Teaching Case

CyberKnife Stereotactic Radiosurgery for an Unusual Case of Large Brain Metastases From Ewing's Sarcoma in a Pediatric Patient

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Introduction

Ewing's sarcoma (ES) of bone is a highly aggressive cancer typically diagnosed in childhood and adolescence, with a survival of 70% to 80% for patients with standard-risk and localized disease and ∼30% for those with metastatic disease.[1] In fact, the key adverse prognostic factor is the presence of metastases at the time of diagnosis,[2] especially for extrapulmonary metastases.[3] It has been shown that sites of primary and metastatic tumors differ according to age. Young children (0-9 years) show significantly fewer primary tumors at axial sites (especially fewer pelvic tumors), and they have a significantly higher proportion of smaller tumors.[4] However, primary metastases are significantly more common for tumors originating in the pelvis[5] as pelvic involvement has been associated with large tumor size, an increased incidence of metastasis and poorer survival.[6]

Brain metastases are rare in children with ES but carry a grave prognosis,[7-11] usually occurring with or after lung metastasis.[12] Very few case reports and clinical series have been published on this subject, and the ideal management and the effective therapeutic strategy to adopt are still unclear.[13] Some reports have concluded that surgery is effective in treating selected patients with sarcoma metastatic to the brain.[13,14] Additionally, as sarcomas are radioresistant by nature, metastatic sarcoma to the brain represents a therapeutic challenge.[15] Nevertheless, it has been shown that ES is more radiosensitive compared with other sarcomas.[16,17] More recently, GammaKnife radiosurgery has been suggested as an effective treatment option for patients with radioresistant sarcomatous brain metastases as well as ES.[18,19] Parents and patient have given their informed consent to publish this case. The study protocol was approved by a local research ethics committee (CEC FUNIN SC-002-2021).

Case Report

This 9-year-old boy received a diagnosis of ES in the right iliac bone with extensive metastases to the lung in November 2017. He started systemic treatment (Ewing SEOP 2001 Protocol) until March 2018. Limb salvage surgery was performed, documenting a complete response, 100% tumor necrosis with negative bone resection margins, and surrounding soft tissue. He underwent radiation therapy to the tumor bed using a 3-dimensional (3D) technique (energy = 10 MeV) delivering 48.6 Gy in 27 fractions from September to October 2018. Additionally, 15 Gy in 10 fractions were delivered to the lung tissue (whole lung irradiation) from October to November 2018.

In May 2019, he had recurrent headaches and vomiting for 2 weeks. Cerebral tomography performed in June 2019, documented 2 large intra-axial lesions that

Data generated and analyzed during this study are included in this published article.

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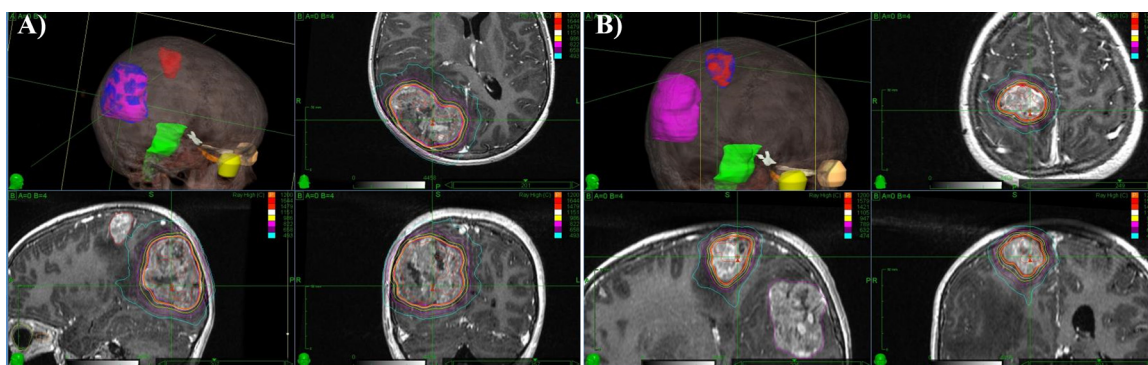
Fig. 1 Gadolinium-enhanced T1-weighted magnetic resonance in sagittal, axial, and coronal plane showing the 3-dimensional reconstruction of the treatment plans before the first stage of treatment. A, Lesion 1. B, Lesion 2.

enhanced the contrast medium. The right parietal lesion was 18 × 18 × 17 mm, and the right parieto-occipital lesion was 39 × 30 × 47 mm. Magnetic resonance imaging confirmed 2 lesions in the right hemisphere with high convexity, the first one with a parietal border area measuring 22 × 18 mm and the second one in the parieto-occipital area measuring 53 × 30 mm. Molecular analysis was performed in the bone marrow but no neoplastic disease was reported. Extracranial metastases were also discarded. The patient was considered for neurosurgery, but he was rejected due to the location and volume of the lesions. Precisely, due to the volume of these lesions, effective radiation doses would not be possible without exceeding the restriction doses to the healthy brain. Therefore, the patient was referred to our Robotic Radiosurgery Center in San Jose, Costa Rica.

