Long-Term Surgical Outcomes of Two Patients with Intracranial Extraskeletal Mesenchymal Chondrosarcoma and a Brief Literature Review

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AJNS 2022;17:235–241.

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Abstract

Objective Intracranial extraskeletal mesenchymal chondrosarcomas (IEMCs) are malignant aggressive neoplasms. IEMCs originate from the meninges or parenchyma. In the current study, we aimed to figure out the importance of gross total resection (GTR) and adjuvant radiotherapy (RT) by evaluating all reported IEMCs through the literature that included our two patients.

Methods and Methods We presented two IEMC patients who were treated at our institutions and followed up for a long duration. To understand the appropriate management for IEMC, we conducted a systematic literature review for previously reported series and cases of IEMCs.

Results We surgically treated two young males with IEMC initially diagnosed at their age of 18 and 20 years. The patients were initially treated with GTR and GTR followed by RT, and followed-up for 218 and 73 months, respectively. Through both the patients, we obtained 83 reported IEMC patients from the literature. The mean age of the reported cases was 24.5 ± 16.0 years (2 months–71 years). Female predominance was 54.2%. The mean progression-free and overall survivals were 27.9 and 39.0 months, respectively. The progressiveness rate was 56%. The presence of progressiveness was a poor prognostic factor ($p = 0.0008$). GTR was achieved in 53.0% of the patients. There was a significant difference between patients who received GTR compared with those who did not receive GTR ($p = 0.035$).

Conclusion Regarding their malignancy and progressiveness, we recommended the maximal surgical resection with wide margins followed by RT as appropriate management for IEMCs with close follow-up. The timely treatment provides high life quality and avoids life-threatening complications.

Keywords
- intracranial extraskeletal mesenchymal chondrosarcoma
- gross total resection
- radiotherapy

DOI https://doi.org/10.1055/s-0042-1750804.
ISSN 2248-9614.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Intracranial extraskeletal mesenchymal chondrosarcomas (IEMCs) are malignant aggressive neoplasms. IEMCs originate from the meninges or parenchyma.[1] IEMCs are characterized by a biospheric histological pattern that is composed of highly undifferentiated hyaline cartilage with calcification and ossification.[1,2] Mesenchymal chondrosarcoma (MC) is considered as a distinct entity that is entirely different from the classical chondrosarcomas.[3]

Considering their quick-growing and high mitotic index properties, opposite to the other chondrosarcoma subtypes, IEMCs are classified as high-grade neoplasms,[1–3] but the rarity of these tumors prevented the pathologists from determining the exact behavior of these tumors. IEMCs possess malignant characteristics, such as quick local aggression or recurrence, distant neural and extraneural axis disseminations, or metastasis, even after gross total resection (GTR).

Although MC was first defined as a separate pathological entity in 1959 by Lichtenstein and Bernstein,[4] very few cases of IEMC have been reported in the literature. Since the first description of IEMC by Dahlin and Henderson in 1962,[2] to the best of our knowledge, only 81 cases of IEMC have been reported in the literature. The appropriate management for these malignant lesions remains debatable. The critic questions always arise here: Is the adjuvant therapy essential? How to approach such lesions? Do radiotherapy (RT) and chemotherapy (ChT) have benefits for such calcified tumors? How do we follow-up these patients? In this study, we presented additional two young male IEMC patients who were treated surgically and followed-up for 218 and 73 months. To figure out the importance of GTR and adjuvant RT, we pooled the obtained data that included our patients.

Materials and Methods

We obtained written informed consent from two reported patients for publication of their cases and accompanying images. Both patients consented to surgical procedures.

