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Primary and radiation induced skull base osteosarcoma: a systematic review of clinical features and treatment outcomes

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Abstract

Purpose: We aim to systematically review and summarize the demographics, clinical features, management strategies, and clinical outcomes of primary and radiation-induced skull-base osteosarcoma (SBO).

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Authors' contributions: All authors contributed to the study conception and design. The study idea was proposed by [Ali S. Haider, BS] and [Tarek Y. El Ahmadieh MD]. The literature search, articles screen, and data extraction were perfumed by [Othman Bin Alamer MBBS], [Ali S. Haider BS], [Navraj S. Sagoo BS], and [Tarek Y. El Ahmadieh MD]. Data analysis was performed by [Othman Bin Alamer MBBS]. The first draft of the manuscript was drafted by [Othman Bin Alamer MBBS], [Ali S. Haider BS], [Navraj S. Sagoo BS]. All authors critically revised and edited the first draft and commented on all versions of the manuscript. The project was supervised by [Tarek Y. El Ahmadieh MD] and [Aaron A. Cohen-Gadol MD, MSc, MBA]. All authors read and approved the final manuscript.

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Methods: PubMed, Scopus, and Cochrane databases were used to identify relevant articles. Papers including SBO cases and sufficient clinical outcome data were included. A comprehensive clinical characteristic review and survival analysis were also conducted.

Results: Forty-one studies describing 67 patients were included. The median age was 31 years (male = 59.7%). The middle skull-base was most commonly involved (52.7%), followed by anterior (34.5%) and posterior (12.7%) skull-base. Headache (27%), exophthalmos (18%), and diplopia (10%) were common presenting symptoms. Sixty-eight percent of patients had primary SBO, while 25% had radiation-induced SBO. Surgery was the main treatment modality in 89% of cases. Chemotherapy was administered in 65.7% and radiotherapy in 50%. Median progression-free survival (PFS) was 12 months, and the overall 5-year survival was 22%. The five-year survival rates of radiation-induced SBO and primary SBO were 39% and 16%, respectively ($P < 0.05$).

Conclusion: SBO is a malignant disease with poor survival outcomes. Surgical resection is the primary management modality, in conjunction with chemotherapy and radiotherapy. Complete surgical resection showed better survival rates compared to partial resection. Radiation-induced SBO has a superior survival outcome as compared to its primary counterpart.

Keywords

Skull-base osteosarcoma; primary osteosarcoma; radiation induced osteosarcoma; systematic review

Introduction

Osteosarcoma is a rare, debilitating neoplasm that may arise from de novo mutation, metastasis from another location, or radiation exposure. It is the most common type of bone cancer in children and adolescents, exhibiting an incidence of 3.4 per million per year.[1] Although it primarily affects long bones, nearly 10% of osteosarcomas present in the head and neck, often manifesting in the mandible and maxilla.[2][3] Primary skull-base osteosarcoma (SBO) or head and neck osteosarcoma (HNO) with skull-base invasion is a considerably rare presentation.[4] In contrast to long bone osteosarcoma, which usually presents in the first and second decades of life, head and neck osteosarcoma (including SBO) often presents in the third and fourth decades.[5] Predisposing factors include prior radiation and underlying conditions such as Paget disease.[6–9]

Regardless of the involved site, the mainstay of treatment consists of gross total resection, with adjuvant chemotherapy and radiotherapy. However, anatomical constraints are often a barrier to complete resection. Given the rare incidence of disease, most conclusions about SBO are derived from single institution reports and registries. With the paucity of data in the literature and discrepancy among the reported cases regarding SBO, the clinical features remain indistinct and a consensus on a standardized treatment protocol has not yet been reached.[4, 10–12] In this literature review, we aim to summarize the demographics, clinical features, management strategies, and clinical outcomes of SBO to inform where additional research is needed.

Methods

Literature Search

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] PubMed, Scopus, and Cochrane databases were searched from inception to June 2020. A medical subject headings (MeSH) term and keyword search of each database were conducted using the Boolean operators OR and AND. Terms used were as follows: “skull,” “base,” and “osteosarcoma.” Identified papers were uploaded into Mendeley, and duplicates were eliminated.

Study Selection

Pre-established inclusion and exclusion criteria were deductively defined. Studies were included if they met the following criteria: 1) English language, 2) prospective or retrospective studies involving at least one patient, 3) patients with histologically confirmed SBO in any age group, 4) available data on clinical features and treatment outcomes. Studies were excluded if they: 1) did not adequately identify and report on clinical outcomes or management of SBO or 2) were meta-analyses, reviews, editorials, letters, or books.

Two authors (O.B.A. and N.S.S.) independently assessed the titles and abstracts of all extracted papers based on the inclusion and exclusion criteria. Studies that met inclusion criteria were then further evaluated independently with full text review by the same two authors. Eligible studies were selected based on the pre-specified criteria, and disagreements between the two authors were resolved via a third author (A.S.H). References of the included articles were also screened to retrieve any relevant papers.

Data Extraction

Data from included studies were extracted by one author (O.B.A.) and confirmed independently by two other authors (A.S.H. and N.S.S.) to ensure accuracy. Extraction variables included: 1) author’s name, 2) date of publication, 3) study design, 4) sample size, 5) gender, 6) prior interventions (radiotherapy or chemotherapy), 7) management course and treatment modalities used (radiotherapy, chemotherapy, surgical approach), 8) complication, and 9) survival. Terms “gross-total resection” or “complete surgical resection” were considered equivalent to “complete resection.” Likewise, the terms “sub-total resection,” “near-total resection,” and “debulking” were considered equivalent to ‘partial resection.’

Data Synthesis

The primary outcomes of interest were the clinical features, management course, and survival analysis of both primary SBO and HNO with skull-base invasion. The secondary outcomes of interest were complications with a comparison between primary SBO and radiation- induced SBO. Meta-analysis was precluded due to heterogeneity in outcome measures and the limited number of studies. Moreover, evaluation of the risk of bias across the papers was not conducted given that all included studies were observational studies for which there is no validated tool to assess for risk of bias.[14]

Statistical Analysis

Means and ranges were used to summarize continuous variables, while frequencies and percentages were used to summarize categorical variables. Overall and progression-free survivals were illustrated using Kaplan–Meier curves. The log-rank test was used to compare survival curves of primary, radiation-induced, and metastatic SBO and compare survival curves of complete and partial resection in patients who received adjuvant therapy. A P-value <0.05 was considered significant for all analyses. Analyses were performed using the statistical software SPSS V.25 (IBM Corp, Armonk, New York).

