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REVIEW ARTICLE

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Osteosarcoma of the sphenoid sinus extending to ethmoid sinus—report of a rare case with review of literature giving special emphasis on treatment and outcome

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Abstract

Background Osteosarcoma usually arises from primitive bone-forming mesenchymal cells. Metaphyseal growth plates of long bones are the usually affected site. Though it is the most common primary bone malignancy, only 6–10% of osteosarcomas are craniofacial. In the sinonasal region, the commonly involved sites reported in the literature are maxillary and ethmoid sinus. Sphenoid sinus has been the least commonly involved site among the paranasal sinuses and only a handful of cases have been reported.

Methods A rare case of osteosarcoma involving the sphenoid and ethmoid sinus was presented to our institute and he was managed surgically and with postoperative chemotherapy. Further, an internet-based literature search was conducted to detect cases of osteosarcoma involving sphenoid sinus only as well as combined sphenoid and ethmoid sinus.

Results About 13 articles (13 patients), which fulfilled our inclusion and exclusion criteria were included in our study. Out of the 14 patients (including the present case), 5 patients (100%) who underwent both modes of adjuvant therapy were alive during the final follow-up. On the other hand, among those who received single adjuvant therapy, only one patient was alive (33.3%) and two patients died (66.6%).

Conclusion Osteosarcomas are highly malignant primary bone neoplasms with rare occurrence in the head and neck region. It constitutes a therapeutic challenge because of its anatomical location and the known side effects of chemotherapy. Timely intervention with a multidisciplinary approach is necessary to avoid death in these patients.

Keywords Osteosarcoma, Osteogenic sarcoma, Sphenoid sinus, Ethmoid sinus, Sinonasal

Background

Osteosarcoma is the most common primary malignant neoplasm of bone affecting mostly the long bones [1]. Metaphysis seems to be the commonest site of origin. The gross incidence of osteosarcoma is 0.3/100,000/year. The median age of diagnosis is 16 years [2]. The occurrence of osteosarcoma is rare in the head and neck accounting for only about 6–10% of osteosarcomas [3]. Osteosarcoma of long bones is common in the second decade, whereas osteosarcoma in craniofacial regions are common in the third and fourth decade of life [4, 5]. Most commonly they occur secondary to radiotherapy to any other tumor. In the craniofacial region, the most commonly involved site is the mandible and other sites include sphenoid sinus and ethmoid sinus [6]. Here we report a rare case of osteosarcoma of the sphenoid sinus

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extending to the ethmoid sinus with a comprehensive review of the literature.

Case report

A 19-year-old male came with complaints of headache, and bilateral nasal obstruction for 1 year associated with on and off mucoid nasal discharge for 3 months. He also complained of an inability to perceive smell and blurring of vision for 3 months. He denied any history of previous radiation exposure. On anterior nasal examination, a pink globular mass was seen occupying the nasal cavity on both sides. Ophthalmological examination showed a vision of finger counting at 2 m on the right side and 3 m on the left side. A computerized tomography (CT) scan showed a large expansile hypodense lesion with a peripheral irregular rim of calcification occupying the sphenoid sinus, ethmoid sinus, and nasal cavity on both sides. The lesion was also seen distorting the posterior part of the anterior skull base till planum sphenoidal and was also seen compressing the optic canal on the right side (Fig. 1A–C). Contrast-enhanced magnetic resonance imaging (CEMRI) showed a T1 isointense, T2 hyperintense cystic mass with multiple internal septations, and a thin peripheral rim of enhancement in the region of sphenoid and posterior ethmoidal sinuses. The lesion was seen extending superiorly to the midline anterior skull base and sellar floor causing scalloping and thinning of the bone. The lesion was completely extradural and was lifting the olfactory nerve superiorly and pushing the bilateral optic nerve and optic chiasma posteriorly. The pituitary gland was seen separate and was not involved by the lesion (Fig. 1D–F). Trans nasal endoscopic approach was taken and near total excision of the mass was done. The mass was pink, globular, multicystic, mildly vascular, filled with straw-colored fluid, and was seen arising from bilateral sphenoid sinus and extending to ethmoid sinus. A small part of the tumor in the region of the midline anterior skull base was left behind (Fig. 2A). The patient had uneventful postoperative events. Postoperative CT showed a small residual mass in the anterior skull base (Fig. 2B). Histopathological examination of the mass showed osteoid deposited as an anastomosing network of delicate trabeculae in a lace-like pattern at places. The space between trabeculae was filled with tumor cells showing irregular hyperchromatic nuclei and brisk mitotic activity (Fig. 3A–C). Tumor cells were positive for SATB2, beta-catenin-focal cytoplasmic positive (Fig. 3D–F). The findings were suggestive of conventional osteoblastic osteosarcoma. PET CT findings showed no evidence of distant metastasis. The patient was referred for chemotherapy and he was started on cisplatin, adriamycin, and ifosfamide. However, after 2 cycles of chemotherapy patient was lost to follow-up.