To understand the appropriate management of IEMC, we identified the publications reported series or cases of IEMC. The selection criteria were: full-text published in English and accessed by MEDLINE, GOOGLE SCHOLAR, and PUBMED databases irrespective of the setting, study design, or details. Then, we analyzed the pooled sample after adding our two patients. The search for "intracranial extraskeletal mesenchymal chondrosarcoma," "intracranial mesenchymal chondrosarcoma," and "meningeal mesenchymal chondrosarcoma" is mentioned in our databases up to October 1, 2020. We excluded the cases that reported bone destructions, epidural location, tumors originating from skull bones, or reports that did not identify non-skeletal situations.

Statistical Analysis

For analysis of pooled data, we utilized Fisher's exact test by using the SPSS 24.0 statistical package. We assessed the statistical differences between groups in the same patients by a paired *t*-test. For categorical data such as the comparison between the presence of prognostic factors and progression-free survival (PFS) or overall survival (OS), we utilized an independent sample *t*-test. The significance level was determined when a p-value <0.05. All applied tests are two-tailed. We used Kaplan-Meier plots to evaluate the factors affecting overall survival.

Results

Case 1: An 18-year-old boy presented to our outpatient clinic with a 1-month history of headaches. An MRI revealed a capsulated heterogeneously intense enhancing tumor measuring $4.9 \times 4.5 \times 4.2$ cm and predominantly located in the right temporoparietal region (►**Fig. 1**). Presumptive diagnosis indicated that it was an atypical meningioma. At the surgery, the tumor was attached to the dura. The patient underwent GTR. The lesion was found to be compatible with MC. The patient was discharged on POD3 with no neurological deficits. No adjuvant treatment was applied. The postoperative metastatic work-up (PET-CT) demonstrated no extracranial involvement. The patient experienced an uneventful postoperative course up to POM22. In his control-visit, a new MRI demonstrated lobulated heterogeneously enhancing mass measuring $5.2 \times 3.8 \times 3.2$ cm in the same first operation field (►**Fig. 2**). The tumor was resected completely (►**Fig. 3**). The diagnosis was confirmed histopathologically to be a recurrence of the first tumor. The patient received RT. On his POM73, he had been free of tumor recurrence or extracranial metastatic lesions. The patient had attended his school. He works as an accountant for more than 2 years.

Case 2: A 20-year-old male with a 3-month history of severe headaches, difficulties in concentration and speech, and blurred vision was referred to us. Neurological examination was intact except for the right optic nerve with visual acuity of 6/12 and dysarthria. An MRI revealed capsulated heterogeneously intense enhancing right parietal mass measuring $5.6 \times 5.2 \times 4.6$ cm. On July 3, 1999, he received GTR and adjuvant RT. Intraoperatively the tumor was attached to the dura. Resection of the attached dura and duraplasty with an autograft fascia were performed. MC diagnosis was histopathologically confirmed. We discharged the patient on POD3 with no neurological deficits. In January 2001, March 2007, September 2011, June 2013, and February 2015, the patient received multiple mandibular and maxillary surgeries for several metastases. In the last surgery in June 2013, the maxilla was completely resected. The adjuvant RT was given. In September 2005, the patient received total resection for right femur metastasis and received RT. In February 2015, a total mandibular resection and repeat intensity-modulated RT were applied. After RT, the old parietal surgical wound opened. We applied a debridement operation by removing the craniotomy flap. In mid-April 2017, the patient presented to the ER with 3 days' duration of difficulties in speech, changes in consciousness, and severe headaches. A multilobulated capsulated heterogeneously enhancing large left frontotemporal mass