Results

Study Selection

The initial database search identified 325 articles (Medline: 148, Scopus: 174, Cochrane: 3). After duplicate removal, a total of 245 studies were screened by abstract and title, of which 199 were excluded, leaving 46 full-text studies. Of these, 25 articles failed to meet the inclusion criteria and subsequently excluded. References were additionally screened and identified 20 articles. A total of 41 studies (2 case series and 39 case reports) were included in this systematic review (Fig. 1).[4, 7, 12, 15–51]

Patient Demographics and Clinical Characteristics

A total of 67 patients with histologically confirmed SBO were analyzed. Patient demographics and clinical characteristics are collectively and individually presented in Tables 1 and 2, respectively. There were 40 males (60%) and 27 females (40%), and the median age at diagnosis was 31 years (range 9–78). Of 55 patients with reported tumor locations, 29 (52.7%) tumors involved the middle skull-base, 19 (34.5%) involved the anterior skull-base and 7 (12.7%) involved the posterior skull-base. Additionally, the most common involved structure was the sphenoid bone (n=15; 22.4%), followed by the sphenoid sinus (n=8; 21%) and the temporal bone (n=6; 9%). The most commonly reported symptoms included headache (27%), exophthalmos (18%), and lastly, diplopia (10.4%).

Most of the reported tumors were primary SBO (n=46; 68.4%), followed by radiation-induced SBO (n=17; 25.4%) and metastatic SBO (n=4; 6%). Among the radiation-induced SBO cohort, various initial pathologies were present, including: craniopharyngioma, adenoid cystic carcinoma, squamous cell carcinoma, and embryonal rhabdomyosarcoma, with pituitary adenoma being the most common pathology. Additionally, the median dose of radiation and latency period were 5100 cGy and 13 months, respectively. Of all included patients in this study, only 21 were found to have data on histopathologic tumor subtypes, of which 9 (43%) were osteoblastic, 7 (33.3%) chondroblastic, 4 (19%) telangiectatic, and 1 (4.8%) fibroblastic. Also, metastases were reported in 5 cases. Two primary skull-base osteosarcomas metastasized to the liver and shoulder bones, while other two metastatic cases of SBO showed further metastases to the lung and multiple facial bones. However, only one patient with radiation-induced SBO showed distal metastasis, involving the lungs. Initial management involved surgical resection in sixty patients (89.6%), out of which 53 patients reported surgical details. Out of those 53 patients with details on method of resection, 29 (54.7%) were complete resections, and 24 (45.3%) were partial resections. Out of the total

study cohort, forty-four patients (65.7%) received chemotherapy, and 34 (51%) received radiotherapy with a median dose of 5000 cGy (interquartile range: 4500–5500).

Survival outcomes and analysis

While 37 (55.2%) patients had a complete remission, disease progression was reported in 13 (19.4%) cases, and recurrence was reported in 17 (25.4%) cases with a median progression-free survival (PFS) of 12 months (range: 0.2 – 143 months). A five-year PFS is provided in Fig. 2A. There were 33 (52%) deaths reported with a median overall survival of 12 months (range: 1.5–66 months). Five-year overall survival is shown in Fig.2B. Additionally, a five-year survival analysis indicates that radiation-induced OS had a significantly better overall survival than the primary OS (log-rank test, $P < 0.05$, Fig. 3). Patients who received adjuvant therapy and underwent complete surgical resection had a better outcome than patients who received adjuvant therapy with partial resection; however, it was statistically insignificant ($P = 0.59$) (Fig. 4).

Discussion

Osteosarcoma of the skull base is a rare and challenging condition. The pathogenesis of osteosarcoma remains obscure; however, various risk factors such as trauma, benign bone lesions, environmental factors, and genetic predisposition have been implicated in the literature.[6, 52, 53] This systematic review aimed to provide a comprehensive summary of the current literature regarding SBO. With a collective total of 67 patients, this study represents the largest analysis of SBO to date, examining the patient background, surgical management, clinical outcomes, recurrence, and survival associated with this tumor.

Clinical features and outcomes

The median age for the included cases of SBO was 31 years. This is unlike the incidence of long bone osteosarcoma (LBO), which is bimodally distributed by age, and peaks in adolescence (second and third decades) and in the elderly (seventh decade).[54] In addition, there was a male predominance (59.7%) seen across the included cases similar to long bone osteosarcoma.[54] The clinical symptoms and tumor locations in our study were intuitively associated: Exophthalmus, diplopia, and decreased visual acuity were seen with tumors involving the orbital cavity while nasal congestion and epistaxis were seen with tumors invading the nasal cavity. Overall, most patients presented with headaches, exophthalmos, and diplopia (27%, 18%, and 10%, respectively). In contrast, a case series by Guo et al. reported facial lump as the primary symptom.[4] This is likely attributed to the fact that most included cases were secondary osteosarcomas due to radiation’s direct impact on skull bones.

In our analysis, the most common location for SBO was the middle skull-base (52.7%), and the most involved structure was the sphenoid bone (22.4%). Likewise, the sphenoid was reported as the most commonly involved bone by chondrosarcoma as well.[55] Due to the condensed anatomy and proximity to adjacent structures, most tumors in our study invaded multiple compartments with some tumors exhibiting facial, nasal, oral, or ophthalmic

extensions. As such, a management strategy involving a multidisciplinary approach with otolaryngology, oral maxillofacial surgery or ophthalmology is warranted in these patients.

Imaging and Histopathology

Of the included cases, CT scans typically highlighted a mixture of osteoblastic-osteoclastic lesions with a predominance of one type, hypertonicity indicating calcification, and irregular margins. Similar findings were also reported in HNO as well as in LBO.[56–58] MR imaging predominantly revealed an iso-intense heterogeneous tumor on T1-weighted images and hypo-intense heterogeneous tumor on T2-weighted images with contrast enhancement. Likewise, a recent case series by Luo et al., reported parallel MRI features suggesting consistency among cases.[57] However, due to the ambiguity involved in imaging cues, biopsy is required for a definitive diagnosis.

