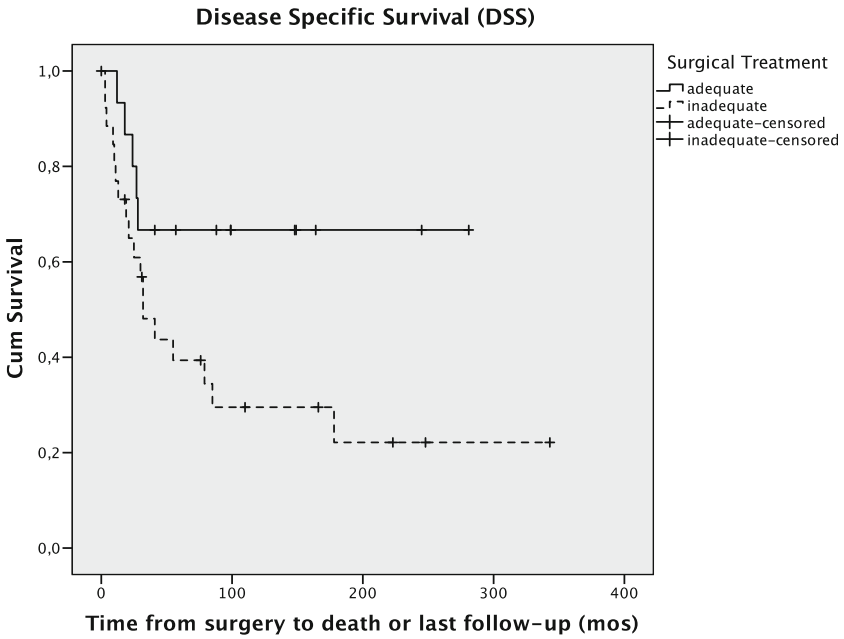

Fig. 4 Disease-specific survival for the whole study population, stratified by surgical margins

based on CFOS including extragnathic bones of the head [5, 18, 20, 24, 26, 29–33, 36, 38, 42–44, 51, 53, 63, 68–70] (Table 2). Three publications were reviews of the relevant literature [21, 27, 54]. Overall survival rates of approximately 60–70% at 5 years, ranging from 9.5 to 74%, have been reported in published studies on CFOS [5, 18, 20, 24, 26, 29–33, 36, 38, 42–44, 51, 53, 63, 68–70]. However, several of these cohorts comprised patients with both low- and high-grade CFOS. Fifty-eight patients were included in the largest reported multicenter study [70], and 38 patients with high-grade CFOS participated in the largest single-institution study [20].

Overall survival rates in our cohort were 70.5 and 44.7% at 2 and 5 years of follow-up, respectively, and corresponding DSS was 73.0 and 49.8%. Interestingly, an improvement in the DSS rate was noted with time (DSS at 5 years was 41.7% when the primary treatment was administered prior to 2000, compared to 63.7% when it was initiated after 2000). The survival rates in our study compare favorably with the relevant international figures, despite the obvious bias in our disfavor when comparing cohorts containing both low- and high-grade CFOS.

