

Effective local control of a giant calvarial hemangioma in a child by proton beam therapy: A case report and literature review

ZHIPENG SHEN^{1,2}, MASASHI MIZUMOTO³, YOSHIKO OSHIRO⁴, YONGLONG JIN^{5,6},
JIE WANG⁷, SHUYAN ZHANG⁸, CHAO LIU⁸, ZISHEN WANG⁷, WEI WANG⁹, YINUO LI³,
WEIWEI WANG⁸, JUN ZHAO⁸ and SHOSEI QINGSHUI SHIMIZU XIANGXING^{3,8}

¹Department of Neurosurgery, Children's Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang 310058, P.R. China;

²National Clinical Research Center for Child Health, Hangzhou, Zhejiang 310058, P.R. China; ³Department of Radiation Oncology,

University of Tsukuba, Tsukuba, Ibaraki 305-8576, Japan; ⁴Department of Radiation Oncology, Tsukuba Medical Center Hospital,

Tsukuba, Ibaraki 305-8558, Japan; ⁵Department of Radiotherapy, The Affiliated Hospital of Qingdao University, Qingdao,

Shandong 266000, P.R. China; ⁶School of Public Health, Qingdao University, Qingdao, Shandong 266071, P.R. China;

⁷Department of Radiotherapy Physics and Technology, Hebei Yizhou Cancer Hospital, Zhuozhou, Hebei 072750, P.R. China;

⁸Department of Pediatric Radiation Therapy Center/Pediatric Proton Beam Therapy Center, Hebei Yizhou Cancer Hospital, Zhuozhou,

Hebei 072750, P.R. China; ⁹Department of Radiology, Hebei Yizhou Cancer Hospital, Zhuozhou, Hebei 072750, P.R. China

Received July 29, 2024; Accepted October 23, 2024

DOI: 10.3892/etm.2024.12763

Abstract. Intraosseous hemangiomas are rare, benign tumors, predominantly affecting the vertebrae, calvarium and other bones. These lesions, although slow progressing, can lead to complications such as visual disturbances and structural deformities. Standard management includes surgical interventions and more recently, advanced radiation therapies such as proton beam therapy (PBT) have been explored due to their precision and minimized damage to surrounding tissues. The current study presents a compelling case of a 10-year-old female patient diagnosed with a giant calvarial hemangioma located at the cranio-orbital junction. Although it was initially managed with surgery and chemotherapy, the tumor recurred. Given the recurrence and proximity to critical structures, PBT was employed. The treatment was administered over 28 fractions, with a total dose of 50.4 Gy. The patient exhibited good tolerance to the treatment, experiencing only minor acute side effects such as hair loss and skin pigmentation. At 14 months post-PBT, a marked reduction in tumor size was revealed with no further progression, indicating effective local control of the hemangioma. In addition, the side effects had improved markedly, highlighting the long-term benefits and efficacy of PBT in managing this challenging case. This is the first case in

which PBT has been used to manage a calvarial hemangioma in children to the best of the authors' knowledge. The current case highlights the potential of PBT in treating complex intraosseous hemangiomas where conventional therapies are ineffective. Further research into long-term outcomes is necessary to establish PBT as a crucial approach for similar cases.

Introduction

Intraosseous hemangiomas are rare, benign tumors originating from blood vessels, constituting <1% of all bone tumors (1). These lesions are typically found in vertebral bodies and several reports have also documented their occurrence in the calvarium, including the orbital region (2,3). Although most hemangiomas are considered benign, intraosseous epithelioid hemangiomas can exhibit intermediate behavior with the potential for locally aggressive features (2,4). Epidemiological data indicate a higher incidence in females compared with males, predominantly affecting individuals in the 40-50 year old age group (5). Intracranial hemangiomas may be asymptomatic, but in certain instances, tumor enlargement can result in headaches, visual disturbances (due to optic nerve compression) and morphological changes (6).

Surgical intervention is the standard treatment when hemangiomas cause deformity or impair the function of adjacent organs due to their enlargement, occasionally supplemented with sclerotherapy (7). Radiation therapy is a crucial modality for certain types of hemangiomas, particularly when surgical options are unfeasible or pharmacological treatments are ineffective (8). Radiation therapy not only alleviates symptoms but has also been reported to significantly reduce or eradicate tumors in hemangiomas beyond the bone (9). For intracranial hemangiomas, radiation therapy is primarily employed for lesions located in surgically inaccessible areas or for recurrent hemangiomas post-surgery, for example cavernous sinus

Correspondence to: Dr Shosei Shimizu (Qingshui Xiangxing), Department of Pediatric Radiation Therapy Center/Pediatric Proton Beam Therapy Center, Hebei Yizhou Cancer Hospital, 301 Bao Zhang Ji Di, Matou, Zhuozhou, Hebei 072750, P.R. China
E-mail: 23s.shimizu@yz-proton.com

Key words: intraosseous hemangioma, proton beam therapy, calvarium tumors, pediatric oncology, radiation therapy

hemangiomas with fractionated radiotherapy and stereotactic radiosurgery being the preferred technique (10,11).