Grossly, osteosarcoma shows osteoid production by neoblastic mesenchymal cells and heterogeneous areas of necrosis and hemorrhage.[59] Neoplastic cells, mainly osteoblasts, can present with considerable polymorphism, such as spindle cells, ovoid, small round cells, fusiform, epithelial, plasmacytoid, and round cells.[17, 60] Moreover, the pathological tumor grading system is based on the extent of local destruction and tumor cell differentiation level ranging from grade 1 and 2 (low-grades) to grade 3 and 4 (high-grades) osteosarcoma.[61] Osteosarcoma immunohistochemically is mainly positive for vimentin, S100, and neuron-specific enolase; however, it is negative for actin, myoglobin, and cytokeratin.[48] Histopathologically, osteosarcoma can be divided into four categories based on the predominant cell type: Osteoblastic, Chondroblastic, Telangiectatic, and Fibroblastic.[60] Of 21 cases that reported the histopathological diagnosis, the osteoblastic type was the most common (42.9%), followed by chondroblastic (33.3%), telangiectatic (19%), and fibroblastic (5%). This mirrors literature on LBO, which has the greatest prevalence of osteoblastic, followed by chondroblastic and fibroblastic, respectively.[62] However, the results of HNO were less concordant. While histological subtype distributions similar to this study were documented in HNO, other authors reported different distributions in HNO with chondroblastic as the most common type, followed by fibroblastic and osteoblastic.[63, 64]

Treatment and Survival

While most of our cohort underwent surgery, nearly 45% failed to achieve complete resection, which emphasizes the complex anatomy and surgical challenges of the skull-base. Generally, intra-operative estimation by the neurosurgeon has been used to determine partial, subtotal, or total tumor resection. However, neurosurgeons have begun to adopt objective measures, like post-op scanning, to determine the extent of resection. While most authors in our cohort relied on neurosurgeons' estimation intraoperatively along with resection margin testing, almost none of the included articles reported employing objective measures like volumetric analysis on the post-operative scans.

Generally, the five-year survival rate in long bone osteosarcoma is between 70%−80%, and roughly 60% in HNO.[65, 66] In his literature review, Guo et al. reported that the 5-year survival rate in 47 patients with SBO was 37.8%, with a median of 42 months.[4] In contrast, our five-year overall survival rate was 22%, with a median of 12 months and

a range of 0.2–143. The poor survival observed in our study is most likely attributed to the anatomic complexity and close proximity of SBO to vital intracranial structures, thus limiting the total resection in a considerable portion of cases. The choice and the effect of adjuvant therapy in SBO have not yet been investigated thoroughly in the current literature. However, data on HNO have shown controversial results. While some authors support adopting adjuvant therapy, including chemotherapy and radiotherapy, in conjunction with surgical resection in HNO, others presented results showing a significant survival benefit with surgical resection alone.[67, 68] These data contradict the results of LBO, which demonstrated a clear survival benefit of adjuvant therapy that allows limb-sparing procedures rather than traditional amputation in some cases.[69–71] On the other hand, some evidence exists that chemotherapy enhances survival outcomes in craniofacial osteosarcoma; therefore, several authors advocate employing the chemotherapy protocols used for OS of the long bones for craniofacial osteosarcoma.[72, 73] Similarly, an SBO case series found that patients who underwent comprehensive treatment—which includes surgical resection in conjunction with chemotherapy and/or radiotherapy—demonstrated a better overall survival rate than the patients who underwent resection alone and showed a significantly longer median survival duration.[4] These findings support adopting a comprehensive treatment approach in osteosarcoma of the skull base.

In our cohort, the authors' choice of chemotherapy agents and radiotherapy concepts were variable and case-based due to the lack of standard protocol in treating SBO. While most articles did not specify the chosen chemotherapeutic agents, few adopt standard chemotherapy regimens like CDOP (Cyclophosphamide, Doxorubicin, Oncovin, Prednisone), which is typically employed to treat non-Hodgkin lymphoma.[16] Also, other commonly reported chemotherapeutic agents include Cisplatin, Ifosfamide, and Adriamycin. Similarly, radiotherapy modalities were rarely reported, and in our cohort, merely two authors reported the employed radiation concept, while the reset contented with mentioning the radiation dose only. One article reported employing 3-dimensional conformal radiotherapy and used 6MV photon-linear accelerator for dose delivery, whereas the other reported adopting CyberKnife radiotherapy.[18, 25] However, this modality resulted in cerebrospinal fluid leakage that needed further management.

In patients who received adjuvant therapy, our analysis indicated a minimal difference in 5-year survival rates between the complete surgical resection and partial surgical resection groups. However, two-year survival rates showed a noticeable survival difference between the complete surgical resection (63%) and partial surgical resection (42%) groups, although this failed to meet statistical significance ($P = 0.59$). Likewise, some authors reported similar survival outcomes in HNO.[66, 74] In an article by Smith et al., patients who underwent surgical resection with negative margins had a five-year survival of 64%, in contrast to only 32% for patients with a positive margin.[66] Our cohort demonstrates a metastasis rate of 7%, in concordance with the current data on head and neck osteosarcoma.[2, 12] In contrast, literature illustrated higher micrometastasis and overt metastasis rates in long bone osteosarcoma, reaching 80% rate of pulmonary micrometastasis.[75] Although our pool included only one case of radiation-induced SBO with pulmonary metastasis, data showed that the lungs are the primary organs for metastasis in radiation-induced SBO.[7]

Besides tumor progression, local recurrence was the leading cause of death and was reported in 25% of our patients. This high percent can potentially be attributed to limited tumor resection and the limited use of intraoperative frozen sections to confirm margin negativity.[4]

Primary vs. radiation-induced osteosarcoma of the skull base

Although widely recognized an effective modality for treatment of HNO, radiation therapy has been associated with short- and long-term morbidity and may predispose to the development of a secondary malignancy.[76, 77] Few cases of radiation-induced SBO have been reported in the literature, and a comprehensive clinical understanding of this condition remains indistinct. According to Salvati et al., the incidence of radiation-induced osteosarcoma is estimated to range from 0.01% to 0.03% of all irradiated patients.[28] In contrast, our study reported 17 cases (25%) presenting with radiation-induced SBO. Our pooled analysis indicates that pituitary adenoma is the most common pathology of initial radiation therapy, contrasting the most comprehensive case series, which reported retinoblastoma as the most common initial pathology.[7] Initially, the diagnosis criteria of radiation-induced SBO indicated a latency period of at least 5 years.[78] However, shorter latency periods have been reported by serval studies including our study which indicates a short latency period with a median of 13 months.[79–81]Moreover, the median overall survival in radiation-induced SBO cases was reported in the literature as 41 months.[47] However, our pooled analysis indicated a median overall survival of 29 months among radiation-induced SBO cases. In comparison, radiation induced osteosarcoma of the long bones has a 5-year survival rate of 17%, which is worse than the survival rates seen in primary LBO (70%).[82],[83] However, our study showed that radiation-induced SBO has a better 5-year survival rate than primary SBO with statistical significance ($p<0.04$) (Figure 3). Although our overall 5-year survival rate was 22%, stratifying our data indicated an excellent 5-year survival rate of 39% in the radiation induced SBO group comparing to the primary SBO group (16%). The most likely explanation is that the radiation-induced tumors tend to be lateral and superficial, making complete excision more feasible and accessible.[4]