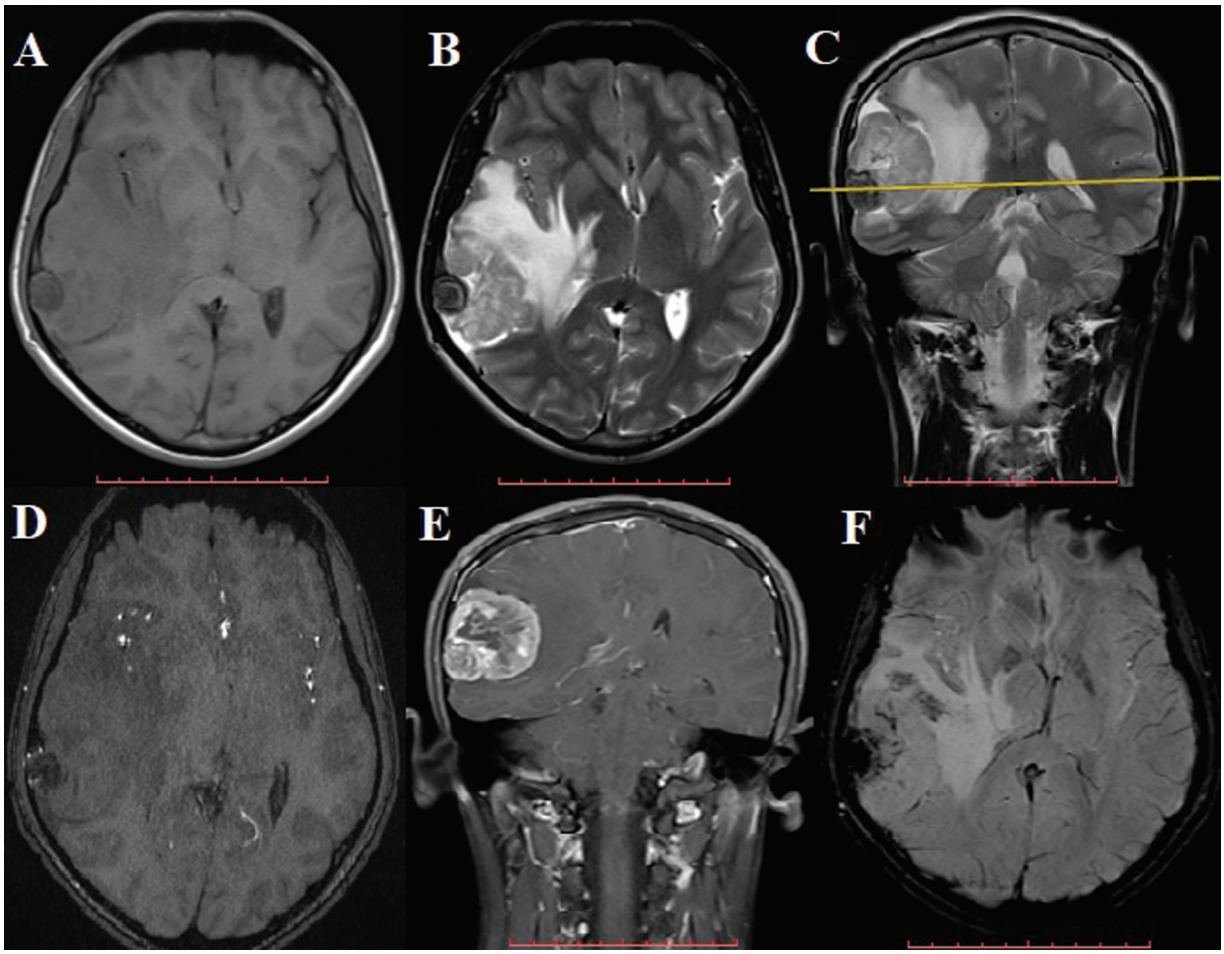

Fig. 1 An 18-year-old boy presented to our outpatient clinic with a 1-month history of headaches. His neurological examination was intact except for increases in DTRs. A contrast-enhanced MRI showed a well-capsulated heterogeneously enhancing tumor measuring 4.9 × 4.5 × 4.2 cm. The tumor was predominantly located in the right temporoparietal region. It was surrounded by diffuse vasogenic peritumoral edema. The lesion made a 7 to 8 mm shift to the left side and extending into the underlying brain parenchyma. (**A**) T1WIs demonstrated the lesion with two compartments. The lateral small compartment was hypointense. It was surrounded by the larger one located medially. The larger compartment demonstrated slight hypointensity compared with gray matter. (**B**) T2WI-axial images showed the lesion with separate two components. The lateral one was hypointense. The medial one was hyperintense. (**C**) T2WI-coronal images demonstrated diffuse edema. (**D**) TOF-MRA sequences showed that the lateral compartment was hypointense the same as those appearing in a high vascularized nodule. The medial compartment was a slight inhomogeneous iso-hypointense. (**E**) Contrast-enhanced T1WIs showed intense heterogeneously enhanced mass with two components. (**F**) Brimmed prominent blooming lesion (nodule) surrounded by the larger compartment that showed a slight hyperintensity.

