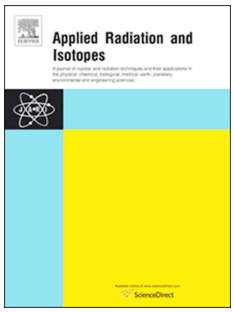

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Using Salvage Boron Neutron Capture Therapy (BNCT) for Recurrent Malignant Brain Tumors in Taiwan

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Abstract

Radiation therapy has an irreplaceable role in modern oncologic therapy, thanks to the advanced radiation techniques developed in recent decades. However, photon-resistant cases are sometimes encountered. Boron Neutron Capture Therapy (BNCT) is a highly selective radiotherapy technique due to the high tumor to tissue ratio of boronophenylalanine (BPA), the unique medication used for the BNCT treatment reaction. In this study, we report on three special patients with malignant brain tumors treated with BNCT.

Introduction

Malignant glioma is one of the most aggressive and common primary brain tumors worldwide, occurring not only in adults, but also in children. With the incidence rate of 3.19/100,000 and a median survival of 15 months[1,2], an advanced strategy is urgently needed to improve the disease prognosis. The current treatment usually consists of surgical resection with a maximal-safe area followed by photon-based radiation therapy and oral alkylating chemotherapy[3].

Radiation therapy is an indispensable part of modern oncologic therapy, with advanced radiation techniques including Gamma knife radiosurgery, proton beam irradiation, and carbon ion irradiation, had been developed in the past decades. However, some limitations remain in terms of radioresistant tumors, including glioblastoma[4], melanoma[5], and sarcoma[6]. Hence, new treatment strategies are needed for such patients. Boron Neutron Capture Therapy (BNCT) has shown promise in treating glioblastoma with several Japanese studies reporting a

significantly increased median survival time[7,8]. It is a highly selective radiotherapy technique due to the high tumor to tissue ratio of boronophenylalanine (BPA), the medication used for the BNCT treatment reaction.

Other than glioblastoma, another rare cause of malignant brain tumor is mismatch repair syndrome. Mismatch repair syndrome is associated with biallelic DNA mismatch repair mutations in genes such as MLH1, MSH2, MSH6 and PMS2, leading to constitutional mismatch repair deficiency (CMMR-D)[9]. In a previous study of 92 patients with CMMR-D was reported, neoplasms are divided into four major groups, hematological malignancies, brain tumors, Lynch syndrome-associated tumors, and other malignancies[10]. In our study, one 11-year-old girl was diagnosed with mismatch repair syndrome with brain tumor expression, and was recruited for BNCT treatment.

Materials and Methods

Patients

The three patients who received BNCT treatment in Taiwan are described in Table 1. All patients received craniotomy and concurrent chemoradiation therapy (CCRT) for the initial brain tumor, and received a second craniotomy after brain tumor recurrence and histologically proven glioblastoma. All patients in this study were referred to the Radiation Oncology Department of Taipei Veterans General Hospital(TVGH), and received compassionate BNCT at Tsing Hua Open-pool Reactor (THOR) after approval by Institutional Review Board (IRB) of TVGH and Taiwan's Food and Drug Administration (TFDA). All patients or their parents/legal guardians provided written informed consent to participate. The recursive partitioning analysis (RPA) stage was described by Carson et al. during 2007, and was used for prognosis prediction for glioblastoma patients[11]. The patient number represents the serial number of patients receiving BNCT under the protocol of compassionate BNCT treatment in Taiwan.

1. Patient 2, a 35-year-old woman with a history of right temporal insular anaplastic astrocytoma diagnosed in May 2013. Her initial symptoms were intermittent numbness in her left body, and left hemianopsia. She received craniotomy and post operation CCRT (60Gy/30fx) with Temozolamide, but tumor recurrence was identified in February, 2015. She received a second craniotomy in July 2015, which the surgical pathology showed to be glioblastoma. The patient was followed and BNCT was performed on 2017/5/26.