Proton beam therapy (PBT), favored for its precision and dosimetric advantages, employs the ‘Bragg peak’ of high-energy proton beams to selectively target tumor (12). This modality is particularly effective for tumors situated in sensitive or complex anatomical regions, demonstrating superior treatment outcomes (13). PBT can minimize potential damage to the temporal lobe and other critical brain structures (14), preserve renal function during abdominal irradiation (15,16) and protect long-term cardiopulmonary function following lung cancer irradiation (17).

Only one case of radiation therapy for calvarial hemangiomas has been previously reported (18). However, there are no records of PBT for primary calvarial hemangiomas and the optimal dosing, therapeutic outcomes and potential adverse effects remain undetermined. The current report presents the first case of a giant calvarium hemangioma that was well controlled with PBT, as well as a comprehensive literature review.

Case report

Two surgeries and the hemangioma diagnosis. The patient was a 10-year-old girl who presented with left eye proptosis in February 2020 at Beijing Tongren Hospital (Beijing, China). Computed tomography (CT) and magnetic resonance imaging (MRI) results revealed a ~50x32x65 mm tumor in the left cranio-orbital junction. The patient subsequently underwent a craniotomy for tumor resection and the surgical margins were positive for tumor cells. Postoperative histopathology findings revealed irregular proliferation of bone trabecular within mature cortical bone, with osteoblasts visible surrounding the bone trabeculae. The stroma was loose and rich in dilated, thin-walled blood vessels, consistent with the features of an intraosseous hemangioma. Following surgery, the patient received chemotherapy at another hospital. According to our thorough review of past medical records, the patient was treated with propranolol, cyclophosphamide and vincristine, followed by the immunosuppressive drug sirolimus. Propranolol dosing was weight-based, starting at 0.5 mg/kg/day and increasing to 2 mg/kg/day, with careful monitoring of heart rate and blood pressure. Vincristine was administered intravenously at 1.5 mg/m² weekly. Cyclophosphamide was administered at a dose of 500 mg/m². Chemotherapy was administered for 6 cycles. Sirolimus was administered orally with a starting dose of 0.8 mg/m² per day.

However, the MRI results in May 2022 showed progression of the tumor. In July 2022, the patient underwent a second craniotomy for tumor resection, 2 years after the first surgery. Following the second craniotomy, microscopic analysis showed new bone trabecular surrounded by osteoblasts. Irregular vascular proliferation was observed between the trabeculae, further supporting the suspicion of intraosseous hemangioma. The resection had positive surgical margins for tumor cells. The final diagnosis of intraosseous hemangioma was based on the presence of irregular vascular proliferation between the bone trabeculae, a hallmark of the condition. Osteoid osteoma was excluded because it usually presents as a small, well-defined lesion with central nidus composed of osteoid

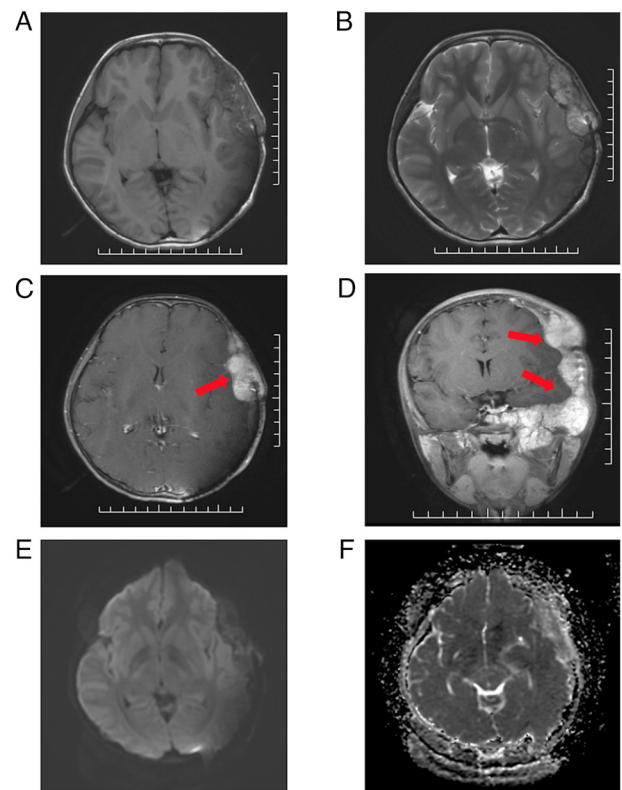


Figure 1. Cranial MRI findings prior to PBT (scale bar, 10 mm). A large blood-rich flow-like lesion measuring 96x71x112 mm was observed in the left middle cranial fossa, left supraorbital wall, pterygoid, frontal, parietal and temporal bones, compressing adjacent brain parenchyma. Red arrows indicate the tumor location. (A) T1WI: Hypointense lesion with scattered small hyperintense areas in the temporal region. (B) T2WI: Hyperintense lesion with linear, low-intensity areas in the temporal region. (C) Post-contrast T1WI in axial planes: Markedly enhanced lesion with hyperintensity. (D) Post-contrast T1WI in coronal planes: Strongly enhanced lesion extending into the left orbit, pterygoid, frontal, parietal and temporal bone areas. (E) DWI: Lesion with heterogeneous hyperintensity. (F) ADC maps: Lesion with reduced ADC values. MRI, magnetic resonance imaging; PBT, proton beam therapy; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; DWI, Diffusion-weighted imaging; ADC, apparent diffusion coefficient.