measuring 8.2 × 6.2 × 5.6 cm was seen on contrast-enhanced MRI (►**Fig. 4**). Neurological examination revealed that he was lethargic and had not full responses to alters. We applied NTR due to abundant bleeding. He required ICU care post-operatively and died of disease on POD93.

Literature Review

With our two patients, we obtained 83 reported IEMC patients from the literature. The mean age of the reported cases is 24.5 ± 16.0 years (2 months–71 years). Female predominance was 54.2%. The mean progression-free and overall survivals were 27.9 and 39.0 months, respectively. The 1- and 10-year survival rates were 82.6 and 13.9%, respectively. The progressiveness rate was 56%. The presence of progressiveness is a poor prognostic factor ($p = 0.0008$). Gross total resection was achieved in 53.0% of the patients (44 of 83 IEMCs). Kaplan–Meier survival plot showed GTR. The plot showed a significant difference between patients with IEMC who received GTR compared with those who did not receive GTR ($p = 0.035$; $X^2 = 4.45$). Power is low = 0.475 (►**Fig. 5**). After pooling all data regarding adjuvant RT that applied after first surgeries on 37 of 83 patients, we found that RT improved tumor local progression ($p = 0.0003$, OR = 6.2 '2.3–17.0'); however, it had no impact on OS ($p = 1.0$, OR = 1.13 '0.34–3.74'). We found that local recurrence and/or distant metastasis increases the mortality of IEMCs ($p = 0.0008$, OR = 0.17 '0.06–0.49').

Discussion

Despite the aggressive treatment modalities, GTR followed by RT, IEMCs have a high propensity for extra- and intra-neural axis dissemination.[1,5] Embolization may be considered before surgical intervention in the cases presenting