Limitations

The limitations of this study – many of which stem from the paucity of SBO in the literature – warrant further discussion. In addition to the small sample size, there was heterogeneity in the outcome data which challenged the statistical power. Unstratified factors limited survival rates; a specific example was the difference between the survival rates of radiation-induced SBO and primary SBO. Although our analysis showed a better 5-year survival rate in the radiation-induced SBO group, the factor of radiation could be confounded with better management courses and more favorable tumors for resection.

Conclusion

SBO is a rare, debilitating neoplasm that may arise as a result of a de novo mutation, metastasis from another location, or radiation exposure. In addition to adjuvant radiation therapy and chemotherapy, complete surgical resection should be pursued as a means of treating this tumor. SBO demonstrated a poor five-year survival rate at 21%. However,

radiation-induced SBO was shown to have a better overall survival in contrast to primary SBO. In order to have a clear understanding and an agreement on treatment protocols, further prospective studies with sufficient sample size are necessary.

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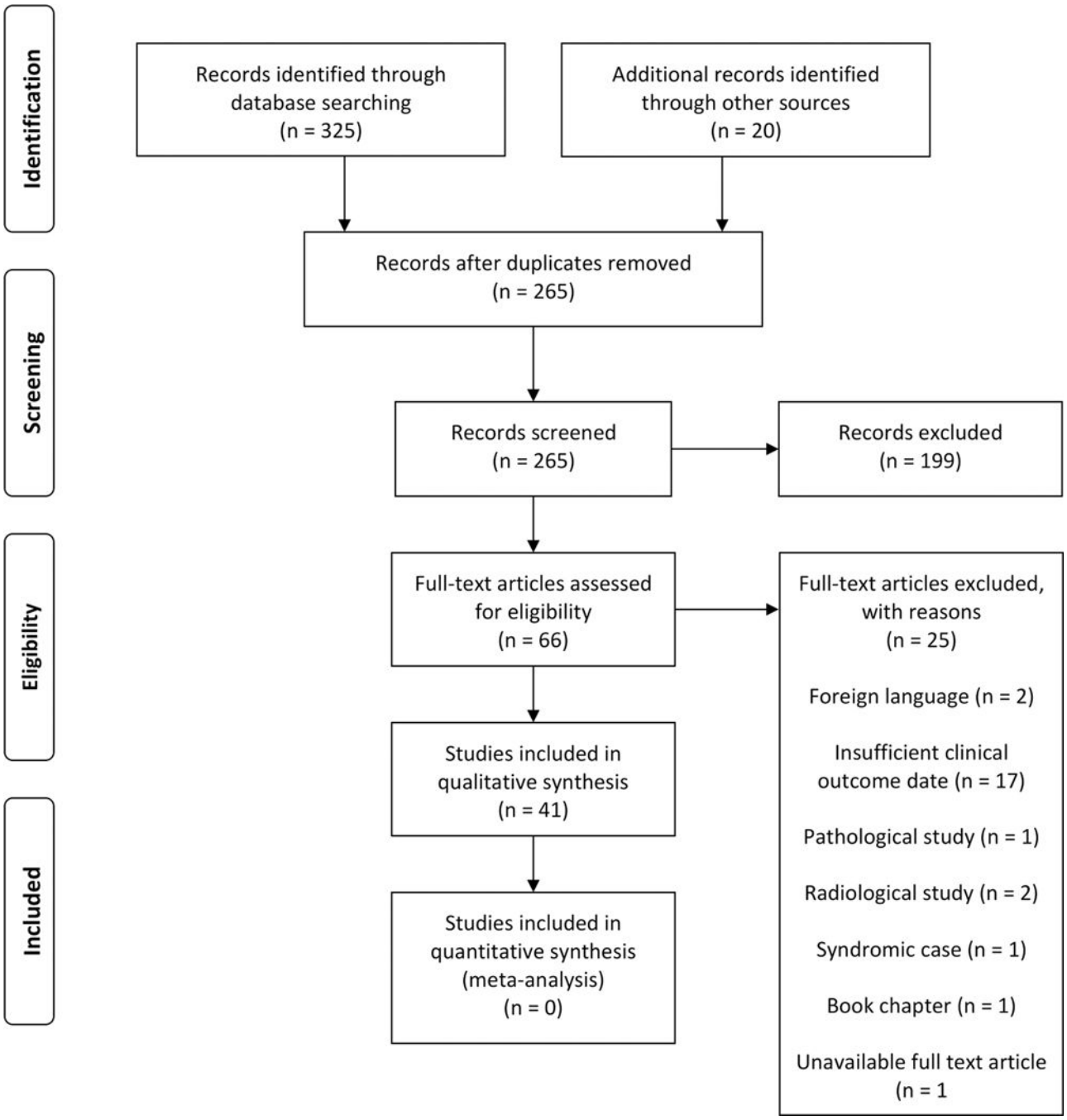

Figure 1.
PRISMA flowchart illustrating the search strategy and data selection based on the inclusion and exclusion criteria.