tissue and osteoblasts surrounded by reactive sclerotic bone, which contrasted with the loose, vascularized stroma and lack of a central nidus in the present case. Immunohistochemistry results were: CD31(+), CD34(+), D2-40(-), Factor VIII (F8)(+), Ki67 (3%) and EMA(-). CD31(+), CD34(+) and F8(+) and further supported the diagnosis of hemangioma, as these markers are typically expressed in endothelial cells, the primary cell type in hemangiomas (19). CD31 and CD34 are well-established markers for vascular endothelial cells, indicating blood vessel proliferation (20). D2-40(-), a lymphatic endothelial marker, helps exclude other vascular tumors such as lymphangiomas. Ki67, with a low proliferation index (3%), is consistent with a benign lesion and EMA(-) helps rule out differential diagnoses, such as meningioma. An attempt was made to retrieve the patient's original medical report; however, the initial hospital did not specify the exact localization of the positive staining (that is, nucleus, cytoplasm, or cell membrane).

Second recurrence of tumor. In August 2023, the patient presented with subcutaneous swelling on the left side of the

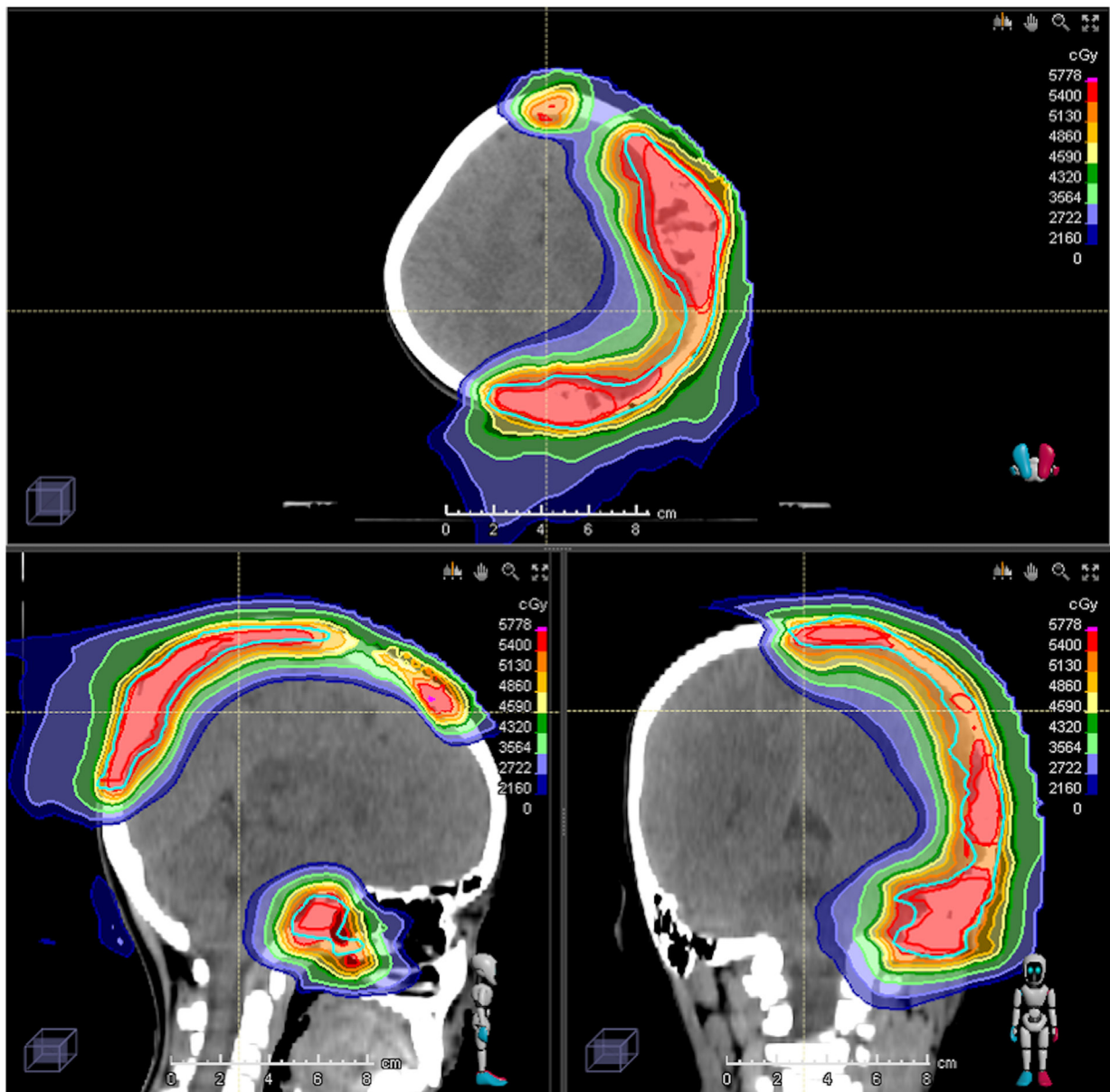


Figure 2. Dose distribution of pencil beam scanning modulated proton therapy. The different colored curves indicate the areas covered at different doses. CTV includes the tumor-adjacent area with an additional 5-mm margin. PTV adds a 3-mm margin to the CTV to account for setup errors. CTV, clinical target volume. PTV, planning target volume.