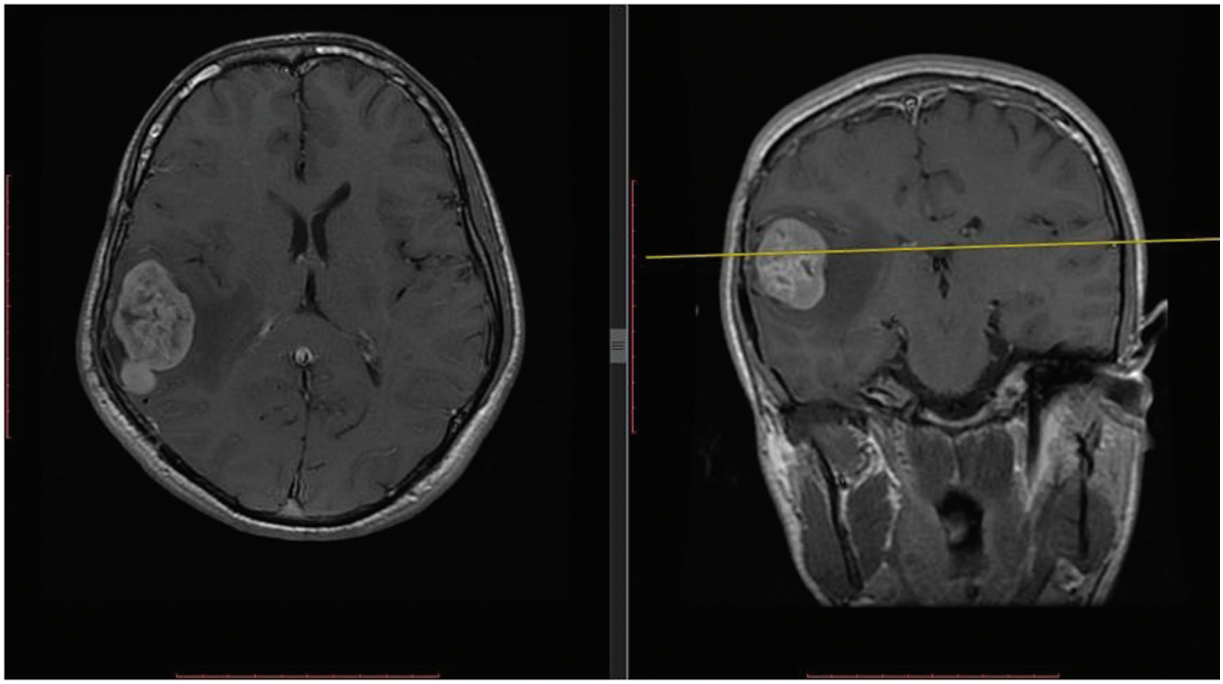

Fig. 2 The 22nd postoperative contrast-enhanced MRI of case 1 showed an intense enhanced tumoral mass in the same initial tumor field that believed to be a recurrence of the initial resected tumor. The left side is an axial T1WI and the right side is a coronal T1WI.