2. Patient 10, a 45-year-old woman with a history of right mesial temporal brain

tumor diagnosed in May, 2016. Her symptoms first presented as face paresthesia and loss of consciousness during daily activity. She received right anterior temporal lobectomy and hippocampectomy followed by post operation CCRT (59.4Gy/33fx) with Temozolamide. Pathology showed anaplastic astrocytoma, Ki-67=40. However, tumor recurrence was noted in August 2017, with more extensive tumor involvement, including the right posterior mesial temporal area, the temporoparietooccipital area, and the deep temporoparietal periventricular area. The patient underwent a second craniotomy in September 2017, which the surgical pathology showed glioblastoma. She continued her outpatient follow up, and BNCT was performed on 2017/10/13.

3. Patient 15 was an 11-year-old girl with genetically proven mismatch repair syndrome, MSH6 mutation positive. This rare genetic disease included the development of multiple malignancies including right frontal glioblastoma, T lymphoblastic lymphoma, and left posterior fossa medulloblastoma. Variable symptoms had occurred including massive pleural effusion due to lymphoma, and hydrocephalus caused by medulloblastoma. Craniotomy, craniospinal irradiation, and chemotherapy with cisplatin, vincristine, and cyclophosphamide were prescribed for medulloblastoma in December 2012. Glioblastoma was discovered in February, 2015, with craniotomy and post operation CCRT were done immediately after diagnosis. However, during regular image follow-up for a previous brain tumor, brain Magnetic Resonance Imaging (MRI) on September 2017 showed lobulated cystic lesions in left paramedical cerebellum. Repeat craniotomy was thus performed on 2017/9/13 and the lesion was confirmed as glioblastoma. BNCT was done on 2017/11/29, and the patient received nivolumab (anti-PD 1 immunotherapy) after BNCT treatment.

Treatment protocol

Before the treatment was arranged, all patients underwent 4-borono-2-18F-fluoro-phenylalanine (FBPA) positron emission tomography (PET) in the TVGH Department of Nuclear Medicine. The purpose of this examination was to confirm the distribution of L-(4-10borophenyl) alanine (L-BPA), the boron-containing drug that was used widely as the boron carrier for BNCT. The tumor-to-normal tissue ratio (T/N ratio) and the tumor-to-blood ratio (T/B ratio) were calculated through the maximum standardized uptake value (SUV) of the brain and the tumor. A T/N ratio above 2.5 is considered adequate BPA uptake of the tumor[12]. As BNCT is not a standard treatment in Taiwan, these patients were treated under the emergent application for compassionate treatment. The whole treatment protocolwas approved by the TVGH IRB and TFDA. BNCT was verified as legal to perform at Tsing-Hua University.

As the neutron beam produced by the neutron reactor consists of many different beams including gamma ray and photon beam components, the total amount of radiation delivered to a tissue was cumulated and defined as Gray-equivalent (GyE). We formulated a limitation of maximum normal brain dose, mean brain dose, and mean optic nerve dose of 10 GyE, 2 GyE, and 8 GyE respectively, with a tumor mean dose of 20-40GyE. The THOR plan was used for dose calculation.

On the day of treatment, all patients received a continuous infusion of L-BPA for a total infused dose of 450 mg/kg body weight. The dosage was divided into 180 mg/kg per hour for 2 hours before BNCT, and 90 mg/kg per hour for drug concentration maintenance during the neutron irradiation process. Blood boron concentration was evaluated through inductively coupled plasma with atomic emission spectroscopy (ICP-AES) during the first and second hour of L-BPA infusion, and after the neutron irradiation. The boron concentration during the second hour is also the boron concentration when the neutron irradiation begins. As described in previous studies[13], this infusion strategy can maintain the boron concentration during BNCT, and the expectation of blood boron concentration is between 25 and 35 ppm before neutron irradiation. The exact blood boron concentration is reported in Table 2, with Patient 15 receiving only one serum boron concentration examination before BNCT due to the difficulty of performing phlebotomy. (Figure 1)

BNCT was conducted at THOR, with the reactor power of 1.2 to 2.0MW with epithermal neutron beam. All patients were admitted to the Neurological Surgery Department of TVGH, and head for THOR at the morning of the BNCT operation. The patient was then returned to TVGH on the same day after BNCT was done.