Material and methods

As clinico-radiologico-pathological study of sphenoethmoidal osteosarcoma is limited to a few single patient cases reports and case series, we planned to

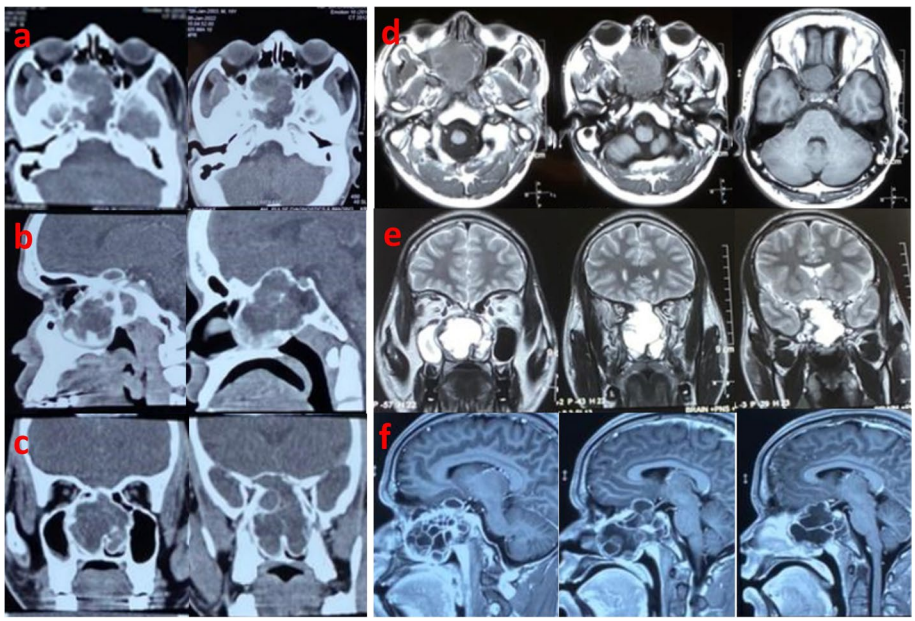

Fig. 1 Preoperative contrast CT (**a**, **b**, **c**) and contrast MRI (**d**, **e**, **f**) shows an expansile lytic cystic lesion with peripheral rim enhancement in the region of the posterior ethmoidal and sphenoid sinus