Therapeutic intervention

The patient was treated in 2 stages using the Cyber-Knife robotic radiosurgery system (Accuray Inc., Sunnyvale, CA). This strategy was decided from the beginning, after considering the volume and location of the lesions. Notably, the patient didn't receive any kind of therapy other than radiation therapy. In the first stage (July 2019) 2 large-volume lesions (volume lesion 1 = 74.34 cm^3, volume lesion 2 = 8.98 cm^3) were treated with individual treatment plans on alternate days using the single-session SRS modality defined by gadolinium-enhanced T1-weighted magnetic resonance (Fig. 1). A total dose of 12 Gy (100% dose) was delivered to both lesions, obtaining a coverage of 97.49% and 98.75% of the volume of lesion 1 and 2, respectively. The new conformity index (nCI) obtained was 1.10 and 1.14, and the heterogeneity index (HI) was 1.37 and 1.32 for lesion 1 and 2, respectively. The dose gradient index was evaluated after the Paddick's gradient index (GIPaddick) and the DGI as previously proposed,[20] obtaining GIPaddick = 2.5 and 2.7 and DGI = 38 and 78 for lesion 1 and

2, respectively. Regarding the brain V12 (volume of the healthy brain that receives a dose of 12 Gy) it was reported as 4.42 cm^3 and 1.02 cm^3 for each individual treatment plan, and a V12 of 15.01 cm^3 was obtained considering both plans.

Before the second stage of treatment, a gadolinium-enhanced T1-weighted magnetic resonance showed an important reduction in the volume of both lesions (volume lesion 1 = 8.69 cm^3, volume lesion 2 = 0.60 cm^3), which corresponds to a reduction of 88% for lesion 1 and 93% for lesion 2 after the first stage of treatment (Fig. 2). In this second stage (August 2019) and due to the good response to treatment, the 2 lesions were treated together with the same treatment plan. The prescription, in this case, was 15 Gy (100% dose) obtaining an average coverage of 96.08%. For this stage, the brain V12 was 7.59 cm^3. The new conformity index obtained was 1.32, and the heterogeneity index was 1.28. The dose gradient obtained was GIPaddick = 3.4 and DGI = 59 for the treatment of both lesions together.

After both stages of treatment, the patient remains under follow-up and new magnetic resonance images were obtained ∼20 months (May 2021) after the second stage of treatment. The magnetic resonance imaging confirmed a very good response because both lesions resolved, and no other lesions were observed elsewhere in the brain (Fig. 3). Notably, the Mini Mental Status Examination score obtained before the first stage of treatment was 26, and the score obtained 1 month after the second stage of treatment was 28. After another assessment performed more than 2 years after the second stage of treatment (April 2022), we confirmed that the patient remains asymptomatic and unaffected by any discomfort and lives a normal life.

Discussion

ES of bone is a typical malignancy of childhood and adolescence. Metastatic disease is the main adverse prognostic factor, with most patients presenting metastases to
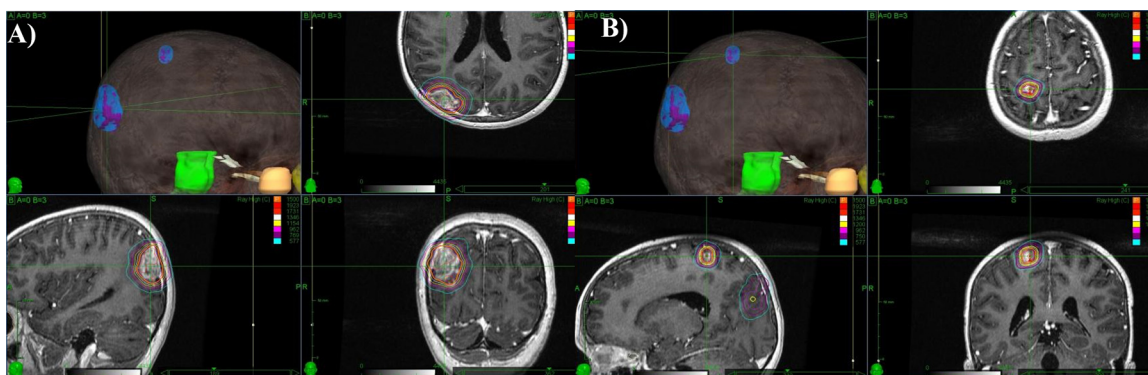
Fig. 2 Gadolinium-enhanced T1-weighted magnetic resonance in sagittal, axial, and coronal plane showing the 3-dimensional reconstruction of the treatment plans before the second stage of treatment. A, Lesion 1. B, Lesion 2.