Treatment Evaluation and Assessment for Adverse Effects

Response to the BNCT treatment was evaluated using the RECIST tumor response criteria[14], which categorized the treatment effect into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Patients underwent MRI at least 4 weeks after BNCT for treatment response evaluation. Adverse effects including skin damage and neurological deficit after radiation were graded according to the Common Terminology Criteria for Adverse Events (CTCAE). The final survival analysis was done in July 2019.

Results

Tumor responses and the main complications are described in Table 3. All three patients had tumor regression during the first MRI follow up within three months

after BNCT, and the adverse effects were tolerable. Most of the adverse effects were skin reactions, which is also frequently seen in external beam radiotherapy.

Patient 2

A 35-year-old female presented with left side numbness and left visual defect since August 2012 was diagnosed with right temporal lobe anaplastic astrocytoma. Her neurological symptoms deteriorated as she received craniotomy and CCRT, and progressed to left hemiparesis as she came to our institute for BNCT. Her T/N ratio was 4.7, which indicates a significant uptake of boron containing drug. The total BNCT irradiation time was 22.35 minutes, and the final tumor dose was 27.10 GyE, with the brain maximum dose as low as 9.08 GyE. The patient received MR spectroscopy (MRS) 4 days and 3 months after BNCT, which showed marked regression of the tumor. Tumor mass effects, including headache and dizziness, were relieved after BNCT. However, MRS showed a marked reduction in NAA and marked elevation of choline complex, which may indicate a viable tumor component along the margin of the area of tissue loss. (Figure 2)

Patient 10

A 45-year-old female with face paresthesia and loss of consciousness during May 2016 was diagnosed with right occipital lobe anaplastic astrocytoma. The patient suffered from headache and generalized tremor, but she was still able to perform daily activity in order to live independently. Her T/N ratio after the FBPA PET survey was 2.0, which just met the minimal requirement for BNCT treatment. BNCT irradiation time was 20.65 minutes, and the tumor average dose measured 11.82 GyE, with a brain average dose of 7.82 GyE. The patient received MRI follow up one month after BNCT, and tumor regression was noted. The patient also claimed relief of the neurological symptoms after the BNCT treatment. However, tumor recurrence was found in April 2018, and chemotherapy was arranged for further management. (Figure 3)

Patient 15

An 11-year-old girl was diagnosed with medulloblastoma when she was 8 years old. She received craniotomy and CCRT during December, 2012, but tumor recurrence was then found in March 2015, which was later proven to be anaplastic astrocytoma. T lymphoblastic lymphoma was later found as pleural effusion developed. A genetic survey was then performed, and showed mismatch repair syndrome. Two anaplastic astrocytoma were found, one in the cerebellar and one in the frontal lobe. (Figure 4)

Thus, the BNCT plan for this patient was divided into two parts, performed on the same day. The dosage of each tumor and normal tissue was calculated as the combination of the two irradiation planning results. The patient received irradiation for 16.3 minutes for the right cerebellar tumor from the back of the patient, and irradiation for 16.02 minutes for the left frontal tumor from the top of the patient. The average dose for the left cerebellar tumor was 27.75 GyE, with 29.02 GyE for the frontal tumor. The combined brain maximum dose was 6.53 GyE. The patient had a significant improvement in neurologic symptoms, and was able to make handicrafts the next morning. However, lymphoma progression with malignant pleural effusion and respiratory failure were noticed.