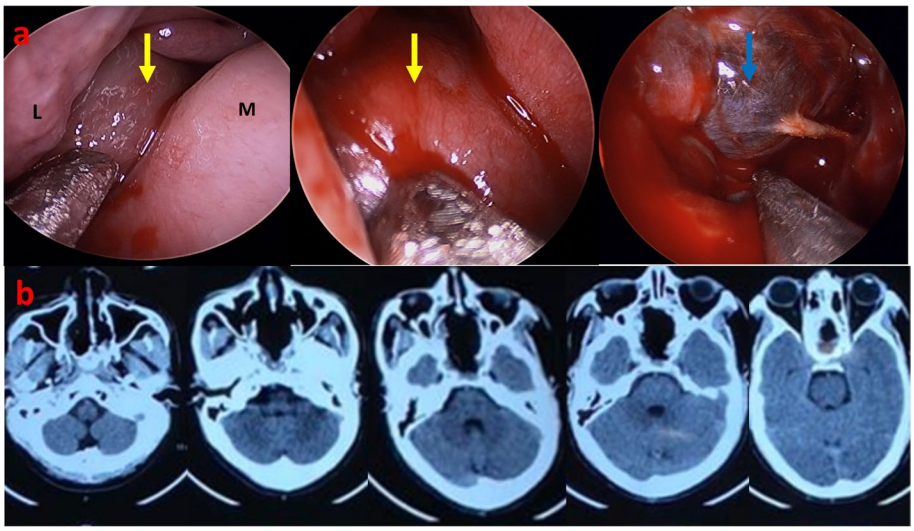

Fig. 2 Intraoperative imaging showing the cystic lesion occupying nasal cavity (**a**). Postoperative CT showing near total excision (**b**). IT—inferior turbinate, MT—middle turbinate, S—nasal septum. Yellow arrow represents the tumour

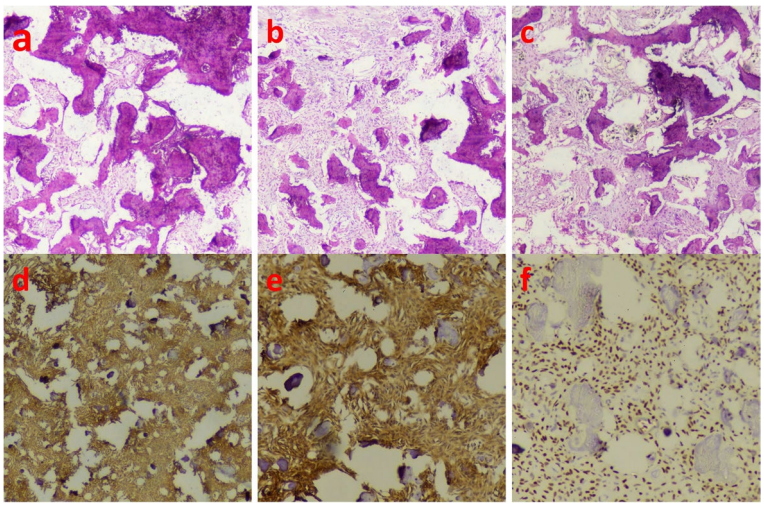

Fig. 3 Hematoxylin and Eosin stain of the mass showed osteoid deposited as an anastomosing network of delicate trabeculae in a lace-like pattern at places. The space between trabeculae was filled with tumor cells showing irregular hyperchromatic nuclei and brisk mitotic activity (**a**, **b**, **c**). The tumor also shows Beta Catenin (**d**, **e**) and SATB2 (**f**) positivity on immunohistochemistry staining

review all the cases of osteosarcoma involving sphenoid sinus only and with an extension to ethmoid sinus described in English literature. An internet-based search (PubMed, MEDLINE, Scopus) for the published reports describing cases of spheno-ethmoidal osteosarcoma was done using key words: sphenoid sinus, ethmoid sinus, sinonasal, osteosarcoma, and osteogenic sarcoma. We included all such cases available in English literature from 1996 upto till date. Lesions limited to the sphenoid sinus and with extension to the ethmoid sinus were included. Both primary and radiation-induced, high-grade, and low-grade osteosarcomas were included. The cases reported as sinonasal and skull base osteosarcoma involving other sinuses like frontal and maxillary sinuses were excluded. From each published report, we excerpted the following information: age, sex, prior radiation details, presenting clinical features, location, surgical management and approaches, histopathology, immunohistochemistry, adjuvant therapy, follow-up, and final outcome. If certain information was not available in the publication, we recorded that parameter as NR: "not reported"; and

the case in question was not included in the denominator for that particular parameter during the analysis.

