Advances in Radiation Oncology (2025) 10, 101736

advances in radiation oncology

www.advancesradonc.org

Teaching Case

First Application of Boron Neutron Capture Therapy for Recurrent Clival Chordoma With Brainstem Abutment

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Received 24 June 2024; accepted 5 February 2025

Introduction

Chordomas, rare and slow-growing malignant neoplasms with an incidence rate of 0.08 per 100,000, encompass 32% of the skull base, including clival chordoma.[1] Achieving en bloc resection for chordomas is crucial.[2] However, for clival chordoma, its proximity to vital neural structures complicates en bloc resection. Moreover, clival chordoma surgeries often use endonasal endoscopic skull base surgery, further complicating en bloc resection attainment. In cases where chordomas are deemed inoperable, particularly in challenging anatomic regions, particle radiation therapy (RT) is commonly employed because it provides optimal dose coverage while delivering lower radiation doses to critical organs, thereby reducing toxicity.[3] A meta-analysis has indicated that particle therapy yields superior overall survival rates compared with conventional photon therapy for inoperable chordomas.[4] Recent studies indicate that particle beam therapy has become the first-line treatment for skull base chordomas.[5] Nonetheless, particle therapy may not be suitable for all cases, especially for patients requiring reirradiation because of recurrence, as radiation tolerance limits must be carefully considered in such instances.

Boron neutron capture therapy (BNCT) may be a favorable solution in such scenarios. The principle of BNCT relies on the preferential absorption of boron-containing compounds by tumor cells compared with normal tissues. Subsequently, irradiation with thermal neutrons induces a reaction with boron, rapidly releasing high-energy lithium-7 and α particles. The range of these particles in cells is only 4 to 5 μm and 8 to 9 μm, respectively, which corresponds to the size of a single cell. This allows for the selective destruction of tumor cells while preserving normal tissue cells. Such characteristics make BNCT particularly suitable for tumors located near the brainstem. There are 2 main

Sources of support: This work had no specific funding.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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https://doi.org/10.1016/j.adro.2025.101736

methods for neutron generation: accelerators and reactors. Because of factors such as compact machine size, better controllability, and the absence of nuclear waste issues, accelerators are gradually becoming the mainstream option.

In this study, the patient presented with clival chordoma and had previously undergone multiple surgical resections and proton therapy. Six years later, recurrence was observed, with magnetic resonance imaging (MRI) revealing an abutment of the brainstem tissue. Following a discussion with the patient, the decision was made to undergo BNCT. To the best of our knowledge, this study represents the first investigation of the use of BNCT for clival chordoma treatment. The treatment outcomes observed in this study might offer chordoma patients a novel therapeutic option.

Case Presentation

In 2016, a 71-year-old female presented with diplopia and blurred vision attributed to right abducens palsy, nasal soreness, mild headache, and tinnitus. Pathologic examination subsequently confirmed a diagnosis of clival chordoma. The patient initially underwent an endoscopic endonasal resection at another medical institution on December 29, 2016, which left residual tumor tissue. A right pterional craniotomy was conducted on May 8, 2017, to address the residual tumor; however, only partial removal was achieved. Therefore, the patient received adjuvant proton therapy from September 6, 2017, to October 24, 2017, over a total of 49 days with a radiation dose of 6600 cGy in 30 fractions. The radiation doses received by the tumor and normal organs during proton therapy are listed in Table 1. Notably, the pituitary gland and optic chiasm were exposed to relatively higher doses. Despite this procedure, the tumor recurred again, necessitating another endoscopic endonasal resection in November 2018. Because of the proton dose reaching the maximum tolerable levels for the pituitary gland, the patient did not undergo additional adjuvant RT.