head and preauricular region. The MRI findings suggested hemangioma recurrence. MRI revealed a large blood-rich lesion measuring $\sim 96 \times 71 \times 112$ mm in the left middle cranial fossa, left supraorbital wall, pterygoid, frontal, parietal and temporal bones (Fig. 1). T1-weighted imaging (T1WI) (Fig. 1A) showed the lesion with heterogeneous hypointensity, while T2-weighted imaging (T2WI) (Fig. 1B) revealed the lesion with heterogeneous hyperintensity and linear low intensity areas. Post-contrast T1WI images (Fig. 1C and D) showed that the lesion was markedly enhanced with hyperintensity extending into the left orbit, pterygoid, frontal, parietal and temporal bone areas. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps (Fig. 1E and F) showed heterogeneous hyperintensity and reduced ADC values. In addition, there was compression of the adjacent brain parenchyma.

Physical examination revealed the patient exhibited normal development and clear consciousness. Subcutaneous swelling was palpable on the left side of her head, left preauricular area and left occipital region. The swellings were firm and non-tender. The patient exhibited normal muscle strength and tone, with no meningeal irritation signs. Brudzinski's and Kernig's signs were negative (21). Since she had undergone two surgeries, both of which recurred, the patient was referred to Hebei Yizhou Cancer Hospital (Zhuozhou, China) in order to undergo PBT as a treatment option.

The present study was performed in accordance with the principles of the Declaration of Helsinki (2013 version). Approval was granted by the Ethics Committee of Hebei Yizhou Cancer Hospital (approval no. 2024LLSC03). As the patient was a minor, written informed consent was obtained from the patient's legal guardians.

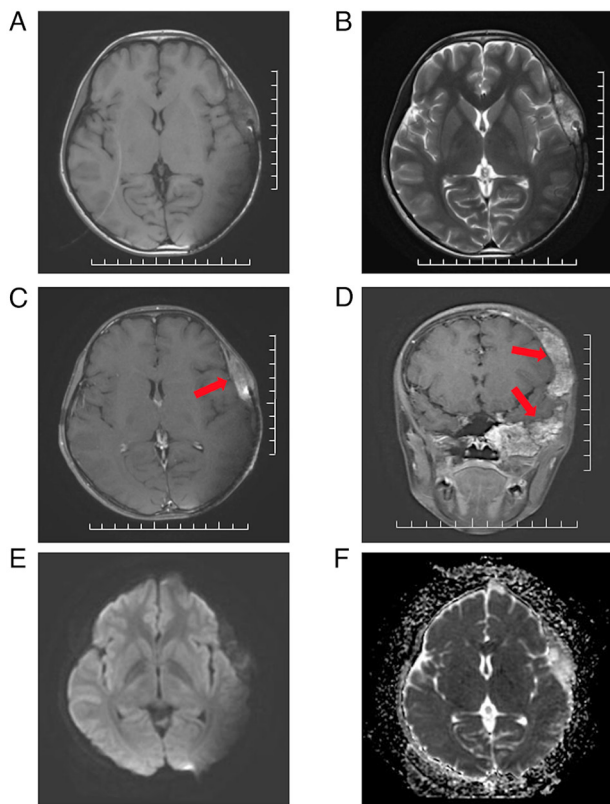


Figure 3. Cranial MRI findings 14 months following PBT (scale bar, 10 mm). The lesion was reduced to a size of 57x35x76 mm. Red arrows indicate the tumor location. (A) T1WI: Mixed high and low signals were observed in the temporal region. (B) T2WI: Heterogeneous hyperintensity with a significant reduction in lesion size. (C) Post-contrast T1WI in axial planes: Reduced lesion size with diminished enhancement in the temporal region. (D) Post-contrast T1WI in coronal planes: Significant shrinkage of the lesion in the left orbit, parietal and temporal bone regions and weakening of enhancement, with some areas showing complete response. (E) DWI: Lesion with low signal intensity. (F) ADC maps: Lesion with increased ADC values. MRI, magnetic resonance imaging; PBT, proton beam therapy; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; DWI, Diffusion-weighted imaging; ADC, apparent diffusion coefficient.

PBT and dose distribution. PBT is an advanced form of radiotherapy that uses protons rather than traditional X-rays (photons) to treat cancer. The physical properties of protons allow for precise dose deposition, with most energy being released at a specific depth in tissue, known as the 'Bragg peak'. This characteristic enables PBT to deliver a highly targeted dose to the tumor while sparing surrounding healthy tissues from unnecessary exposure, making it particularly advantageous for treating tumors in sensitive areas, such as the brain or near critical structures.

In the present case, the gross target volume for PBT was defined as the contrast-enhanced region plus the tumor-adjacent area on MRI. The clinical target volume (CTV) was defined as the tumor-adjacent area with an additional 5-mm margin to cover potential areas of tumor cell infiltration. Instead of including the entire initial tumor area, the CTV encompassed only the residual or recurrent tumor and its attachments. Finally, to compensate for setup errors, a 3-mm margin was added to the CTV to define the planning target volume (PTV). Pencil beam scanning (PBS) intensity-modulated proton therapy (IMPT) is an advanced delivery technique in PBT.



Figure 4. Image of patient's scalp 14 months post-PBT. A large craniotomy scar is visible in the left parietal-occipital-temporal region. Hair regrowth is observed in the affected area, with the new hair appearing fine. The hair density shows a gradual increasing trend over time. PBT, proton beam therapy.