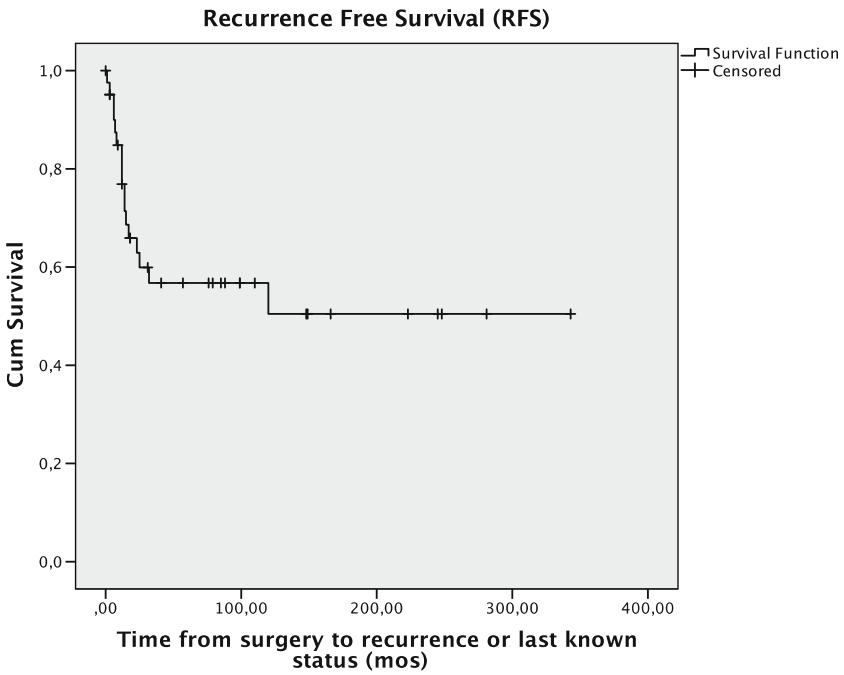

Fig. 5 Recurrence-free survival for the whole study population

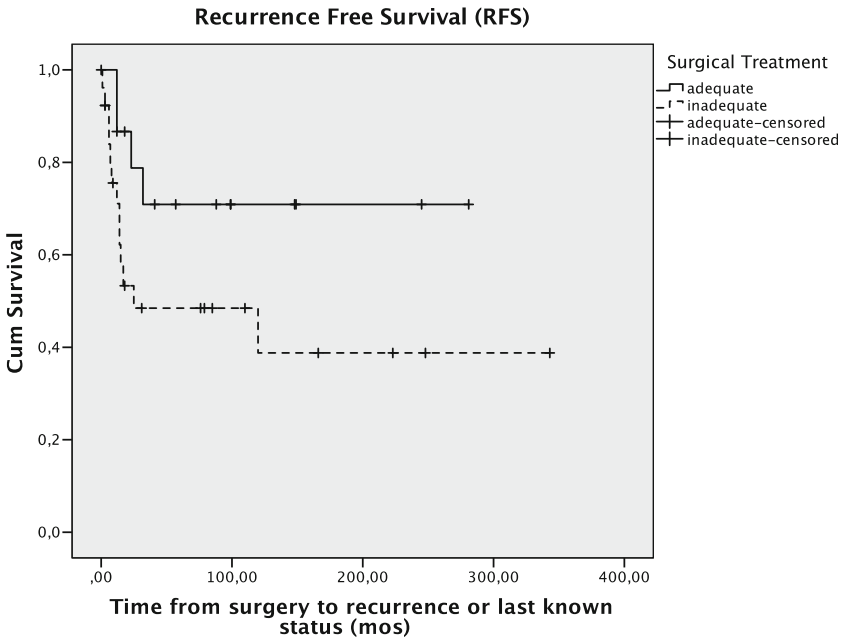

Fig. 6 Recurrence-free survival for the whole study population, stratified by surgical margins

Surgical resection of a primary tumor with negative surgical margins is crucial, preferably in combination with adjuvant ChT, when treating OS in the long bones [1, 8, 71–73] CFOS is more challenging to treat as radical resection with negative surgical margins may lead to very severe functional and visible defects. Malignant tumors involving the infratemporal fossa were considered to be unresectable in the past owing to their perceived biological aggressiveness, the difficulty in achieving negative histological margins, and the associated surgical morbidity and mortality [74]. It has also been noted that surgeons are reluctant to perform resections that seriously affect cosmesis and function in younger patients [21]. However, progress within the fields of surgery and radiology has facilitated the use of more aggressive resection and advanced reconstructive techniques, leading to decreased morbidity and improved survival rates in patients with CFOS resection.

The frequency of negative surgical margins in our cohort improved from decade to decade and impacted significantly on survival (p value = 0.042). The effects of adequate surgery on survival are well documented.