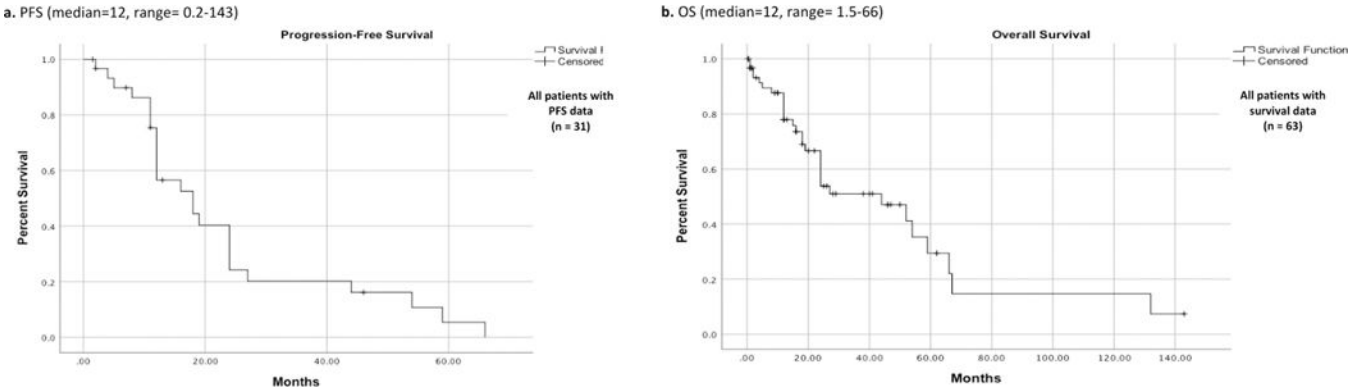

Figure 2.

Kaplan-Meier survival curves for **a.** PFS (n = 31) and **b.** OS (n = 63) for the overall pooled cohort. PFS, progression free survival; OS, overall survival.

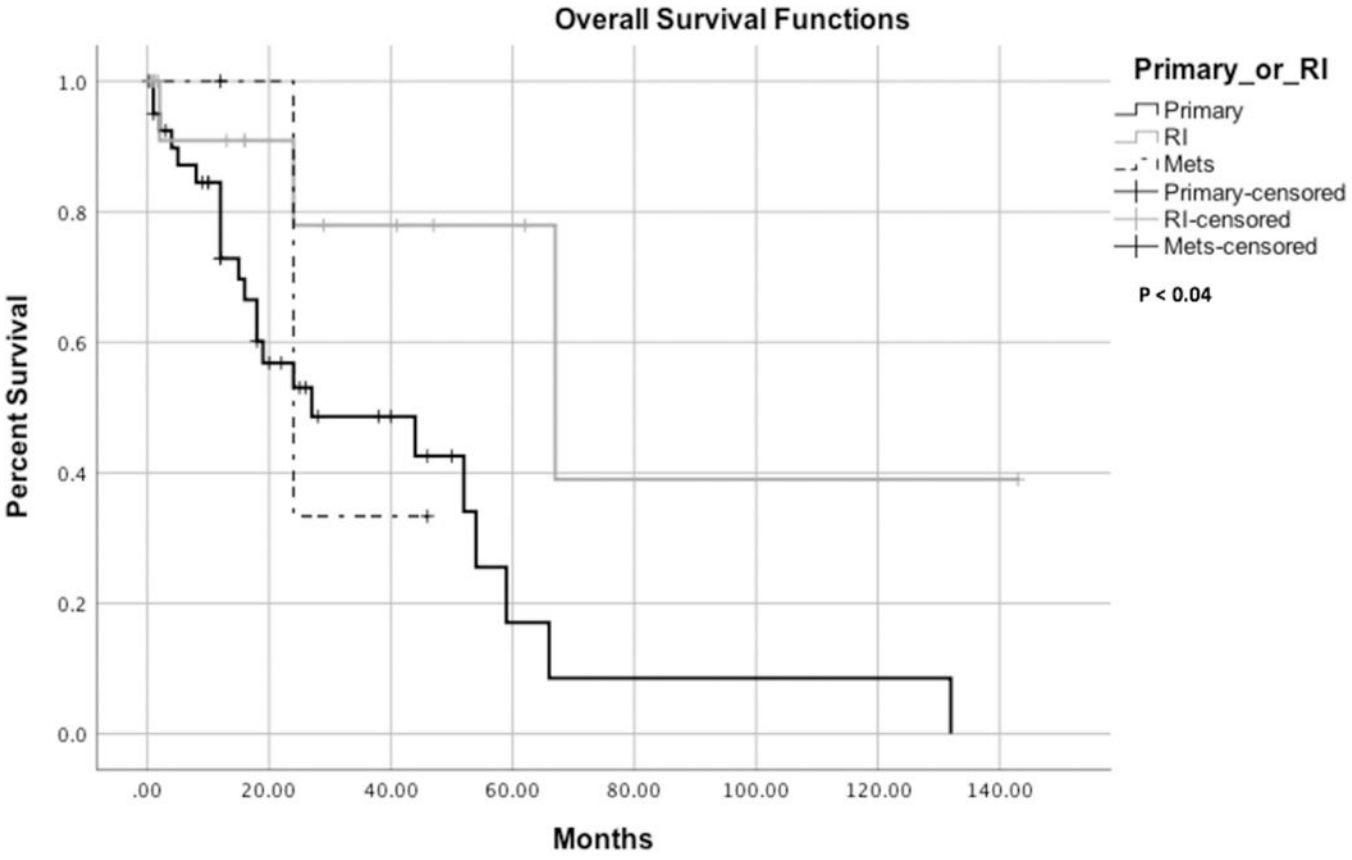

Figure 3.

Kaplan-Meier survival curves comparing the overall survival of primary, metastatic and radiation induced osteosarcoma. RI, radiation induced; Mets, Metastatic.