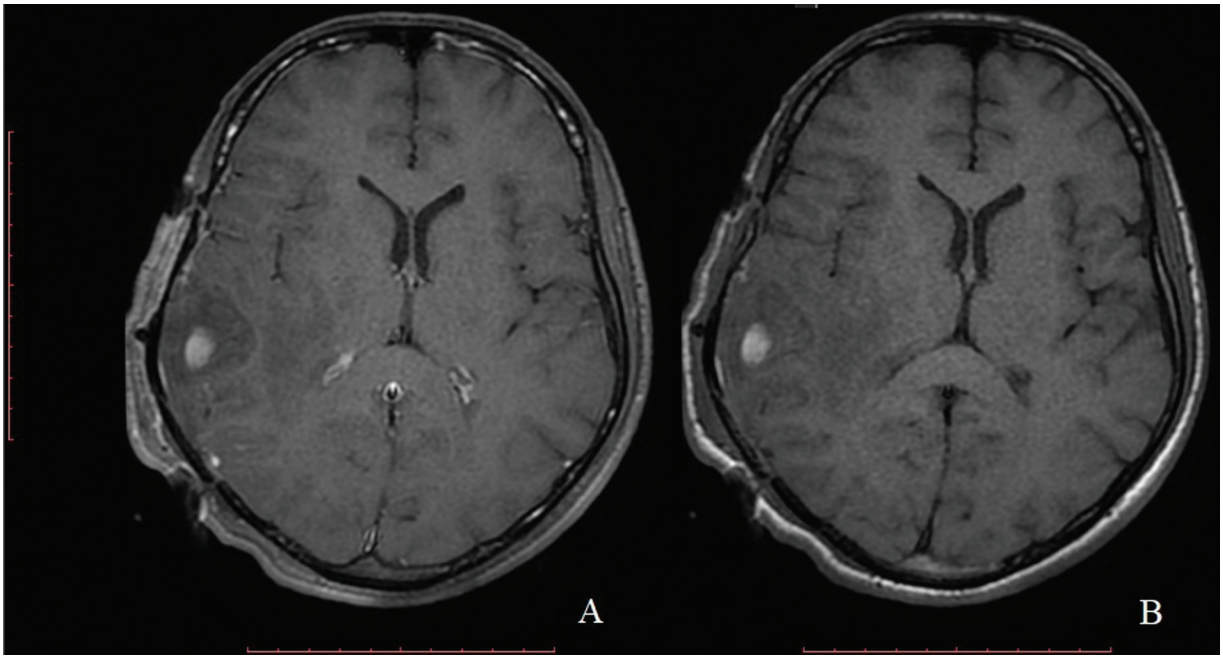

Fig. 3 (**A, B**) Early postoperative case 1 after the second operation showed no residue tumoral mass. On the left side (contrast-enhanced T1WI) and the right (T1WI) revealed a postoperative hemorrhagic area with no residual tumor mass.