Results

After a thorough literature search, we selected 13 articles fulfilling our inclusion and exclusion criteria. Out of the 13 articles, 3 articles [4, 7, 8] referred to cases that had involvement of both sphenoid and ethmoid sinus, whereas others had involvement of sphenoid sinus only [3, 6, 9–16]. The information was recorded in a table (Table 1). The present case was also included in the statistical analysis.

Analysis of 14 cases (including the present case) showed that the patients were in the age range of 9–78 years (upto 18 years: 5, 19–40 years: 4, 41 years and above: 5). Out of the 14 lesions, 6 lesions were seen in males, and 8 lesions in females (M: F = 0.75:1). Most of them presented with the prominent symptoms of headache, diminished vision and diplopia for a duration ranging from 6 days to 60 months. Development of the tumor was preceded by a history of radiation exposure in the same location in 3 patients (for pituitary adenoma in 2 patients [12, 14] and for craniopharyngioma in 1 patient [7]).

Neurological deficits were seen in 6 out of 14 patients at admission [6, 9, 11, 13, 15, 16]. Diplopia was seen in 5 patients and was due to the involvement of clivus and cavernous sinus [9, 11, 13, 15, 16]. Reduced visual acuity and vision loss was the second most common neurological deficit and was seen in 3 patients [6, 13, 16]. In one case due to the extensive disease-causing involvement of the jugular foramen and hypoglossal canal, there was dysphagia, hoarseness, and tongue deviation [11]. Proptosis was seen in 1 patient [16]. None of the 14 patients presented with hemiparesis, aphasia, pyramidal signs, or clinical features of intracranial hypertension. All the patients had undergone radiographic assessment (CT, MRI) for characterization of the lesion and exact delineation of its extent. Lesion pertaining only to the sphenoid sinus was seen in 2 cases [12, 14] and lesion limited to the sphenoid and ethmoid sinus was seen in 2 cases [4]. Involvement of middle and posterior skull base was seen in 4 patients [3, 9, 11, 15], middle skull base in 6 patients [6, 10, 12–15], and anterior and middle skull base in 4 patients [4, 7, 8]. Metastatic workup details were available for 7 patients [3, 4, 6, 9, 11, 13, 16], and out of them 1 patient had leptomeningeal enhancement at T6-7 disc level and nerve root enhancement in the distal thecal sac [11].

Preoperative tissue diagnosis was obtained in 2 cases (FNAC: 1, not reported: 1) and it matched with the final histopathological diagnosis [10, 16]. Intraoperative frozen section analysis to characterize the lesion was done only in 2 cases and it matched with the final histopathological report [6, 11].

About 12 patients underwent surgical treatment. Out of them, 6 patients had subtotal resection [8, 12, 13, 15, 16], 2 had gross total resection [3, 9] and the extent of surgery was not reported in 4 patients [4, 6, 10, 14]. With regards to the approach, trans nasal endoscopic approach was followed in 6 patients [3, 4, 6, 8, 12], and open frontobasal approach was done in 1 case [9] and approach was not reported in 5 patients [10, 13–16]. Histopathologic type was fibroblastic in one case [14], chondroblastic in 1 case [16], and osteoblastic in the present case. Out of the 5 lesions whose immunohistochemistry reports were available, 3 were positive for Vimentin [11, 12, 16], 1 was positive for Vimentin and SATB 2 and the present case was positive for SATB 2 and Beta Catenin.