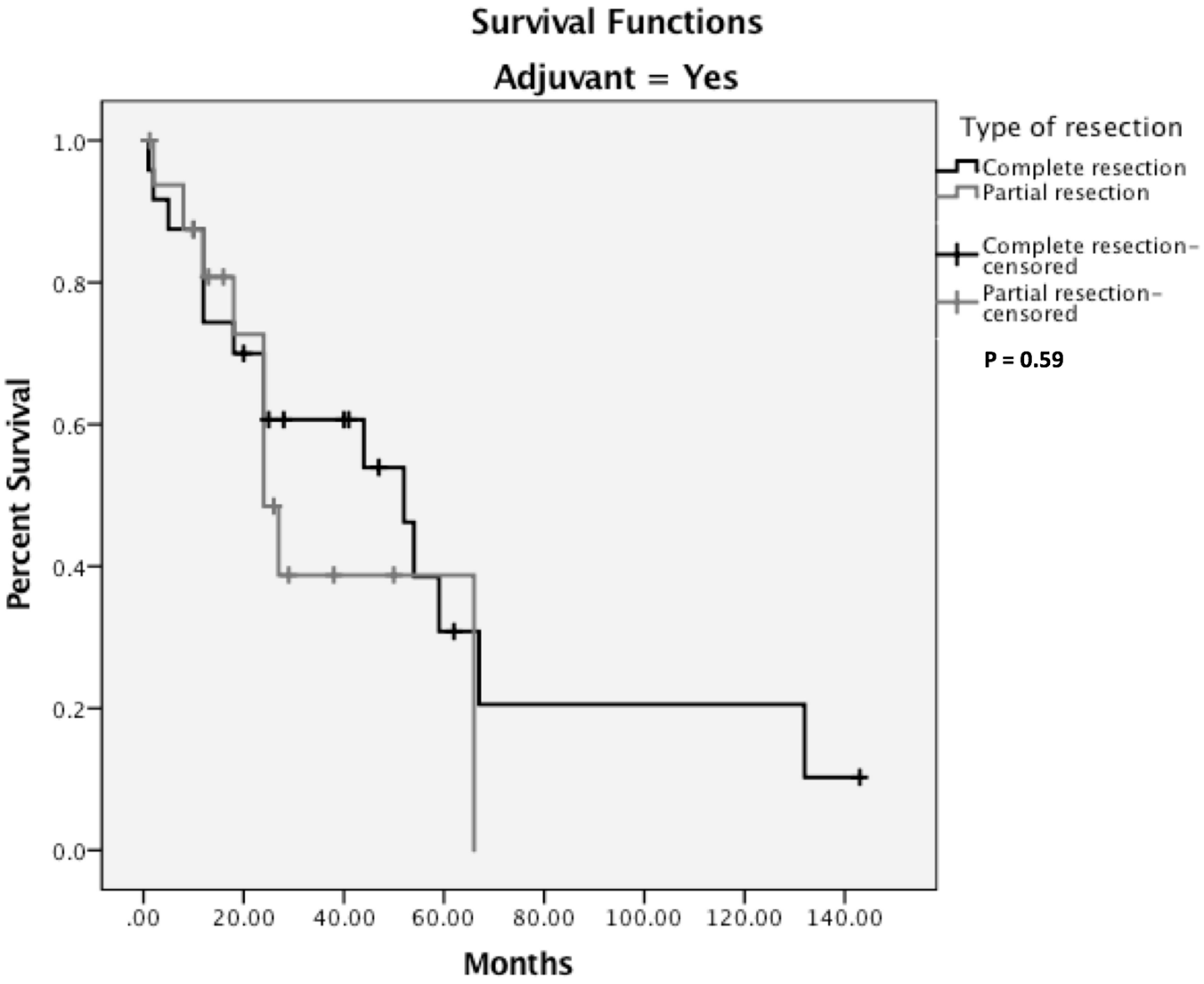

Figure 4.
Kaplan-Meier survival curves comparing complete resection and partial resection in patients received adjuvant therapy.

Table 1.

verview of all the included articles.

ocation	Primary/Mets/Radiation Induced/Recurrence				CPS	Histopathology		Tumor size (cm)	Primary treatment				Outcome			
		IF radiation induced				Grade	Type		Surgery		Chemotherapy	Radiation	Recurrence	PFS	OS	status
		Site of Initial Radiation Therapy	Dosage	Time before diagnosis					Yes/No	Type of surgery						
TF	Primary		--	--	Headache / confusion/ Intracranial hemorrhage	--	Fibroblastic	2×2	Yes	--	MTX, LCVN, BLMN, VCR	--	No	11	11	D
PTF	primary		--	--	Headache, diplopia CN3 Palsy	--	Osteoblastic	--	Yes	GTR	CPN, DXCN, IFD, ETD	No	No	11	11	A
Rt poglossal anal, SS	primary		--	--	tongue deviation, dysphagia, hoarseness, headache, Rt CNX/ XI/ XII Psy	High	--	--	No	--	CPN, DXCN, IFD, ETD, MTX, Intrathecal(MTX)	Yes, Total 7000 cGy	No	11	12	A
SB, TB, MX, TL	RI	Undifferentiated carcinoma of the nasopharynx.	70 Gy	11 years	headache, homolateral facial pain, numbness, diplopia, exophthalmia	--	--	--	No	--	IFD, CPN, DXCN	No	No		1	D
, ST, CS, , SB, left MSB	Primary		--	--	left ear pain, loss of vision, proptosis and pain of the left eye, VI CN palsy.	--	Chondroblastic	--	Yes	STR	MTX, LCVN, CPN, ADMN	Yes	No	--	2	A
b, ms, es, orbit	primary		--	--	Epistaxis	--	--	--	Yes	GTR	No	No	Yes	--	22	D
Msb, mn, ppf	primary		--	--	Facial lumps	--	Osteoblastic	--	Yes	NTR	No	Yes	Yes	--	38	D
SB, MX	primary		--	--	Facial lumps	--	--	15	Yes	GTR	Yes	Yes	Yes	--	20	D
SB, MX, MS	primary		--	--	Epistaxis	--	--	--	Yes	GTR	No	Yes	yes	--	40	D