with an extreme hypervascularity on TOF-MRA. Including our two cases, GTR was achieved only in 53.0%. The important factors affecting the achievement of a GTR included adherence to critical neurovascular structures, the invasive nature of the IEMCs to parent vessels, and reasons leading to immature operations such as intraoperative abundant bleedings. GTR improved the OS. After pooling all data regarding adjuvant RT that applied after first surgeries on 39 of 83 patients, we found that RT improved tumor local progression; however, it had no impact on overall survival. We found that local recurrence and/or distant metastasis increases the mortality of IEMCs. All published cases with recurrence or metastasis reported that adjuvant RT was applied unless the patient's general status prevents.[1,5,6] Adjuvant ChT may had benefited in some cases, but no study recommended it to be the first-line treatment modality.

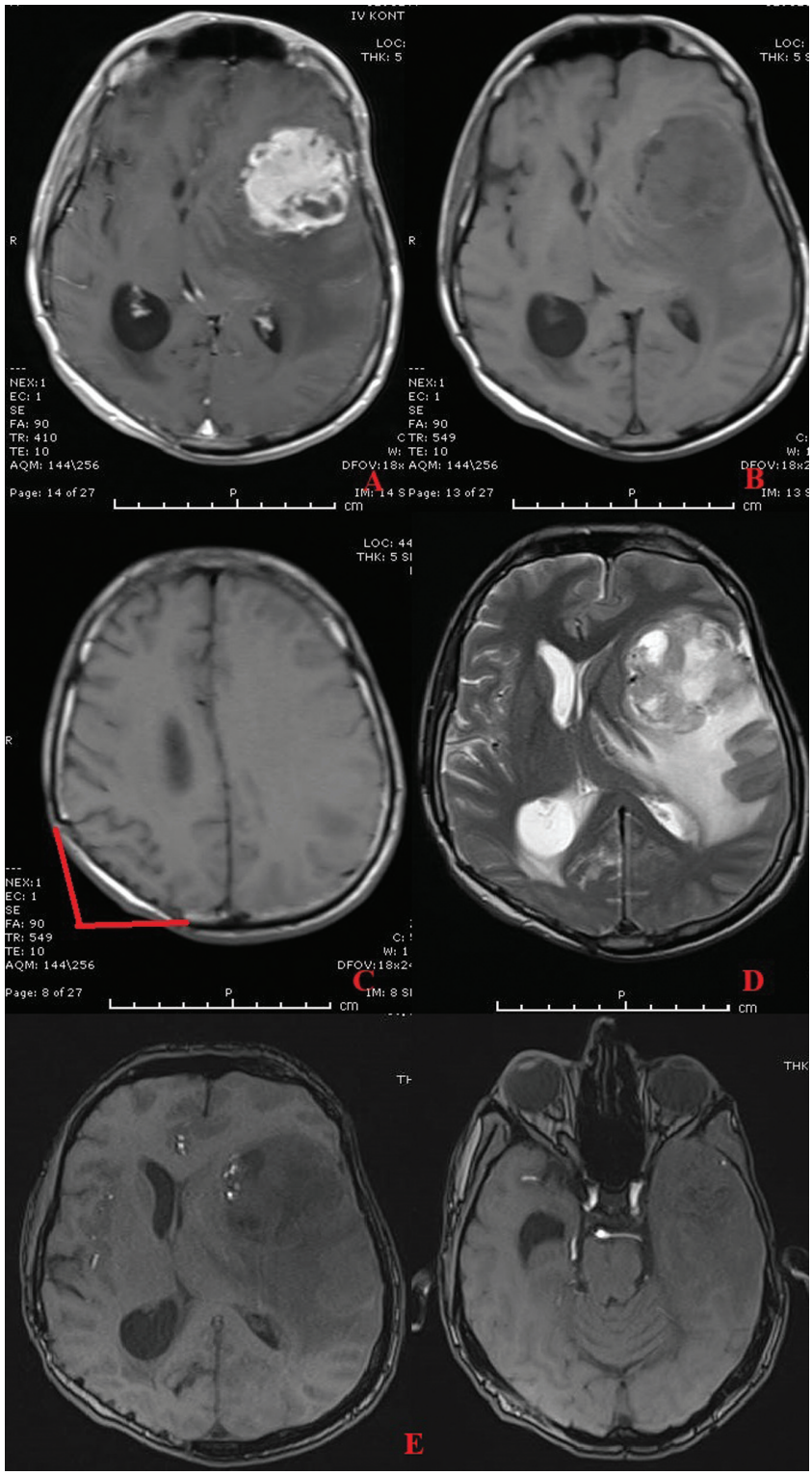

Fig. 4 A 38-year-old male patient referred to us with 3 days' duration of difficulties in speech, changes in consciousness, and severe headaches. An enhanced MRI demonstrated multilobulated heterogeneously enhancing mass measuring 8.2 × 6.2 × 5.6 cm located in the left fronto-temporal region and surrounded by diffuse vasogenic edema. The patient received GTR followed by RT for right parietal IEMC 18 years ago. Over 18 years, the patient had received multiple mandibular and maxilla surgeries and twice adjuvant RT for several metastases. (**A**) Contrast-enhanced T1WIs showed a multilobulated heterogeneous intense enhanced tumor with distributed hypointense areas. (**B**) T1WIs showed a mild hypointense lesion with a brimmed hypointense nodule. (**C**) T1WIs demonstrated the previously applied craniectomy. There is no local recurrence of the parietal lesion that resected 18 years ago. (**D**) T2WI showed heterogeneous hyperintense surrounded by diffuse vasogenic edema while the medial nodule was hyperintense. (**E**) TOF-MRA sequences revealed that the lateral compartment was hypointense the same as those seen in the high vascularized nodules. The medial compartment was mildly inhomogeneous iso-hypointense. The left- and right-sided images, respectively showed the frontal and temporal extensions of the lesion.