All the 12 patients treated surgically received adjuvant therapy, either in the form of radiotherapy in 2 cases [8, 10] or chemotherapy in 4 cases [4, 6, 14], or a combination of these in 6 patients [3, 9, 12, 13, 15, 16]. Out of the 2 patients who did not undergo surgery 1 received both chemotherapy and radiotherapy as the disease was extensive [11] and the other 1 received only chemotherapy [7].

Out of 14 patients, the final outcome was available for only 9 patients (follow-up range 5–24 months) in which one patient was not operated on. In the remaining 8 patients, 5 patients [3, 9, 12, 13, 15] underwent both CT and RT and the remaining 3 underwent either of the 2 [8, 10, 14]. All 5 patients (100%) who underwent both modes of adjuvant therapy were alive during the final follow-up. On the other hand, among those who received single adjuvant therapy, only one patient was alive (33.3%) and two patients died (66.6%).

One of the patients developed a cerebrospinal fluid leak about 1 month after surgery and was repaired endoscopically [8], 1 patient died 8 months after surgery due to locally extensive disease [10] and 1 patient died 7 months after surgery due to the persistence of disease [14].

Discussion

Origin

Osteosarcoma usually affects older children and young adults. It is the most common malignant bone tumor in children and represents < 1.7% of the head and neck malignant tumors in children. Metaphysis of long bones like the distal femur and the proximal tibia are the commonly involved sites in 55–70% of cases [13, 16]. Primary osteosarcoma in the extraskeletal tissues is very rare with incidence more common in males than in females [17]. Out of the skull osteosarcomas, the cranial vault is the frequently involved site compared to the skull base [13]. It may occur primarily or secondary to bone diseases like Paget's disease, osteomyelitis, or after irradiation

Table 1 Table showing the review of cases previously reported in literature and their findings and outcomes

S. No.	Author	Age/ Sex	Prior radiation	Clinical presentation	Extent	Surgery	Approach	Histopathology/ Type	Immunohistochemistry	Chemotherapy	Radiotherapy	Recurrence	Follow up (months)	Outcome
1	Yamada et al (2012) [12]	75/F	Yes	Frontal headache	Sphenoid sinus	Yes, 3 times	Trans nasal endoscopic, Subtotal	NR	Vimentin +, High Ki 67, Anti cytokeratin -	Ifosfamide, Cisplatin, Etoposide	Yes	No	24	Alive
2	Gadwal et al (2001) [10]	9/M	No	Headache, lethargy	Sphenoid sinus, sella turcica erosion	Yes	NR	Grade 1	NR	No	Yes (4500 Gy)	Yes	8	Dead with locally extensive disease
3	Malalis et al (2013) [6]	18/F	No	Headache, vision loss	Sphenoid sinus, left cavernous sinus, compression of left optic nerve	Yes	Trans nasal endoscopic	Grade 2	NR	Cisplatin, Doxorubicin, Etoposide, Ifosfamide	No	NR	NR	NR
4	Huber et al (2008) [14]	52/M	Yes	NR	Sphenoid sinus	Yes	NR	High, fibroblastic	NR	Adriamycin, Cisplatin	No	Persistence	7	Dead
5	Geetha et al (1999) [13]	38/M	No	Diplopia, Obesity, decreased visual acuity	Sphenoid sinus, sellar, suprasellar extension	Yes	Subtotal resection	NR	NR	Adriamycin, Cisplatin, Holoxan	Yes 55 Gy	No	12	Alive
6	Chennupati et al (2008) [11]	14/F	No	Dysphagia, Hoarseness, diplopia, right cranial nerve 6, 10, 11, 12 palsy	Sphenoid sinus, clivus, hypoglossal canal, jugular foramen	No	N/A	High	Vimentin +, Cytokeratin -, Desmin -, smooth muscle actin -, neurofilament protein -	Cisplatin, Doxorubicin, Methotrexate, Etoposide, Ifosfamide	7000 cGy	NR	NR	NR
7	Ellison et al (1996) [16]	11/F	No	Left eye pain, left eye proptosis, vision loss, cranial nerve 6 palsy	Sphenoid sinus, pterygopalatine fossa, cavernous sinus, sella turcica, sphenoid bone, middle cranial fossa	Yes	Subtotal resection	Chondroblastic	S 100 +, Vimentin +, Actin -, Myoglobin -, cytokeratin -	Methotrexate, Leucovorin, Cisplatin, Adriamycin	Yes	NR	NR	NR
8	Guo et al (2017) [15]	55/F	No	Diplopia	Sphenoid sinus, clivus	Yes	Subtotal resection	NR	NR	Yes	Yes	No	5	Alive
9	Kachhara et al (1999) [9]	38/M	No	Diplopia, Cranial nerve 6 palsy	Sphenoid sinus, Sella, suprasellar, clivus	Yes	Frontobasal, Gross total	NR	NR	Cisplatin, Adriamycin, Ifosfamide	55 Gy	No	18	Alive
10	Mathkour et al (2016) [3]	29/M	No	Frontal headache	Sphenoid sinus, clivus	Yes	Trans nasal endoscopic, Gross total	High	NR	Yes	Yes	No	24	Alive