In PBS, a highly focused proton beam, with a diameter of just few mm, is scanned across the tumor in a layer-by-layer approach, ensuring precise coverage of the tumor volume. The intensity of the proton beam is modulated to optimize the dose distribution within the tumor while minimizing exposure to surrounding healthy tissue. This technique is particularly useful for irregularly shaped or complex tumors, such as those located in the brain. PBS IMPT was employed in the current case to precisely deliver high radiation doses to the tumor with minimal collateral damage to adjacent critical structures. A total prescribed dose of 50.4 Gy in 28 fractions was delivered. The PBT dose distribution is illustrated in Fig. 2. Regarding organs at risk, the maximum doses were as follows: Brainstem, 50 Gy; left cochlea, 50 Gy; left lens, 5.5 Gy; optic chiasm, 42 Gy; left optic nerve, 50 Gy; and spinal cord, 18 Gy. The patient was positioned using a head shell and cone beam computed tomography for alignment before each irradiation.

During PBT, acute adverse events included hair loss in the irradiated area starting at 21.6 Gy/12 fractions, complete hair loss at 30.6 Gy/17 fractions and red-black pigmentation at 37.8 Gy/21 fractions. Epidermal peeling occurred at 48.6 Gy/27 fractions.

Treatment outcomes and evaluation. At 14 months post-PBT, the cranial MRI findings (Fig. 3) showed a significant reduction in tumor size from the initial measurements to 57x35x76 mm. DWI indicated markedly hypointensity in the lesion area, with an increase in ADC values. No significant edema or necrosis was observed 14 months after irradiation.

Based on the MRI results, the activity of the calvarial hemangioma markedly decreased 14 months after the completion of PBT, with tumor shrinkage, indicating effective local

control of the hemangioma. Additionally, the patient's hair loss symptoms had improved. An image of the patient's scalp was captured 14 months post-PBT and showed a large craniotomy scar on the left parietal-occipital-temporal region (Fig. 4). Hair regrowth was observed in the affected area, with the new hair appearing fine, though the density showed a trend of gradual increase.

No neurological deficits were observed following PBT. The patient's limb muscle strength and tone were normal, physiological reflexes were present and no pathological signs were detected. The complete blood count results showed a white blood cell count of 7.00×10^9 cells/l, a neutrophil count of 4.66×10^9 cells/l, a hemoglobin level of 135 g/l, a platelet count of 331×10^9 cells/l and C-reactive protein at a level of <0.01 mg/l. Evaluation of organ function, including liver and kidney function as well as cardiac enzymes, revealed no abnormalities.

As the effects of PBT may continue to manifest several years post-treatment (22), it was advised that the patient should continue to be monitored with follow-up observations in the future.

Discussion

Hemangiomas can be histologically classified into three types: Cavernous, capillary and mixed, all of which are benign tumors with no reports of malignant transformation (23). While epithelioid hemangiomas are typically considered benign, intraosseous epithelioid hemangiomas can exhibit intermediate behavior with the potential for locally aggressive features (4). Intraosseous hemangiomas can occur in any part of the body, but are most commonly found in the vertebrae, followed by facial bones and the skull. Within the skull, the frontal bone has the highest prevalence, followed by the parietal and temporal bones, while the incidence in the occipital bone is lower (24). The specific etiology of hemangiomas remains unclear; however, a possible association with a history of trauma has been previously suggested (25). Typically, intraosseous hemangiomas are asymptomatic, but they can occasionally evolve into painful, swollen areas that are palpable on the surface (26). Osseous hemangiomas are frequently detected through imaging examinations such as CT and MRI (27,28). However, the gold standard for diagnosis is histopathological examination. Characteristic well-formed vascular channels and trabecular bone surrounded by osteoblasts can be observed (23). When the tumor causes significant pain or neurological symptoms, or poses a risk of pathological fractures, surgical excision becomes the treatment of choice (29). In addition, embolization may be considered before surgery (30).

Surgical resection, including microscopic or endoscopic approaches, is an optimal treatment for intraosseous hemangiomas (31). In a previous study, the recurrence of completely excised hemangiomas was relatively rare (32). When total resection cannot be achieved in certain cases, adjuvant gamma-knife radiosurgery (GKRS) is occasionally conducted as an alternative. Lee *et al* (33) reported the results of GKRS for 31 cavernous sinus hemangiomas. A total of 21 patients received GKRS as a primary treatment, while 11 received GKRS as adjuvant treatment after surgery and all patients

had $>50\%$ reduction in tumor volume at 6 months post-GKRS without late adverse events. However, GKRS is indicated for small tumors, whereas large tumors such as the present case are difficult to be managed.

The efficacy of radiotherapy for large hepatic hemangioma has been reported in previous studies. Gaspar *et al* (34) reported cases controlled through X-ray radiation therapy, while Shimizu *et al* (9) reported a case of giant hepatic hemangioma controlled by PBT. By contrast, there are few reports on PBT for intracranial osseous hemangioma. A literature search on PubMed using the keywords 'Radiation therapy, Calvarial hemangiomas' yielded only one report on the effects of radiation therapy on calvarial hemangiomas. Liu *et al* (18) reported a case of a 50-year-old female patient who achieved local control of a calvarial hemangioma through radiation therapy, using 6 MV X-rays with 3D-CRT technology across 30 fractions to deliver a total of 60 Gy. However, the situation is more complex for children, as the risk of growth disturbances and secondary tumors due to radiation therapy must be considered while attempting to control the tumor.