In August 2022, the patient experienced a recurrence of diplopia, which persisted for approximately 1 year. As the symptoms exacerbated, she sought medical evaluation at our institution. A fluciclovine positron emission tomography (PET) scan on August 17, 2023, identified a 1.7 × 1.4 cm nodule in the right sphenoid with suspected brainstem abutment (Fig. 1A, B). Subsequently, on September 4, 2023, a vestibular function assessment was performed, revealing normal ocular motion and nystagmus, as well as a normal finger-nose-finger test. However, the Romberg test and single-leg stance test demonstrated abnormalities. Given the imaging findings and neurologic symptoms, right cavernous sinus and brainstem abutment were highly suspected. Considering the challenging location for proton therapy and heavy particle therapy, BNCT was elected as the treatment modality. Prior to receiving BNCT treatment, the patient underwent an institutional review board appraisal and signed an informed consent form.

BNCT Setting

Boronophenylalanine (BPA) was the boron drug administered to the patient via intravenous injection in this study. The preparation method for BPA involves dissolving 6.25 mg of BPA in 250 mL of fructose solution. The total administered dose was 0.5 g/kg body weight of BPA. Initially, during the first 2 hours, 0.2 g/kg body

Table 1 Dose (cGy) and volume of different organs in proton therapy

	Proton therapy			
Organ	Max dose	Mean dose	Min dose	Volume (cm^3)
Pituitary gland	7319.4	7035.6	6778.2	0.2
Tumor (GTV)	7728.6	7405.2	5775.0	4.4
Rt eye	369.6	33	6.6	1.5
Rt lens	13.2	6.6	6.6	0.2
Rt CN2	6289.8	3570.6	99	0.2
Lt eye	33	0	0	7.5
Lt lens	13.2	6.6	6.6	0.2
Lt CN2	5860.8	2600.4	26.4	0.2
Optic chiasm	6619.8	5590.2	4659.6	0.2
Brain	7728.6	792	0	1253.9
Brainstem	6685.8	3161.4	99	27.0

Abbreviations: CN2 = optic nerve; GTV = gross tumor volume; Lt = left; Max = maximum; Min = minimum; Rt = right.