Table 1 (continued)

S. No.	Author	Age/ Sex	Prior radiation	Clinical presentation	Extent	Surgery	Approach	Histopathology/ Type	Immunohistochemistry	Chemotherapy	Radiotherapy	Recurrence	Follow up (months)	Outcome
11	Patel et al (2011) [7]	44/F	Yes	NR	Sphenoid and ethmoid sinus, parasellar region, middle fossa	No	N/A	NR	NR	Yes	No	No	16	Alive
12	Yamada et al (2013) [8]	78/F	No	Frontal headache	Sphenoid, Ethmoid sinus, cavernous sinus	Yes	Trans nasal endoscopic, Subtotal resection	NR	NR	No	Marginal dose- 39 Gy Site dose- 55 Gy	No	5	Alive
13	Mitra et al (2019) [4]	17/ F	No	Headache, hemifacial pain, epistaxis, anosmia	Sphenoid, ethmoid sinus	Yes	Trans nasal endoscopic	High	Vimentin +, SATB2 +, Osteopontin +, CD 99 +	Cisplatin, Doxorubicin	No	NR	NR	NR
14	Present case	19/M	No	Headache, nose block, blurred vision	Sphenoid sinus and ethmoid sinus	Yes	Trans nasal endoscopic, subtotal resection	Osteoblastic	SATB 2 +, Beta Catenin +	Cisplatin, Adriamycin, Ifosfamide	No	NR	3	NR

[9]. Osteosarcoma of bones occurs due to interference in bone growth and maturation when the bones are in the phase of high osteoblastic activity and are found to arise from immature bone-forming cells [17].

Clinical features

Our literature review showed that osteosarcoma of sphenoid sinus affects people of almost all age groups, with females affected slightly more than males (M: F = 0.75:1). The most common presentation of osteosarcoma is pain and local swelling and the most common site of distant metastasis is lungs and brain [9]. Other anatomic location-specific symptoms include neurasthenia, headache, dizziness, dental problems like malocclusion and loose teeth, ulceration, stuffy nose, nasal bleeding, double vision, and eye protrusion. The mandible is the commonest site involved in the head and neck due to the reason that the mandible retains growth centers for more than 30 years.

Radiology

Radiological investigations like plain films, CT, and MRI play an important role in delineating the extent of the lesion and thus help in planning surgery [11]. CT and plain radiograph play an important role in defining calcifications and bone destruction which can aid in planning surgery and adjuvant therapy. The characteristic sunray appearance seen in long bone osteosarcoma is absent in skull osteosarcoma due to the thickening of the calvaria at the edge of the tumor as a result of sub-periosteal reaction [9]. On MRI osteosarcomas enhance with contrast and appear isointense on T1 images like in our case. Other investigations that can be done include a radionuclide scan to define the extent of the primary tumor, the presence of any skip lesions, and distance metastasis. Metastatic work up includes chest X-ray and CT chest to identify lung metastasis [11]. Differential diagnosis of osteosarcoma involving the skull base includes chordoma, chondroblastoma, chondrosarcoma, and minor salivary gland pleomorphic adenoma [16].