Discussion

Previous studies have discussed the prognosis of patients with recurrent glioblastoma. Carson et al. (2007) [11]reported an analysis of 333 cases of recurrent glioblastoma, which showed that the factors associated with increased risk of death include increased age, lower Karnofsky Performance Score (KPS), initial and on-study histology of glioblastoma, corticosteroid use, shorter time from original diagnosis to recurrence, and tumor outside the frontal lobe. RPA was done to determine the median survival time of each group. Patient 2 and Patient 10 were categorized into group 2, with a median survival of 17.2 months. Patient 15 was categorized into group 3, with a median survival of 3.8 months.

Kazmi et al. (2019)[15] reported a meta-analysis including 2095 patients with re-irradiation after recurrent glioblastoma. They found a 6-month overall survival rate of 73% and a 12-month overall survival rate of 36%.

We have performed many BNCT cases in Taiwan over the past several years[16,17], including patients with recurrent brain tumors[18], or even head and neck cancers[19], and have accumulated clinical experience to decide the better treatment dosage for patients. The protocol for Taiwan emergent BNCT treatment includes a stricter dose constraint compared to many other BNCT protocols. Matsuda et al. (2009)[20] showed a maximum normal brain dose, skin dose, and average brain dose of 11.4+/-1.5, 9.6+/-1.4, and 3.1+/-0.4 GyE, respectively. In our institute, a treatment protocol of maximum normal brain dose, mean brain dose, and mean optic nerve dose of 10, 2, and 8GyE respectively. Also, Matsuda et al. (2009)[20] reported the minimum tumor dose per gross tumor volume (GTV) was 29.8+/-9.9 GyE. We have a range of tumor mean dose of 20-40 GyE. The reason we formulate a stricter protocol is we consider it safer for patients while there are no definite evidence of brain tolerance of neutron irradiation. However, some studies emphasize the importance of minimal tumor dose to achieve complete response. In histopathological point of

view, Kageji et al. (2014)[21] reported on 23 patients with glioblastoma treated with BNCT, autopsy was performed in 5, salvage surgery in 3, and histopathological study in 8. Result showed that the optimal minimal dose to achieve histopathological cure of glioblastoma at the primary site was 68GyE to GTV. Another BNCT study of locally recurrent head and neck cancer by Koivurono et al. (2019)[22] also reported that a high minimum tumor dose and a small volume were independently associated with longer survival.

Mismatch repair syndrome is a devastating disease, with many associated malignancies reported[5]. Rodríguez-Hernández et al. (2013)[23] reported an analysis of the prognosis and the associated mutations in astrocytoma in mismatch repair syndromes. Their survival analysis showed that the loss of MSH6 expression is significantly associated with a better overall survival in high grade astrocytoma, with 13.8 months compared to 10.1 months. A treatment strategy with CCRT and age under 60 years old were also significant independent prognosis factors for survival in high-grade patients with astrocytoma. Patient 15 matched all three factors favorable for longer survival, but the neurologic deficits caused by the tumor mass effect had hugely influenced her ability to perform activities of daily living. BNCT not only helped control the progression of the tumor and prolonged her survival, but also greatly helped relieve the neurological symptoms.

Conclusions

BNCT is effective for patients with malignant brain tumor, with a significant effect on maintaining good quality of life. It may potentially prolong patient's survival time. As more and more treatment experience of BNCT was conducted worldwide, it might be an authorized standard salvage treatment for glioblastoma and perhaps other malignancies in the future.