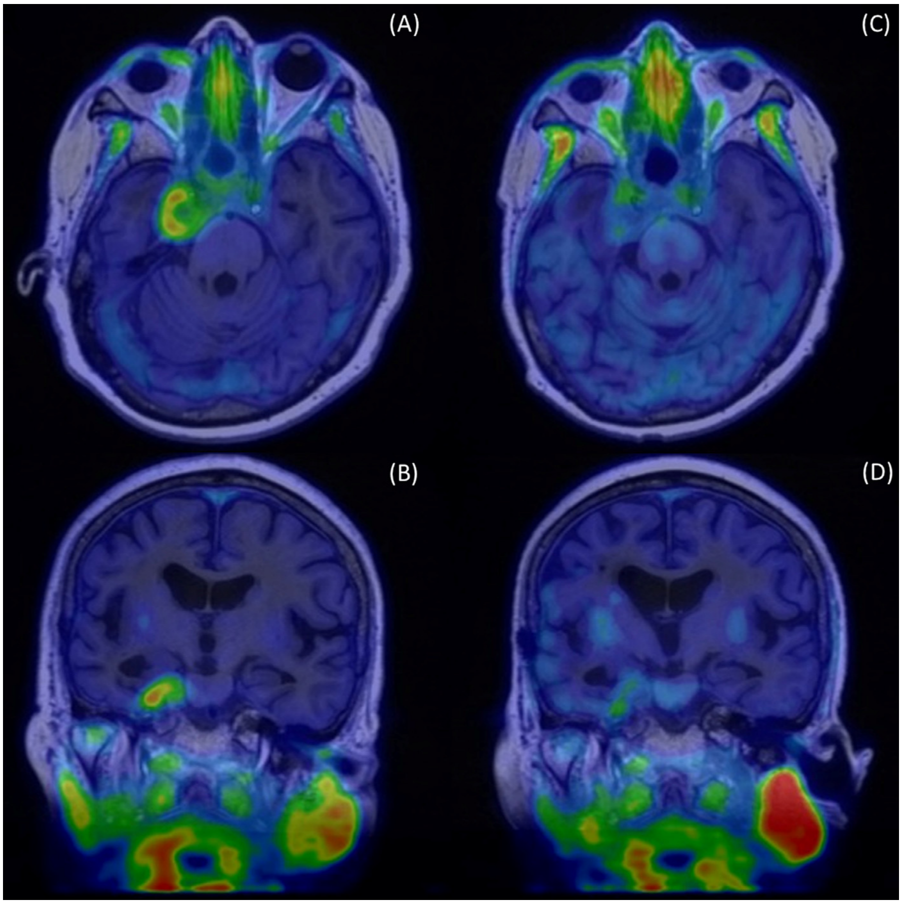

Figure 1 (A) Axial and (B) coronal views of the brain positron emission tomography scan on August 17, 2023, showing a 1.7 × 1.4 cm nodule with a tumor-to-normal tissue ratio of 3.69. (C) Transverse and (D) coronal views of the brain positron emission tomography scan on January 19, 2024, showing a regressive change of the tumor with a tumor-to-normal tissue ratio of 2.83.

weight of BPA per hour was infused. Subsequently, in the last hour, 0.1 g/kg body weight of BPA per hour was infused. Following the initiation of BPA injection, intra-patient BPA concentrations were sequentially monitored at 0, 1, 2, 3, and 3.5 hours, which was done by inductively coupled plasma atomic emission spectroscopy.

The tumor-to-normal tissue (T/N) ratio was determined using fluorine-18–labeled fluciclovine PET imaging. The T/N ratio for the first BNCT was 3.69, and for the second BNCT, it was 2.83 (Fig. 1). However, since fluciclovine was used to estimate BPA uptake, the actual T/N ratio may still have a certain degree of error. Therefore, when calculating the radiation dose to brain tumors, the T/N ratio was conservatively assumed to be 2.5, as 18F-fluciclovine PET may overestimate the precise concentration of boron-containing drug uptake within the tumor.[6]

In this study, the neutron source was derived from a nuclear reactor, emitting epithermal neutrons with an irradiation field in a circular area of 8 cm in diameter. For the first BNCT session, the patient was positioned supine with a neutron incidence angle rotated 30 degrees clockwise from the body midline. For the second BNCT session, the patient was also positioned supine, with the neutron incidence angle rotated 20 degrees clockwise from the body midline. The first BNCT session required a total irradiation time of 25 minutes and 49 seconds, while the second BNCT treatment session lasted 15 minutes and 31 seconds. The treatment planning was conducted using the Simulation Environment for Radiotherapy Applications treatment planning system.

First BNCT and Outcomes

On November 22, 2023, the patient underwent the first BNCT treatment. At the time of treatment, the tumor volume was 3.84 cm^3. During thermal neutron irradiation, the boron concentration in the blood was 23.71 ppm. The maximum dose (Dmax) delivered to the tumor was 28.98 Gy equivalent (Gy-Eq), and the average dose (Dave) was 20.42 Gy-Eq. The Dmax and Dave received by surrounding organs were as follows (Table 2): right eye: 8.23 Gy-Eq (Dmax) and 5.32 Gy-Eq (Dave); right lens: 4.25 Gy-Eq (Dmax) and 3.60

Table 2 Dose (Gy equivalent) and volume of different organs in the first and second boron neutron capture therapies