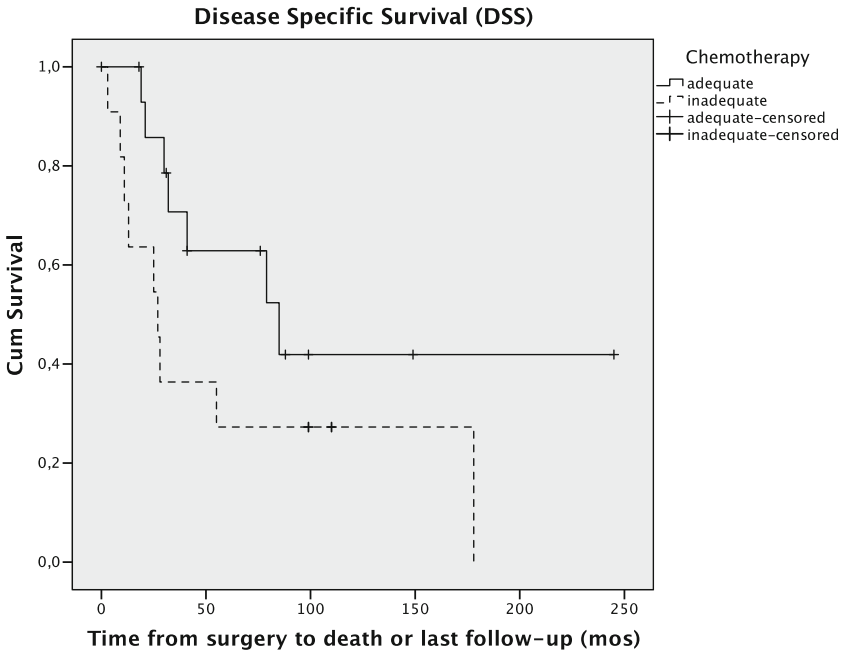

Fig. 7 Disease-specific survival of patients receiving chemotherapy, stratified by treatment adequacy

Table 2 Published articles and main data based on CFOS cohorts with extragnathic bone involvement

Author	Cohort size	High-grade histology	Survival at 5 years follow-up	Origin	Publication year	Inclusion period	Inclusion base
Kragh et al. [63]	44	18	31.4%	Mayo Clinic, USA	1958	1916–1957	Single institution
Caron et al. [36]	43	Unknown	23.3%	Memorial Sloan Kettering Cancer Center, New York, USA	1971	1930–1966	Single institution
Nora et al. [38]	21	19	9.5%	Mayo Clinic, USA	1983	?- 1983	Single institution
Sundaresan et al. [68]	8	Unknown	Appr. 33%	Memorial Sloan Kettering Cancer Center, New York, USA	1985	1972–1983	Single institution
Huvos et al. [69]	19	Unknown	Appr. 60%	Memorial Sloan Kettering Cancer Center, New York, USA	1985	1921–1981	Single institution
Mark et al. [29]	18	4	47%	University of California Los Angeles, USA	1991	1955–1987	Single institution
Vege et al. [42]	34	Unknown	<18%	Tata Memorial Hospital, Mumbai , India	1991	1963–1981	Single institution
Tran et al. [5]	15	14	49%	University of California Los Angeles, USA	1992	1955–1988	Single institution
Wanebo et al. [43]	29	Unknown	45%	Head and Neck Sarcoma Registry, USA	1992	1982–1990	Register, national
Salvati et al. [44]	19	Unknown	Median survival in pre-ChT era 16 months; in ChT era 56% at 2 years	La Sapienza, Rome, Italy	1993	1953–1989	Single institution
Ha et al. [31]	27	20	55%	Johns Hopkins, USA	1999	1946–1998	Single institution
Gorsky et al. [32]	23	Unknown	33.3%	British Columbia Tumor Registry, Canada	2000	1969–1998	Register, national
Patel et al. [24]	44	22	70%	Memorial Sloan Kettering Cancer Center, New York, USA	2002	1981–1998	Single institution
Smith et al. [33]	496 (438)	145	59.7%	University of Iowa, USA	2003	1985–1996	Register, national
Huber et al. [18]	14	11	30.1%	Province of Alberta, USA	2008	1974–1999	Single institution
Jasnau et al. [26]	49	44	74%	Cooperative German-Austrian-Swiss Sarcoma Study Group	2008	1977–2004	Multicenter
Laskar et al. [51]	50	26	Appr. 30%	Tata Memorial Hospital, Mumbai , India	2008	1995–2004	Single institution
Guadagnolo et al. [20]	119	38	63%	MD Anderson Cancer Center, Houston, USA	2009	1960–2007	Single institution
Oda et al. [30]	13	8	72%	University of Washington, USA	2013	1981–1996	Single institution
Lim et al. [53]	15	12	Appr. 70%	Severance Hospital, Korea	2013	2000–2011	Single institution
Boon et al. [70]	77	58	55%	The Netherlands	2016	1993–2013	Multicenter
This paper	42	42	49.8%	Oslo University Hospital, Norway		1980–2015	Single institution

ChT changed the prognosis of CFOS dramatically from 1980 onwards, resulting in a significant increase in survival rates. The existing literature on outcomes in patients with CFOS is hard to interpret because patients who were treated over a prolonged period were grouped in an effort to gather sufficient data for statistical analysis. We identified only four articles reporting on single-center experiences, based on selected time periods after 1980 [24, 30, 51, 53].