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Keyword

boron neutron capture therapy, recurrent glioblastoma, mismatch repair syndrome

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Figure Legends

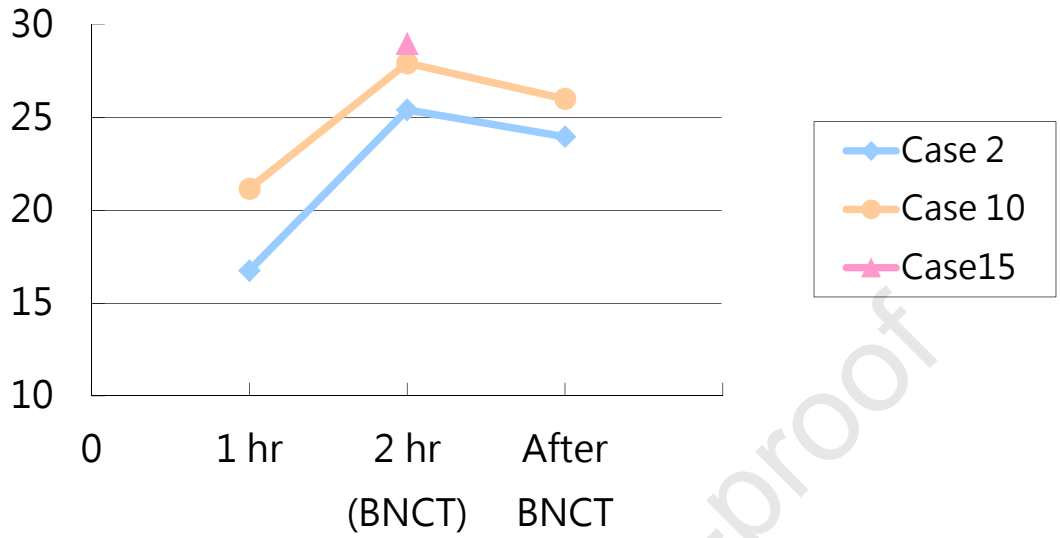

Figure 1. Serum boron concentration level after L-BPA was infused on the day of Boron Neutron Capture Therapy (BNCT).