the lungs and skeletal system at the time of diagnosis. Brain metastases are rare in children with ES but carry a severe prognosis. Although young children (0-9 years) show significantly fewer tumors at axial sites (especially fewer pelvic tumors)[4] our patient received a diagnosis of ES in the right iliac bone with extensive metastases to the lung at the age of 9. This is in line with the evidence suggesting that primary metastases are significantly more common for tumors originating in the pelvis.[5] Only a few cases have been reported on brain sarcomatous metastases, and the ideal management and the effective therapeutic strategy to adopt are still unclear.[13] This is the first report to our knowledge of a pediatric patient with large brain metastases from ES treated with CyberKnife Robotic Radiosurgery System.

One previous case described a 9-year-old boy with 2 brain metastases from ES treated with resection and adjuvant hypofractionated partial-brain radiation therapy (30 Gy in 5 fractions).[21] The patient showed no evidence of disease as of his last follow-up 21 months after the presentation of his brain metastases. Another report of brain metastases from ES described the case of a 9-year-old boy with 3 metastatic deposits within the supratentorial and infratentorial brain tissue, and a 16-year-old-girl with metastasis to the right temporal lobe.[22] In the second case, the tumor was partially removed and chemotherapy and radiation therapy with a total dose of 2700 cGy/t in 9 fractions of 300 cGy/t each were administered. Unfortunately, the patient died of disease progression.

As whole brain radiation therapy has been a mainstay of treatment in patients with brain metastases, hypofractionated partial-brain radiation therapy with limited margins has been suggested as a reasonable approach after gross tumor resection, especially for pediatric patients.[22] However, tumor resection is not a viable option in all cases. Instead, SRS with GammaKnife has been proposed as an effective treatment option for patients with radioresistant sarcomatous brain metastases.[18,19] Indeed, we consider that the use of SRS is especially important in pediatric patients to reduce the amount of radiation to the healthy brain. Thus, given the positive therapeutic outcome in our pediatric patient and considering the volume,
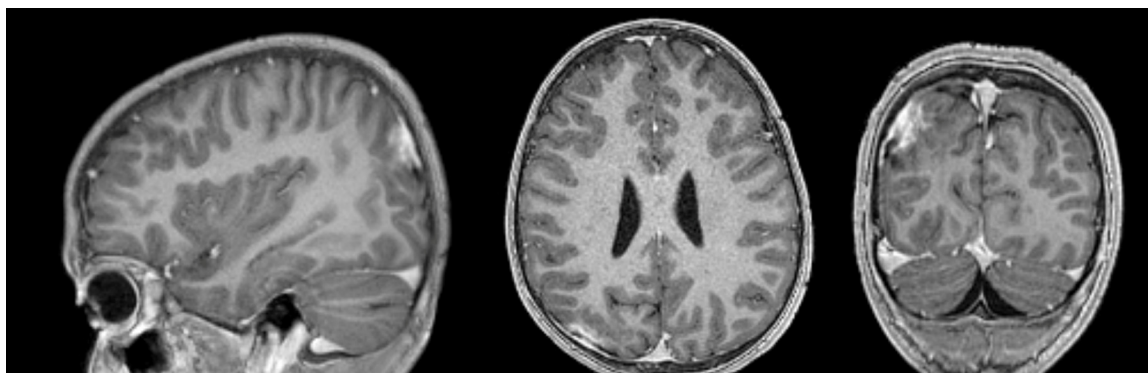

Fig. 3 Gadolinium-enhanced T1-weighted magnetic resonance in sagittal, axial, and coronal plane ∼20 months after the second stage of treatment. Note that both lesions show a complete response. Currently, only a zone of hyperintensity associated with a fibrotic process is observed in the gray matter of the parieto-occipital region where the largest lesion was located.

and location of his 2 metastatic brain lesions, the present case supports the use of CyberKnife SRS for metastatic sarcoma to the brain, especially for pediatric ES.

Conclusions

Metastatic sarcoma to the brain represents a therapeutic challenge as these tumors are generally refractory to radiation therapy. However, compared with other sarcomas, ES normally show a good response to radiation therapy. Although the ideal management and the effective therapeutic strategy to adopt for brain sarcomatous metastases remains to be elucidated, the present case supports the value of CyberKnife Robotic Radiosurgery System for the treatment of large brain metastasis from ES, especially for pediatric patients who could potentially be severely affected by the neurocognitive side effects of whole brain radiation therapy.

Acknowledgments

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