PBT, a radiation therapy method using high-energy proton beams, is particularly suited for pediatric patients and tumors located in complex anatomical areas due to its dosimetric advantages (35). In standard radiotherapy, photons release energy continuously along their path, delivering a significant dose to both the tumor and the surrounding healthy tissues. This increases the risk of side effects, especially when treating tumors near critical structures. By contrast, protons exhibit a unique property known as the 'Bragg peak' where most of their energy is deposited at a specific depth in the tissue, corresponding to the location of the tumor. Beyond this peak, there is a rapid drop-off in dose, resulting in minimal radiation exposure to tissues beyond the tumor. This characteristic of PBT allows for highly targeted treatment, markedly reducing the dose to nearby healthy tissues and critical structures, thereby lowering the risk of long-term side effects (36).

Currently, there are no reports in the literature on intraosseous hemangiomas being treated with PBT. For pediatric benign tumors such as the present case and even inoperable ones, the risks of cognitive decline, visual impairments and secondary cancer associated with traditional radiation therapy are important concerns. In the current case, PBT was selected due to the proximity of the tumor to critical structures and the ability of PBT to deliver a highly conformal dose while sparing healthy tissue, which is critical for achieving effective local control with minimal complications. Takizawa *et al* (37) reported higher predicted Intelligence Quotient scores in children 10 years after PBT compared with X-ray treatment. Gross *et al* (38) also reported generally higher scores in neuropsychological tests conducted on pediatric patients with brain tumors following PBT compared with those after X-ray radiotherapy. In terms of secondary tumors, Dennis *et al* (39) reported that the risk of secondary cancer with intensity modulated radiation therapy for intracranial tumors was 2-fold higher than that of PBT, while Sato *et al* (40) reported no observed cases of secondary malignancies in unresectable meningiomas over a median observation period of 10.5 years after PBT. In addition, in PBS IMPT, it is possible to set the tolerable dose for surrounding tissues in advance. Compared with traditional broad-beam PBT, this method allows for

more concentrated irradiation of the tumor while ensuring the dose to the CTV and further reducing the dose to critical organs (41). The present case used this latest technology, to ensure the patient received the most optimal dose distribution possible, thereby minimizing the risk of secondary cancer and cerebrovascular complications. Long-term assessments of the effects of PBT often become apparent years after treatment, especially for slowly growing tumors or when evaluating the treatment's long-term benefits in reducing recurrence rates.

The current case report presented a pediatric calvarial hemangioma that recurred following two surgeries and chemotherapy. Pre-PBT MRI images showed the tumor was notably large, occupying multiple functional areas within the skull and causing notably deformity. MRI findings 14 months post-PBT showed no progression, reduced activity and well-controlled tumor growth. The disease reported in the present study is a rare condition and information on effective treatment methods is limited. Given its predominance in young females, PBT is considered an effective and beneficial treatment option. The current case reports contribute to the limited but growing evidence supporting the use of advanced radiation therapies in managing rare and complex conditions such as calvarial hemangiomas.

In conclusion, the present study represented the first reported use of PBT to treat a calvarial hemangioma in a pediatric patient. The successful use of PBT in the current case highlights its potential as an effective and less invasive option for managing rare and complex conditions such as calvarial hemangiomas, particularly in cases where conventional treatments have failed.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SSXQ and ZS confirm the authenticity of all the raw data. Conceptualization was by SSXQ, validation by ZS and SSXQ, formal analysis by YL and WeiW and investigation by MM, YO and YJ. JW, CL, ZW, WeiW, JZ and SSXQ were responsible for resources. JW obtained radiotherapy dose distribution data. SZ integrated data and visualised the treatment process. CL gathered patient data. ZW acquired and verified radiotherapy dose distribution data. WeiWeiW collected treatment data. JZ collected follow-up data after patient treatment. MM and YJ were responsible for data curation. ZS and SSXQ wrote the original draft and writing, review and editing was by ZS, YJ, MM, YO and YL. Visualization was performed by SZ, and supervision and project administration were performed by SSXQ. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was performed in accordance with the principles of the Declaration of Helsinki (2013 version). Approval was granted by the Ethics Committee of Hebei Yizhou Cancer Hospital (Zhuzhou, China; approval no. 2024LLSC03). As the patient was a minor, written informed consent to participate was obtained from the patient's legal guardians.

Patient consent to publication

As the patient was a minor, written informed consent for the publication of the case report and images in Figs. 1-4 was obtained from the patient's legal guardians.

Competing interests

The authors declare that they have no competing interests.