	First BNCT				Second BNCT			
Organ	Max dose	Mean dose	Min dose	Volume (cm^3)	Max dose	Mean dose	Min dose	Volume (cm^3)
Tumor	28.98	20.42	13.70	3.84	26.32	20.22	14.45	1.55
Rt eye	8.23	5.32	2.75	8.08	4.98	3.07	1.46	8.87
Rt lens	4.25	3.60	3.10	0.39	2.42	1.91	1.50	0.41
Rt CN2	7.85	5.00	3.06	1.97	4.83	3.17	1.93	2.37
Rt inner ear	6.20	5.15	4.23	1.85	5.48	4.60	3.87	1.85
Rt CN7,8	5.32	4.59	3.75	0.38	4.54	3.90	3.30	0.17
Rt parotid gland	9.20	3.20	1.32	20.44	7.94	3.85	1.52	21.50
Brainstem	3.91	2.19	1.19	24.39	2.78	1.52	0.87	21.41
Rt carotid artery	7.40	5.12	2.75	3.5	5.98	1.72	0.25	7.48

Abbreviations: BNCT = boron neutron capture therapy; CN2 = optic nerve; CN7,8 = facial and vestibulocochlear nerve; Max = maximum; Min = minimum; Rt = right.

Gy-Eq (Dave); right cranial nerve (CN) 2: 7.85 Gy-Eq (Dmax) and 5.00 Gy-Eq (Dave); right inner ear: 6.20 Gy-Eq (Dmax) and 5.15 Gy-Eq (Dave); right CN 7, 8: 5.32 Gy-Eq (Dmax) and 4.59 Gy-Eq (Dave); right parotid gland: 9.20 Gy-Eq (Dmax) and 3.20 Gy-Eq (Dave); brainstem: 3.91 Gy-Eq (Dmax) and 2.19 Gy-Eq (Dave); right carotid artery: 7.40 Gy-Eq (Dmax) and 5.12 Gy-Eq (Dave). Two weeks postirradiation, the patient exhibited mild redness and swelling on the right cheek and oral ulcers, which subsequently improved. PET and MRI follow-up 2 months later showed significant tumor reduction (Figs. 1 and 2), leading to the decision to proceed with a second BNCT session.

Second BNCT and Outcomes

On March 29, 2024, the patient underwent the second BNCT treatment. At the time of this treatment, the tumor volume was 1.55 cc. During thermal neutron irradiation, the boron concentration in the blood was 42.58 ppm. Dmax delivered to the tumor was 26.32 Gy-Eq, and Dave was 20.22 Gy-Eq. The Dmax and Dave received by surrounding organs were as follows (Table 2): right eye: 4.98 Gy-Eq (Dmax) and 3.07 Gy-Eq (Dave); right lens: 2.42 Gy-Eq (Dmax) and 1.91 Gy-Eq (Dave); right CN 2: 4.83 Gy-Eq (Dmax) and 3.17 Gy-Eq (Dave); right inner ear: 5.48 Gy-Eq (Dmax) and 4.60 Gy-Eq (Dave); right CN 7, 8: 4.54 Gy-Eq (Dmax) and 3.90 Gy-Eq (Dave); right parotid gland: 7.94 Gy-Eq (Dmax) and 3.85 Gy-Eq (Dave); brainstem: 2.78 Gy-Eq (Dmax) and 1.52 Gy-Eq (Dave); right carotid artery: 5.98 Gy-Eq (Dmax) and 1.72 Gy-Eq (Dave). Postirradiation, the patient experienced headaches but no other significant side effects. An MRI follow-up on March 13, 2024, indicated that the tumor exhibited stable disease (Fig. 2). Since this patient received only BNCT treatment at our hospital, with all other treatments completed elsewhere, the patient returned to their original health care facility after BNCT and was currently undergoing stable follow-up.

Discussion

This case report describes a patient with recurrent clival chordoma, subsequently found to have involvement of the right cavernous sinus region and brainstem abutment. The patient had previously undergone 3 surgeries, 1 photon therapy, and 1 proton therapy. Because of tumor invasion into the brainstem, conventional treatments were deemed ineffective. However, after 2 sessions of BNCT, significant tumor reduction was observed. This represents the world's first case of using BNCT to treat chordoma. The case report highlights the excellent potential of BNCT for this type of cancer.