ocation	Primary/Mets/Radiation Induced/Recurrence				CPS	Histopathology		Tumor size (cm)	Primary treatment				Outcome			
		IF radiation induced				Grade	Type		Surgery		Chemotherapy	Radiation	Recurrence	PFS	OS	status
		Site of Initial Radiation Therapy	Dosage	Time before diagnosis					Yes/No	Type of surgery						
MSB, IF	primary		--	--	Facial lumps	--	--	--	Yes	GTR	Yes	Yes	Yes	--	132	A
SB, MN, IF	primary		--	--	Facial lumps	--	--	--	Yes	GTR	No	No	--	--	--	--
ASB, ES	primary		--	--	Headache	--	Chondroblastic	--	Yes	GTR	Yes	Yes	Yes	--	28	D
SB, MS, IF	primary		--	--	Facial lumps	--	osteoblastic	--	Yes	GTR	No	No	Yes	--	18	D
B, Clivus region	primary		--	--	Headache	--	osteoblastic	--	Yes	NTR	Yes	Yes	Yes	--	50	D
SB, PSB, IF, PS	primary		--	--	Exophthalmos	--	osteoblastic	--	Yes	NTR	No	No	No	--	3	D
SB-MSB, Orbit, IF, PS	primary		--	--	Toothache, loose teeth	--	--	--	Yes	GTR	Yes	No	--	--	--	--
SB-PSB, PS	primary		--	--	Dysphagia	--	chondroblastic	5.5	Yes	NTE	No	Yes	Yes	--	10	D
sb-msb, nx, if, ps	primary		--	--	Toothache, loose teeth	--	--	10	Yes	GTR	Yes	Yes	Yes	--	25	D
Asb, ms	primary		--	--	Neoplasm in gums	--	--	3.7	Yes	GTR	No	Yes	Yes	59	59	A
Asb, es	primary		--	--	Exophthalmos	--	chondroblastic	4.5	Yes	GTR	Yes	Yes	Yes	54	54	A
Msb, if	primary		--	--	Facial lumps	--	chondroblastic	7	Yes	GTR	Yes	Yes	Yes	44	44	A
sb, es, ms	primary		--	--	Epistaxis	--	--	6.5	Yes	GTR	Yes	Yes	Yes	--	52	A
sb-msb, mn, if	primary		--	--	Toothache, loose teeth	--	--	15	Yes	GTR	No	No	Yes	--	12	D
Msb-psb, s, clival	primary		--	--	Diplopia	--	--	6	Yes	STR	Yes	Yes	Yes	5	5	A
S, ES, SS, SB, clivus	Primary		--	--	Epistaxis, Eye pain	--	chondroblastic	4.9	Yes	GTR	Yes	Yes	No	12	12	A

ocation	Primary/Mets/Radiation Induced/Recurrence				CPS	Histopathology		Tumor size (cm)	Primary treatment				Outcome			
		IF radiation induced				Grade	Type		Surgery		Chemotherapy	Radiation	Recurrence	PFS	OS	status
		Site of Initial Radiation Therapy	Dosage	Time before diagnosis					Yes/No	Type of surgery						
SB, NC, ES, FS, orbit	primary		--	--	Headache, exophthalmos	--	--	--	yes	STR	ADMN, MTX, CPN, IFD (COSS86)	No	Yes	27	27	LFU
6B, MSB, S, clivus	primary		--	--	Diplopia/CN VI palsy	--	--	4	Yes	GTR	ADMN, IFD, CPN	yes (55 Gy)	No	18	18	A
bit, MSB, IF	Metastatic		--	--	exophthalmos	--	Osteoblastic	--	Yes	embolization, STR	MTX	Yes (4000 cGy)	No	11	24	LFU
, TB, FO, ZB	primary		--	--	diplopia	High	--	--	Yes	GTR	DXCN, VCN, CFD, PDN (CHOP)	No	No	12	12	A
livus, SS	Primary		--	--	Headache	High	--	2.7×2.5×3.2	Yes	GTR	Yes	Yes	No	24	24	A
B greater wing	Primary		--	--	Exophthalmos	--	--	--	Yes	STR	DXCN, CPN	yes (50 Gy)	No	18	18	A
Bilateral rbits, SB	Metastatic		--	--	exophthalmos	--	Telangiectatic	--	NO	--	Yes	Yes	No	--	46	D
Clivus	primary		--	--	Headache, nasal obstruction	High	--	--	yes	GTR	ADMN, CFD, VCN	YES (4500 cGy)	No	12	12	A
, FB, TB	RI	Lt maxillary and orbital adenoid cystic carcinoma	60	12	--	--	--	6×6	Yes	STR	Yes	No	No	--	13	D
late, MS	RI	Nasal cavity squamous cell carcinoma	--	4.5	--	--	--	--	Yes	GTR	Yes	No	No	--	47	D
MX, IF	RI	Lt nasal squamous cell carcinoma	--	14	--	--	--	2.5×2.5	Yes	GTR	Yes	No	No	--	67	A
SS, ES, arasailer region, MSB	RI	Craniopharyngioma	60	9	--	--	--	--	NO	--	Yes	No	No	--	16	D
zygoma	RI	Bilateral retinoblastoma	--	15	--	--	--	--	Yes	GTR	Yes	No	No	--	62	D
MS, ES	RI	Rt retinoblastoma	--	20	--	--	--	5×5×7	Yes	GTR	Yes	No	No	--	2	LFU

ocation	Primary/Mets/Radiation Induced/Recurrence				CPS	Histopathology		Tumor size (cm)	Primary treatment				Outcome			
		IF radiation induced				Grade	Type		Surgery		Chemotherapy	Radiation	Recurrence	PFS	OS	status
		Site of Initial Radiation Therapy	Dosage	Time before diagnosis					Yes/No	Type of surgery						
stoid and jugular oramen	RI	Embryonal rhabdomyosarcoma	50.4	6.75	--	--	--	4.5×3×4.3	Yes	STR	Yes	Yes	No	--	29	D
alate, IF, MSB	RI	Rhabdomyosarcoma	60	18	--	--	--	4×4×4	Yes	GTR	Yes	No	No	--	143	D
bit, ASB, ES	RI	Bilateral retinoblastoma	35	25	--	--	--	3×2.5×2.5	Yes	GTR	Yes	No	No	--	41	D
ASB	primary		--	--	Supraorbital mass	--	osteoblastic	1.8×2.5	yes	GTR	CPN, IFD, CBPN, ETD	No	No	24	24	A
B, MSB, PF,	Primary		--	--	temporal pain, blurred vision	High	Telangiectatic	--	Yes	--	CPN, DXCN	Yes	No	4	4	A
SS, CS	RI	Pituitary adenoma	50	20	Headache	--	--	--	yes (3 times)	STR	iFD, CPN, ETD	Yes	No	24	24	A
SB, FB	primary		--	--	headache, Exomphalos	--	Telangiectatic	4×5	yes	STR	--	--	Prog	12	15	A
S, ES, CS	Primary		--	--	Headache	--	--	--	Yes	STR	No	Yes	No	8	8	A
Sella	RI	Pituitary adenoma	51	10	DLC	--	--	--	yes	STR	No	Yes	prog	--	1.25	D
SB	RI	Craniopharyngioma	110	15	change in memory and mental statuse	--	--	--	Yes	embolization, STR	No	No	prog	--	0.5	D
SB	RI	Pituitary adenoma	44	12	--	--	--	--	Yes	STR	--	Yes (50 Gy)	prog	13	16	D
Sella	RI	Pituitary adenoma	52	14	bitemporal hemianopsia and headache	High	--	--	yes	--	No	No	prog	--	--	--
Sella	RI	Pituitary adenoma	46	5	headache, visual loss	--	--	--	yes	--	No	No	Prog	1.5	1.75	D
Sella + clivus	RI	Craniopharyngioma	50	22	Headache, sinusitis	--	osteoblastic	--	yes	--	No	No	Prog	--	1	D
kull base (Not pecified)	Primary		--	--	--	--	--	--	yes	STR	MTX	No	No	66	66	A