Sundaresan et al. and Salvati et al. were the first to address the effects of ChT on survival and demonstrated dramatically improved prognosis in patients receiving chemotherapy as adjuvant treatment [44, 68]. Smith et al. also reported on improved survival rates in the last two decades of the last century [33]. Kassir et al. assessed the reported effect of adjuvant therapy on the outcome of OS, based on a meta-analysis of the literature between 1980 and 1994 [21]. They did not find any survival benefit from the addition of ChT or XRT to surgery, but this study included unvalidated data in terms of surgical adequacy, while the outcome variables of patients were pooled, irrespective of the margin status. Smeele et al. documented the effect of ChT on survival with respect to CFOS in the same year, only including data from studies that reported on the surgical margins [55]. They found that patients with free margins and who had received chemotherapy treatment had the best survival rates, followed by those with free margins and no chemotherapy.

Patel et al. reported on a noticeable improvement in the ability to exert local disease control over a 5-year period, the distant metastases, and overall survival, when comparing the authors' own historical cohort and a new one treated in the ChT

era. However, they found that the negative surgical margins were the only significant predictor of overall and DSS [24].

Oda et al. also documented the possible benefits of neoadjuvant ChT in 2013 [30]. Boon et al. have recently (in 2016) documented than in patients younger than 75 years of age with surgically resected high- and intermediate-grade OS of the head and neck, treatment with (neo-)adjuvant ChT resulted in a significantly smaller risk of local recurrence [70].

We documented that the administration of neoadjuvant ChT correlated significantly better with survival than surgery alone in patients undergoing adequate surgical resection (p value <0.001). The management strategy consisting of a combination of surgery and ChT was associated with better DSS than surgery and XRT or surgery with both ChT and XRT (p value = 0.015).

High-dose methotrexate (at least 8 g/m^2), doxorubicin, cisplatin, and also ifosfamide are the most commonly used ChT drugs worldwide, but there is still no international consensus on their optimal combination [9, 75]. Cases of head and neck OS—including CFOS—should be evaluated in multidisciplinary teams with surgeons and sarcoma specialists. This kind of cooperation is crucial to identify the best multimodal treatment option for each patient. We have intended to follow treatment protocols for classical—extremity localized—OS, adjusted for age and kidney function [76, 77].

Adjuvant XRT might be indicated postoperatively in cases of non-radical surgery [20–23, 27, 51]. Proton beam therapy may offer some benefit to patients with skull base lesions, as it limits the dose of radiation to the visual apparatus, cranial nerves, and central nervous system, thereby reducing the risk of long-term complications [27]. Hyperfractionated and intensity-modulated XRT should also be considered with regard to reducing the risk of optic neuropathy in selected patients [78].

We propose continuous follow-up for at least 10 years, partly divided between a head and neck surgeon and an oncologist, ensuring the discovery of both local recurrences, distant metastases, and delayed complications related to ChT. We recommend four times yearly during the first year, three times yearly between years 2 to 5, and once per year between years 5 to 10. Chest X-ray should be obtained at each consultation in addition to full blood count in patients who underwent ChT. Magnetic resonance imaging is indicated yearly during the first 3 years or at any time if deemed necessary after clinical evaluation.

Study limitations and strengths

A weakness of this study is that it is based on observational data. CFOS is so rare that it is unlikely that the impact of multimodal treatment would ever be analyzed in a randomized prospective fashion, even within the framework of a multi-institutional study. Our cohort included patients who had been treated for more than three decades. Thus, it was subject to the impact of improvements in radiological, surgical, radiotherapy, and chemotherapy techniques.

Study strengths were the setting, sample size, design, and follow-up duration (long term). The data were restricted to one health center only, reducing the possible confounding effect of differences in access to the healthcare service. Thus, the selection bias that is inherently present in a larger multicentered study was seemingly avoided.

The study reflects the largest single-institution cohort of high-grade CFOS among published series, involving patients solely treated in the ChT era with surgery performed for histologically verified high-grade CFOS. Only endpoints that were verifiable were used with respect to the data quality. Lastly, 100% follow-up was obtained.

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Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval This study was approved by the data protection official at OUH. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study does not contain any studies with animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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