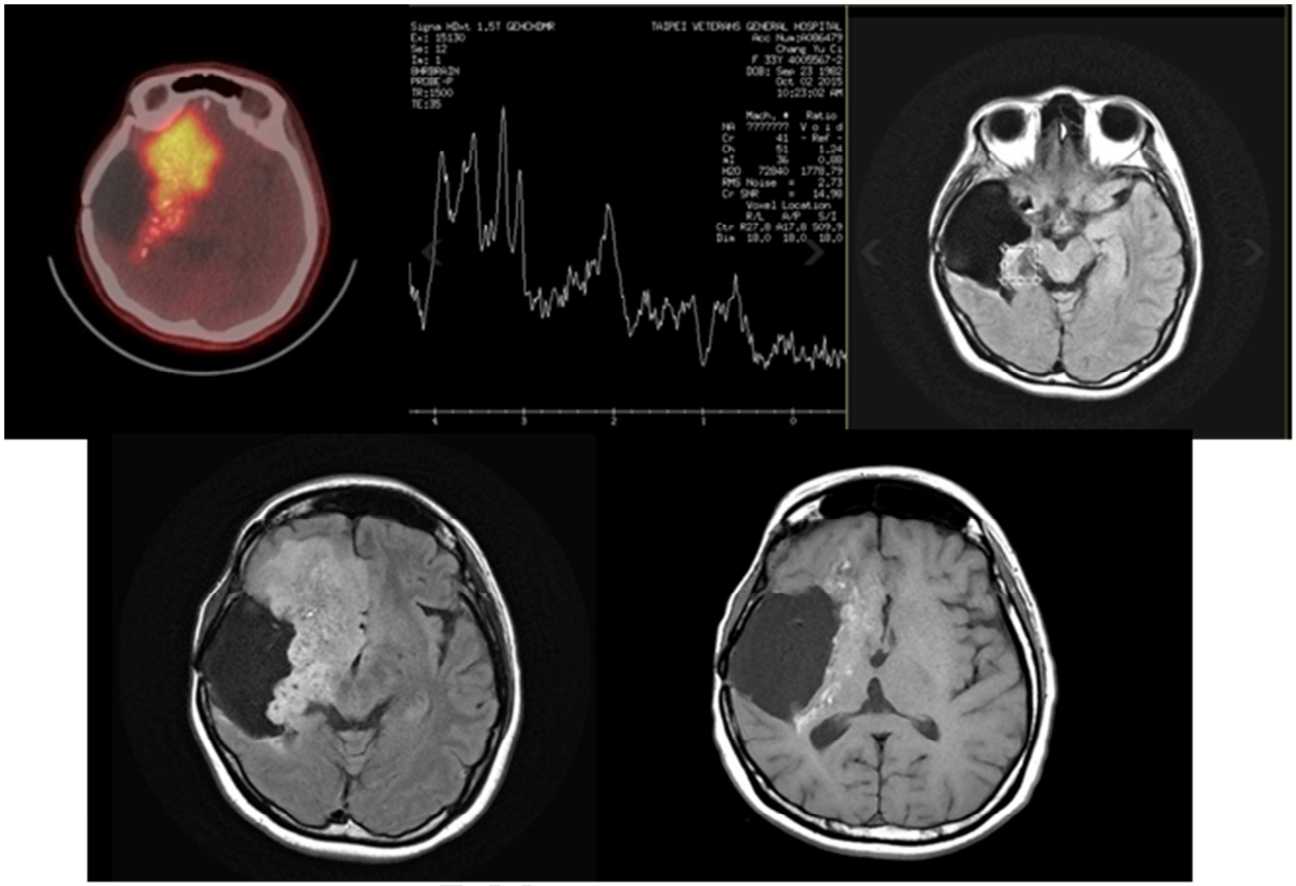

Figure 2. Imaging results for Patient 2. (Left upper) The 4-borono-2-18F-fluoro-phenylalanine (FBPA) positron emission tomography (PET) image of Patient 2, with the tumor-to-tissue (T/N) standard uptake value (SUV) average calculated after radioactive boron-containing drugs were infused into the patient. The T/N ratio of this patient was 4.7, which indicates a high FBPA uptake by the tumor. (Right upper) The Magnetic Resonance (MR) spectroscopy image of this patient. The increased choline peak indicates a viable tumor in the right temporal area. (Left lower) The MR image before Boron Neutron Capture Therapy (BNCT) was conducted. (Right lower) MR image 3 months after BNCT was finished.