In the context of chordoma treatment, the achievement of "en bloc resection" is often a primary goal. Kaiser et al[7] demonstrated that disruption of the patient's capsule increases the local recurrence rate 2-fold compared with cases without such disruption. However, en bloc resection is challenging for clival chordomas because of restricted surgical space and the presence of critical neural and vascular structures nearby. Preservation of neurologic function takes precedence in managing these cases.[8] RT has gained significant importance in managing chordomas that cannot undergo en bloc resection. Conventional RT has been shown to achieve a 5-year progression-free survival rate of 50.54%.[9] In comparison, stereotactic radiosurgery achieves a progression-free survival rate of 55.02%, with a mean time to progression of 48.02 months.[10] Moreover, both conventional RT and stereotactic radiosurgery demonstrate significant improvements in local control rates with higher radiation doses.[11,12]

Therefore, to maintain a high radiation dose for chordoma while minimizing damage to surrounding normal

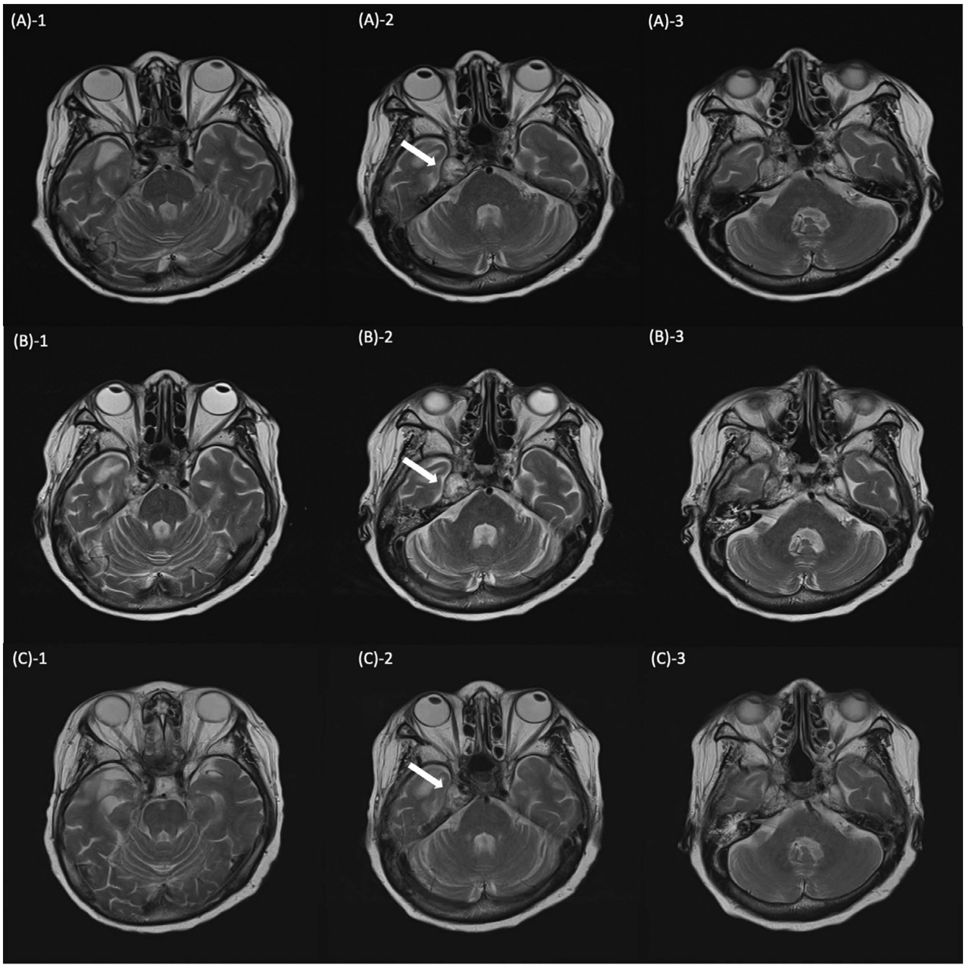

Figure 2 T2-weighted brain magnetic resonance imaging axial view with a 4 mm slice thickness for clival chordoma. (A) Imaging on June 24, 2023, before boron neutron capture therapy (BNCT), (B) on December 22, 2023, after the first BNCT, and (C) on May 13, 2024, after the second BNCT. In all 3 series (A-C), image 2 represents the slice showing the tumor at its largest dimension, while images 1 and 3 correspond to magnetic resonance imaging slices taken 4 mm above and below image 2, respectively.

tissues, particle therapy has emerged as the first-line treatment for chordoma. Zhou et al[4] conducted a meta-analysis comparing conventional RT, stereotactic RT, proton therapy, and carbon ion RT. The meta-analysis indicated that particle therapy, compared with photon therapy, exhibited significant advantages. For tumors located near critical neural structures such as the brainstem, although particle therapy benefits from the Bragg peak effect, reducing the radiation dose absorbed by normal tissues still presents issues with lateral scattering. This can result in some degree of damage to surrounding brain tissues, which may be unacceptable, particularly in brainstem regions. As noted in this study, the proton mean radiation dose to the optic chiasm for this patient reached 55.9 Gy. According to research, doses exceeding 59.4 Gy are associated with the risk of radiation-induced optic neuropathy.[13] The characteristics of BNCT may mitigate such concerns.