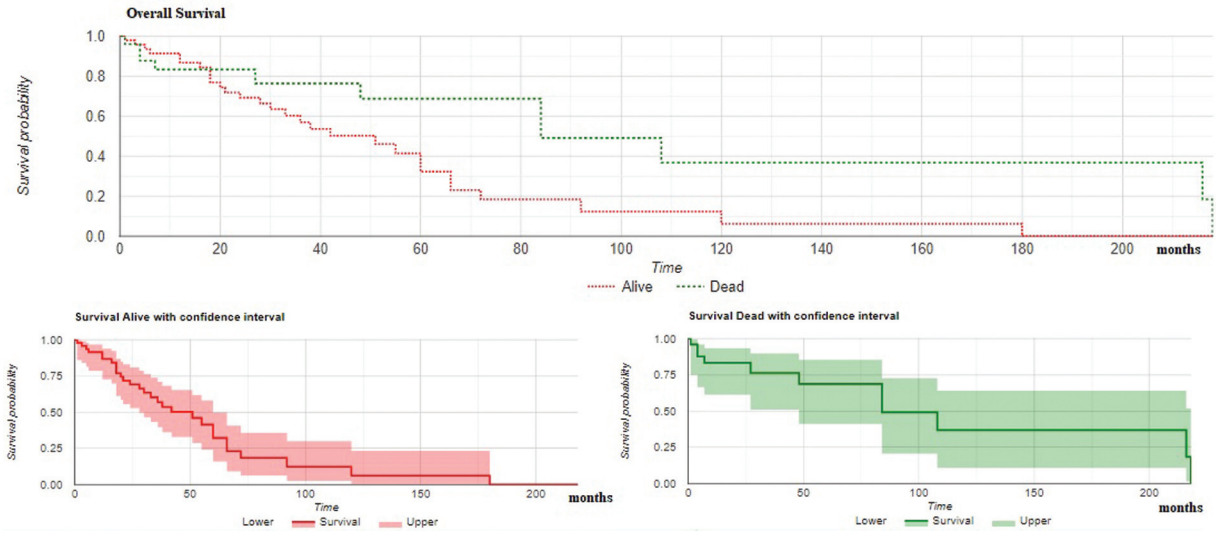

Fig. 5 Kaplan-Meier survival plot showed for GTR. The plot showed a significant difference between patients with IEMC who received GTR compared with those who did not receive GTR ($p = 0.035$; $X^2 = 4.45$). Power is low = 0.475. GTR, gross total resection; IEMC, extraskeletal mesenchymal chondrosarcomas.

IEMCs intraoperatively appear as well-circumscribed, solid rubbery firm, multilobulated, gray or reddish-brown colored masses. They are almost invasive tumors. The main features of the IEMC's cut surface are high vascularity and focal calcification.[5,6] One of the most challenging situation in histopathological diagnosis was when the surgeons took a small biopsy or specimens from one component without pieces from the second one. This is apparent when the specimens are obtained without cartilaginous elements.[1,3,5,6]

Intraoperatively and radiologically IEMCs can be misdiagnosed as atypical meningioma,[7] malignant meningiomas, hemangiopericytoma,[8] schwannomas,[9] metastasis,[10] gliomas,[5] or oligodendroglioma.[11] IEMCs vary from hypo- to isointense on T1WIs with intense heterogeneous enhancement after administering a contrast substance. In T2WIs, IEMCs demonstrate iso- to hyperintensity. However, rarely IEMCs showed hyperintensity in both T1WIs and T2WIs.[1,5] These lesions show iso- to hyperintensity on TOF-MRA and angiography sequences. By this radiological feature, IEMC can mimic arteriovenous malformations.[6,12] Rarely these lesions demonstrate cystic components[10] or extreme hypervascularity on angiographic images.[12]

IEMCs have a high tendency to be locally recurrent or distant metastasized. IEMCs have high cancer morbidity and mortality rates. Among all chondrosarcomas, IEMCs are the most malignant subtypes.[1–5] Local recurrence and metastasis rates were 46.7 and 17.3%, respectively. The progressiveness rate (the presence of at least one of progressiveness) was 56% (42 of 75 reported patients). Considering the shortness of the follow-up period that most survivors with IEMC reported, we believe that this rate is higher than this level. The mean PFS and OS were 27.9 and 39.0 months, respectively. Therefore, all survival cases ($n = 27$) were reported without an acceptable follow-up period (at least 28 months; cannot give us exact data regarding the aggressiveness of IEMCs). Several reports mentioned extracranial metastases of IEMCs. IEMC can metastasize to the mandibular bone and maxilla bones as occurred in our case 2.

Conclusion

Regarding their malignancy and progressiveness, we recommended the maximal surgical resection with wide margins followed by RT as appropriate management for IEMCs with close follow-up. Such patients deserve a close follow-up and timely treatment to increase the overall survival. Timely treatment of recurrence or distant metastasis provides high life-quality, avoids life-threatening morbidities, and raises overall survival.

Informed Consent

We obtained written informed consent from both patients and their relatives for publication of their cases and accompanying images.

Conflict of Interest

None declared.

Authors' Contributions

A.A. contributed toward conceptualization, methodology, software, supervision, formal analysis, statistical analysis, literature review, visualization, investigation, writing—original draft, supervision, writing—review, and validation.

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