References

1. Yao K, Tang F, Min L, Zhou Y and Tu C: Multifocal intraosseous hemangioma: A case report. *Medicine (Baltimore)* 98: e14001, 2019.
2. Choi JS, Bae YC, Kang GB and Choi KU: Intraosseous hemangioma of the orbit. *Arch Craniofac Surg* 19: 68-71, 2018.
3. Akhter AS, El Tecle N, Alexopoulos G, Espinoza G and Coppens J: Intraosseous orbital cavernous hemangioma with frontal extension and dural involvement. *Cureus* 11: e4823, 2019.
4. Ramkumar S: Epithelioid Haemangioma of Bone: A case series and comprehensive literature review reappraising the diagnostic classification of all epithelioid vascular neoplasms of bone. *Cureus* 13: e15371, 2021.
5. Powers DB, Fisher E and Erdmann D: Zygomatic intraosseous hemangioma: Case report and literature review. *Craniofacial Trauma Reconstr* 10: 1-10, 2017.
6. Almeida JA, Gellen PVB, Hiramatsu DM, Santos MAD, Bitencourt L, Marceliano EFV, Galhardi MPW, Marceliano-Alves MF and Marques EF: Cavernous Hemangioma in the Orbital Cavity: Case Report. *Eur J Dent* 16: 230-233, 2022.
7. Ademi Abdyli R, Abdyli Y, Perjuci F, Gashi A, Agani Z and Ahmedi J: Sclerotherapy of Intraoral Superficial Hemangioma. *Case Rep Dent* 2016: 4320102, 2016.
8. Sharma S, Kamal R and Rath AK: Vertebral hemangioma-the current radiation therapy perspective. *Rep Pract Oncol Radiother* 28: 93-101, 2023.
9. Shimizu S, Mizumoto M, Okumura T, Li Y, Baba K, Murakami M, Ishida T, Nakamura M, Hiroshima Y, Iizumi T, *et al*: Proton beam therapy for a giant hepatic hemangioma: A case report and literature review. *Clin Transl Radiat Oncol* 27: 152-156, 2021.
10. Park S, Yoon SM, Lee S, Park JH, Song SY, Lee SW, Ahn SD, Kim JH and Choi EK: Role of fractionated radiotherapy in patients with hemangioma of the cavernous sinus. *Radiat Oncol* 13: 268-273, 2017.
11. Ooi KH and Low SW: Fractionated External-beam Radiation Therapy For Incompletely Resected Intracranial Extra-axial Cavernous Haemangioma: A Case Report. *Cureus* 10: e2285, 2018.
12. Matsuda M, Mizumoto M, Kohzaki H, Sugii N, Sakurai H and Ishikawa E: High-dose proton beam therapy versus conventional fractionated radiation therapy for newly diagnosed glioblastoma: A propensity score matching analysis. *Radiat Oncol* 18: 38, 2023.
13. Senirkentli GB, Ekinci F, Bostanci E, Güzel MS, Dağlı Ö, Karim AM and Mishra A: Proton Therapy for Mandibula Plate Phantom. *Healthcare (Basel)* 9: 167, 2021.
14. Nakamura M, Mizumoto M, Saito T, Shimizu S, Li Y, Oshiro Y, Inaba M, Hosaka S, Fukushima H, Suzuki R, *et al*: A systematic review and meta-analysis of radiotherapy and particle beam therapy for skull base chondrosarcoma: TRP-chondrosarcoma 2024. *Front Oncol* 14: 1380716, 2024.
15. Li Y, Mizumoto M, Oshiro Y, Nitta H, Saito T, Iizumi T, Kawano C, Yamaki Y, Fukushima H, Hosaka S, *et al*: A retrospective study of renal growth changes after proton beam therapy for pediatric malignant tumor. *Curr Oncol* 30: 1560-1570, 2023.