ocation	Primary/Mets/Radiation Induced/Recurrence				CPS	Histopathology		Tumor size (cm)	Primary treatment				Outcome			
		IF radiation induced				Grade	Type		Surgery		Chemotherapy	Radiation	Recurrence	PFS	OS	status
		Site of Initial Radiation Therapy	Dosage	Time before diagnosis					Yes/No	Type of surgery						
ASB	Primary		--	--	--	--	--	--	--	--	yes	yes	prog	--	12	D
SB	Metastatic		--	--	--	--	--	--	--	--	MTX, VCN, CPN, IFD	No	prog	7	12	D
phenoid	Primary		--	--	--	--	--	--	--	--	No	yes	prog	--	9	D
MSB	Metastatic		--	--	Exomphalos	--	osteoblastic	--	yes	STR	YES	Yes	No	24	24	A
ASB	Primary		--	--	--	--	--	--	yes	STR	yes	No	prog	--	26	D
B, MSB, IF	Primary		--	--	exophthalmos, temporal bossing		--	--	yes	STR	No	No	No	1	1	A
Orbit, SB	Primary		--	--	Headacehe, exophthalmos	--	--	--	yes	GTR	MTX/CPN/ tetrahydropyranyl-Adriamycin	Yes (50 Gy)	prog	2	10	D
SB	Primary		--	--	tender enlarged mass	grade II	--	7	yes	GTR	--	No	No	16	16	A
Sella	primary		--	--	--	--	--	--	Yes	STR	No	No	Prog	--	0.2	D
loor and anterior clinoid rocess of la turcica	primary		--	--	headache, diplopia, bilateral XI CN palsy	--	--	--	Yes	Biopsy	Yes	Yes	No	19	19	A
Clivus	primary		--	--	Headache, and visual disturbance/Lateral gaze limitation	Low	Fibroblastic	--	Yes	--	No	No	--	--	--	--
Sellar-prasellar mass nvolving phenoid sinus	primary		--	--	Diplopia and obesity/ decreased visual acuity	--	--	--	Yes	STR	Yes	No	No	12	12	A

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ocation	Primary/Mets/Radiation Induced/Recurrence				CPS	Histopathology		Tumor size (cm)	Primary treatment				Outcome			
		IF radiation induced				Grade	Type		Surgery		Chemotherapy	Radiation	Recurrence	PFS	OS	status
		Site of Initial Radiation Therapy	Dosage	Time before diagnosis					Yes/No	Type of surgery						
Nasal cavity, aranasal uses, and tending to clivus	primary		--	--	Epistaxis/L CN VII palsy	--	Chondroblastic	--	Yes	--	No	Yes	No	46	46	A

a; SS = Sphenoid Sinus; SB = Sphenoid Bone; TB = Temporal Bone; TL = Temporal Lobe; MX = Maxilla; CS = Cavernous sinus; PPF = Pterygopalatine
Sinus; MSB = Meddle Skull Base; IF = Infratemporal Fossa; ES = Ethmoidal Sinus; Ethmoidal Sinus; PSB = Posterior Skull Base; PS = Parapharyngeal Space;
Fronto-Orbital; ZB = Zygomatic Bone; SO = Supra-Orbital; OA = Orbital Apex; SOF = Superior Orbital Fissure; FB = Frontal Bone; CPS = Chief Presenting
GTR = Gross-Total Resection; NTR = Near-Total Resection; STR = Subtotal Resection; VCR = Vincristine; BLMN = Bleomycin; MTX = Methotrexate; LCVN
Doxorubicin; IFD = Ifosfamide; ETD = Etoposide; ADMN = Adriamycin; CFD = Cyclophosphamide; PDN = Prednisone; PFS = Progression- Free Survival; OS =

Table 2.

Data summary of all pooled articles

Characteristic	Value
Cohort size (n)	67
Median age, range (yrs)	31, 9–78
gender	
Male	40 (59.7%)
Female	27 (40.3%)
Most common locations (n = 55)	N (%)
Anterior skull base	19/55 (34.5%)
Middle skull base	29/55 (52.7%)
Posterior skull base	7/55 (12.7 %)
Most common involved structures (n = 55)	N (%)
Sphenoid bone	15 (22.4%)
Sphenoid sinus	8 (12%)
Temporal bone	6 (9%)
others	29 (43.4%)
Most common presenting symptoms (n = 51)	N (%)
Headache	18(27%)
Exophthalmos	12(18%)
Diplopia	5(10.4%)
Others	16(46.6%)
Type of etiology (n = 67)	N (%)
Primary osteosarcoma	46 (68.4%)
Radiation induced osteosarcoma	17 (25.4%)
Metastatic osteosarcoma	4 (6%)
Metastases (n = 5)	N (%)
Primary osteosarcoma (n = 2)	Parietal bone and liver; shoulder bones
Radiation induced osteosarcoma (n = 1)	Pulmonary
Metastatic osteosarcoma (n = 2)	Multiple facial bones; lung and maxilla
Histopathological type (n = 21)	N (%)
Osteoblastic	9 (42.9%)
Chondroblastic	7 (33.3%)
Telangiectatic	4 (19%)
Fibroblastic	1 (4.8%)
Management	N (%)
Surgery	60 (89.6%)
Of reported surgical details (n = 53)	

Characteristic	Value
Complete resection	29 (54.7%)
Partial resection	24 (45. 3%)
Chemotherapy	44 (65.7 %)
Radiotherapy,	34 (50.7%)
Median dose, IQR (cGy, n = 7)	5000, 4500–5500
Outcome	N (%)
Median PFS, range (mos) (n = 31)	12, 0.2–143
Median OS, Range (mos) (n = 63)	12, 1.5–66
Recurrence (n/%)	17 (25.4%)
Disease progression (n/%)	13 (19.4%)
Status (n= 63)	N (%)
Alive (n/%)	30 (48%)
Dead (n/%)	33, (52%)