BNCT uses thermal neutrons and the absorbed isotope boron-10 in tumor cells to induce nuclear reactions, releasing high-energy lithium-7 and α particles, which deposit doses of high linear energy transfer (LET) at 175 keV/μm and 150 keV/μm, respectively. Given that the maximum travel distances of lithium-7 and α particles within tissue cells are only 5 μm and 9 μm, respectively, this range is comparable to the size of a single cell.[14] According to the mechanism described above, BNCT aims to minimize harm to normal tissues. However, recent literature indicates that several associated side effects, such as carotid blowout syndrome[15] and radiation necrosis,[16] may still occur, highlighting a point of concern for future consideration.

Concentrating the high-energy reaction within a single cell enables BNCT to be applied to various tumors in brainstem tissues and pediatric brain tumors, with no significant adverse effects observed after irradiation.[17-19] In this case report, no neurologic symptoms were observed after the first and second BNCT treatments. Additionally, theoretically, tumor cells that are not visible on imaging may still absorb sufficient boron-containing drugs and be killed under neutron irradiation, potentially further reducing the local recurrence rate. However, this hypothesis requires further validation through subsequent research.

Conclusion

In conclusion, this case report presents the world's first instance of using BNCT for clival chordoma, yielding promising outcomes in tumor volume reduction. However, it is important to note that because of the lack of long-term follow-up for this patient, further evidence is required to confirm both safety and prognosis. Additionally, for tumors where en bloc resection is unachievable, preoperative BNCT, by reducing tumor volume, may potentially enhance the likelihood of achieving en bloc resection.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

First and foremost, we extend our highest gratitude to the Nuclear Science and Technology Development Center of Tsing-Hua University for their assistance in developing the treatment plan system and to Taiwan Biotech Co., Ltd. for their production of high-quality L-BPA used in this study. Additionally, we acknowledge Dr Jen-Kun Chen, an expert in biomedical imaging from the National Health Research Institutes, for his outstanding support during this important research. Furthermore, special thanks are extended to clinical research nurse Ms Pei-Yu Lai for her exceptional nursing care during the BNCT treatment process. Finally, we would like to express our gratitude to all members of the Research Center for Boron Neutron Capture Therapy at Tamkang University, under the leadership of Professor Po-Shen Pan, for their unwavering support in facilitating this study. Hung-Ruei Liao was responsible for statistical analysis.

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