Histopathology and Immunohistochemistry

The mean size of the tumor reported in the literature is 6.9 cm [10]. Histologically osteosarcoma shows osteoid production from spindle cell stroma [9]. Osteoid appears as a dense, amorphous, eosinophilic substance that can be difficult to distinguish from dense collagen. The different histological subtypes include fibroblastic, chondroblastic, osteoblastic, telangiectatic, and mixed subtypes [2]. The chondroblastic type is the commonest type among head and neck osteosarcomas [3]. The use of cell blocks, immunocytochemical stains, and electron microscopy play a great role in differentiating osteosarcomas from other sarcomas. Usually, osteosarcomas show positive staining with vimentin and negative staining with cytokeratin. Chondroblastic types are specifically positive for S 100 [16].

Treatment

The mainstay of treatment of osteosarcoma is complete surgical excision and wide surgical margins are associated with improved overall survival [6, 11, 18]. Surgical resection with negative margins is the single most important factor in the success of head and neck osteosarcomas treatment. As per the literature, the survival rate was 75% among patients who had negative resection margins as compared to only 32% in patients who had positive resection margins [15]. However, the location of the tumor in the head and neck makes complete surgical excision almost difficult without any cosmetic defect or functional impairment. Osteosarcomas involving the mandible and maxilla have shown a better prognosis compared to other head and neck osteosarcomas due to the fact that they are easily resectable [11]. In osteosarcomas involving sphenoid sinus, maxillary sinus, ethmoid sinus, sella, and suprasellar region, the chance of leaving a residual tumor is very high leading to local recurrence and reduced survival. So it can be combined with adjuvant therapies like chemotherapy [3, 6, 18] or radiotherapy to improve the overall outcome [9]. The different chemotherapeutic regimens include Doxorubicin, Ifosfamide, Cisplatin, and Methotrexate for a duration of 7 to 12 months [2]. Chemotherapy helped in improving the 5-year survival rate from 20 to 60% [2]. Also, our literature review showed that patients who received both modes of adjuvant therapy had better outcomes. In general head and neck osteosarcoma are less aggressive than long bone osteosarcoma with lung metastasis detected in only 20% of cases in head and neck osteosarcoma as compared to 80% in long bone osteosarcoma [3]. The patients must be followed up at 3 monthly intervals initially and then later at 1 yearly interval for a period of at least 10 ears. Pediatric patients are to be monitored for a prolonged duration to look for long-term side effects of chemotherapeutic agents.

Conclusion

Osteosarcomas are highly malignant primary bone neoplasms with rare occurrence in the head and neck region. It constitutes a therapeutic challenge because of its anatomical location and the known side effects of chemotherapy. Timely intervention with a multidisciplinary approach is necessary to avoid death in these patients. In our study, people who died received a single adjuvant therapy post-surgery, which was either radiotherapy

or chemotherapy. On the other hand, 100% of patients who received combined adjuvant therapy (radiotherapy and chemotherapy) survived. However, a large volume study is definitely the need of the hour to confirm this observation.

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None.

Authors' contributions
RM: conceptualization, validation, investigation, writing—original draft and visualization. SP: conceptualization, validation, investigation, writing—original draft, writing—review and editing, supervision and visualization. RK: conceptualization, validation, investigation, writing—review and editing and supervision. NMN: conceptualization, validation, investigation, writing—original draft, writing—review and editing, supervision and visualization. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
All authors declare that appropriate verbal consent from the patient has been taken for publication

Competing interests
The authors declare that they have no competing interests.

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