16. Li Y, Mizumoto M, Nitta H, Fukushima H, Suzuki R, Hosaka S, Yamaki Y, Murakami M, Baba K, Nakamura M, *et al*: Late Changes in Renal Volume and Function after Proton Beam Therapy in Pediatric and Adult Patients: Children Show Significant Renal Atrophy but Deterioration of Renal Function Is Minimal in the Long-Term in Both Groups. *Cancers (Basel)* 16: 1634, 2024.
17. Jin Y, Shimizu S, Li Y, Yao Y, Liu X, Si H, Sakurai H and Xiao W: Proton therapy (PT) combined with concurrent chemotherapy for locally advanced non-small cell lung cancer with negative driver genes. *Radiat Oncol* 18: 189, 2023.
18. Liu H, Chang X, Shang H, Li F, Zhou H and Xue X: Diffuse cavernous hemangioma of the skull misdiagnosed as skull metastasis in breast cancer patient: One case report and literature review. *BMC Cancer* 19: 172, 2019.
19. Fujii T, Zen Y, Sato Y, Sasaki M, Enomae M, Minato H, Masuda S, Uehara T, Katsuyama T and Nakanuma Y: Podoplanin is a useful diagnostic marker for epithelioid hemangioendothelioma of the liver. *Mod Pathol* 21: 125-130, 2008.
20. Majchrzak K, Kaspera W, Szymaś J, Bobek-Billewicz B, Hebda A and Majchrzak H: Markers of angiogenesis (CD31, CD34, rCBV) and their prognostic value in low-grade gliomas. *Neurol Neurochir Pol* 47: 325-331, 2013.
21. Mehndiratta M, Nayak R, Garg H, Kumar M and Pandey S: Appraisal of Kernig's and Brudzinski's sign in meningitis. *Ann Indian Acad Neurol* 15: 287-288, 2012.
22. Niitsu H, Mizumoto M, Li Y, Nakamura M, Ishida T, Iizumi T, Saito T, Numajiri H, Makishima H, Nakai K, *et al*: Tumor response on diagnostic imaging after proton beam therapy for hepatocellular carcinoma. *Cancers (Basel)* 16: 357, 2024.
23. Jorge MIS, Brinkmann JCB, Corchón AG and Ocaña RA: Diagnostic challenge and management of intraosseous mandibular hemangiomas: A case report and literature review. *J Korean Assoc Oral Maxillofac Surg* 47: 321-326, 2021.
24. Yang Y, Guan J, Ma W, Li Y, Xing B, Ren Z, Su C and Wang R: Primary Intraosseous Cavernous Hemangioma in the Skull. *Medicine (Baltimore)* 95: e3069, 2016.
25. Kirmani AR, Sarmast AH and Bhat AR: A unique case of calvarial hemangioma. *Surg Neurol Int* 7 (Suppl 14): S398-S401, 2016.
26. Myadam S, Kishan V, Deepa A, Shri Puja K and Divya Rani K: Intraosseous hemangioma of the zygomatic bone: A rare site for hemangioma. *Med J Armed Forces India* 72: 85-87, 2015.
27. Ilyas M, Shah SA, Gojwari T, Rafiq S, Ellahi I and Ganaie KH: Classic imaging features of calvarial hemangioma-a case report. *The Egyptian J Radiol Nucl Med* 49: 663-665, 2018.
28. Geng P, Sun X and Liu J: Adopting quaternion wavelet transform to fuse multi-modal medical images. *J Med Biol Eng* 37: 230-239, 2017.
29. Leong S, Kok HK, Delaney H, Feeney J, Lyburn I, Munk P and Torreggiani W: The Radiologic Diagnosis and Treatment of Typical and Atypical Bone Hemangiomas: Current Status. *Can Assoc Radiol J* 67: 2-11, 2016.
30. Dong WK and Chang HC: A Case of Calvarial Hemangioma in Cranioplasty Site. *J Korean Neurosurg Soc* 46: 484-487, 2009.
31. Tomioka Y, Kondo K, Numahata T, Moriwaki Y and Okazaki M: Endoscopic open rhinoplasty enables a cosmetic approach for a rare case of intraosseous cavernous hemangioma in the nasal bone. *Auris Nasus Larynx* 47: 1064-1069, 2020.
32. Sary A, Yavuzer R, Latfoglu O and Çelebi MC: Intraosseous Zygomatic Hemangioma. *Ann Plast Surg* 46: 659-660, 2001.
33. Lee CC, Sheehan JP, Kano H, Akpinar B, Martinez-Alvarez R, Martinez-Moreno N, Guo WY, Lunsford LD and Liu KD: Gamma Knife radiosurgery for hemangioma of the cavernous sinus. *J Neurosurg* 126: 1498-1505, 2017.
34. Gaspar L, Mascarenhas F, da Costa MS, Dias JS, Afonso JG and Silvestre ME: Radiation therapy in the unresectable cavernous hemangioma of the liver. *Radiother Oncol* 29: 45-50, 1993.
35. Peters S, Frisch S, Stock A, Merta J, Bäumer C, Blasé C, Schuermann E, Tippelt S, Bison B, Frühwald M, *et al*: Proton beam therapy for pediatric tumors of the central nervous system-experiences of clinical outcome and feasibility from the KiProReg Study. *Cancers (Basel)* 14: 5863, 2022.
36. Spiotto MT, McGovern SL, Gunn GB, Grosshans D, McAleer MF, Frank SJ and Paulino AC: Proton Radiotherapy to Reduce Late Complications in Childhood Head and Neck Cancers. *Int J Part Ther* 8: 155-167, 2021.
37. Takizawa D, Mizumoto M, Yamamoto T, Oshiro Y, Fukushima H, Fukushima T, Terunuma T, Okumura T, Tsuboi K and Sakurai H: A comparative study of dose distribution of PBT, 3D-CRT and IMRT for pediatric brain tumors. *Radiat Oncol* 12: 40, 2017.
38. Gross JP, Powell S, Zelko F, Hartsell W, Goldman S, Fangusaro J, Lulla RR, Smiley NP, Chang JH and Gondi V: Improved neuro-psychological outcomes following proton therapy relative to X-ray therapy for pediatric brain tumor patients. *Neuro Oncol* 21: 934-943, 2019.
39. Dennis ER, Bussi re MR, Niemierko A, Lu MW, Fullerton BC, Loeffler JS and Shih HA: A comparison of critical structure dose and toxicity risks in patients with low grade gliomas treated with IMRT versus proton radiation therapy. *Technol Cancer Res Treat* 12: 1-9, 2013.
40. Sato H, Mizumoto M, Okumura T, Sakurai H, Sakamoto N, Akutsu H, Ishikawa E and Tsuboi K: Long-term outcomes of patients with unresectable benign meningioma treated with proton beam therapy. *J Radiat Res* 62: 427-437, 2021.
41. Kaulfers T, Lattery G, Cheng C, Zhao X, Selvaraj B, Wu H, Chhabra AM, Choi JI, Lin H, Simone CB II, *et al*: Pencil beam scanning proton bragg peak conformal FLASH in prostate cancer stereotactic body radiotherapy. *Cancers (Basel)* 16: 798, 2024.



Copyright   2024 Shen et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.