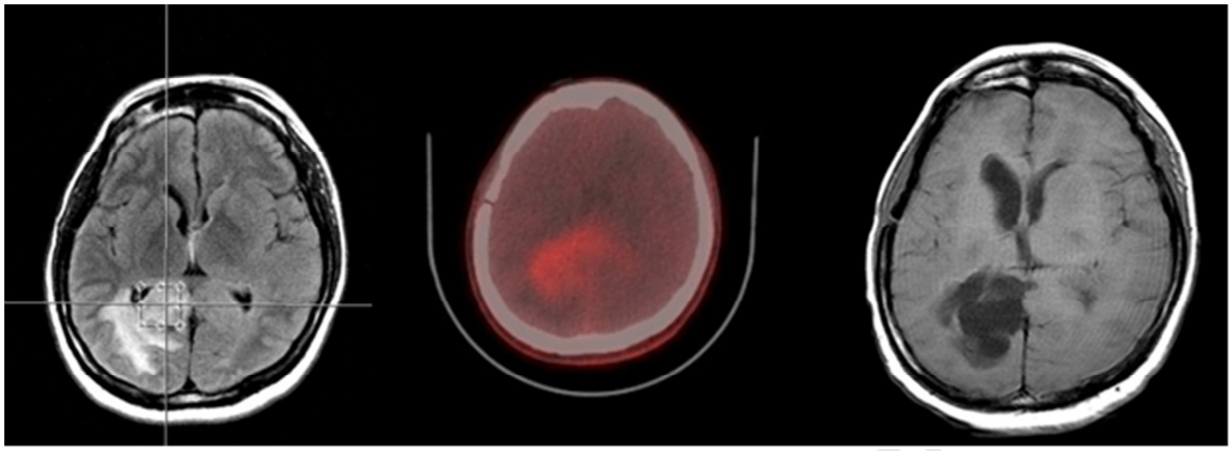

Figure 3. Imaging Results for Patient 10. (Left) Magnetic Resonance Imaging (MRI) showed a viable tumor in the right occipital lobe. (Middle) The 4-borono-2-18F-fluoro-phenylalanine (FBPA) positron emission tomography (PET) image. The tumor-to-tissue (T/N) ratio was 2.0, which just reached the minimal requirement for Boron Neutron Capture Therapy (BNCT) treatment. (Right) MRI image 6 months after BNCT, showing significant shrinkage of the tumor.

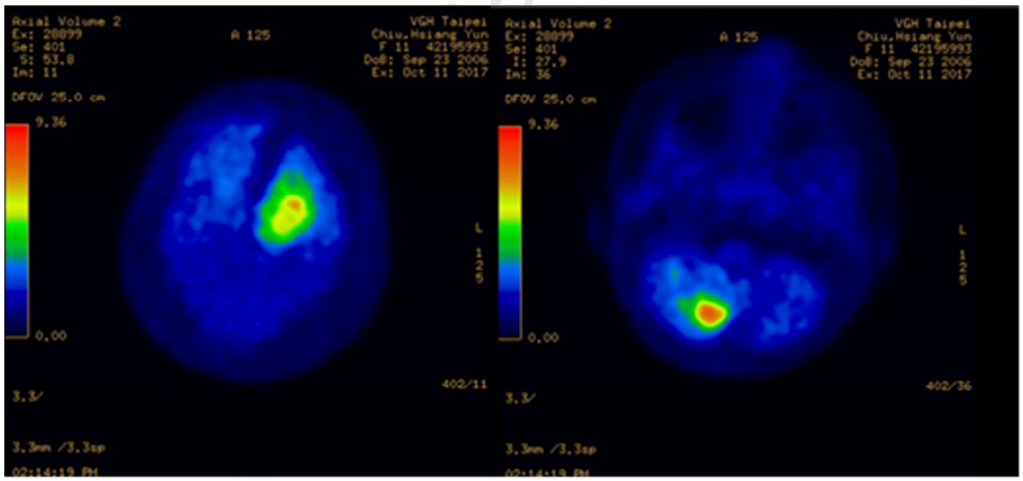

Figure 4. The 4-borono-2-18F-fluoro-phenylalanine (FBPA) positron emission tomography (PET) image of the left frontal and right cerebellum tumor for Patient 15. The tumor-to-tissue ratio was 3.58 for the left frontal tumor and 4.58 for the right cerebellum tumor.

Tables

Table 1. Characteristics of the patient population (n=3).

Patient	Age/ Gender	Initial Histology	Site	T/N ratio	T/B ratio	RPA stage	IDH-1 mutation	Initial symptoms
2	35/F	Anaplastic astrocytoma	Right temporal lobe	4.7	4.7	2	N/A	Left side numbness Left hemianopsia
10	45/F	Anaplastic astrocytoma	Right occipital lobe	2.0	2.17	2	negative	Face paresthesia Loss of conscious
15	11/F	Medulloblastoma (MMR)	Left frontal, Right cerebellum	3.58 4.58	3.58 4.58	3	positive	Variable, due to multiple cancers

T/N: tumor-to-tissue; T/B: tumor-to-blood; RPA: recursive partitioning analysis; N/A: not applicable.

Table 2. Serum boron concentrations before and after Boron Neutron Capture Therapy (BNCT).

	1 hr	2 hr (BNCT)	After BNCT
Patient 2	16.757 ppm	25.421 ppm	23.966 ppm
Patient 10	21.167 ppm	27.935 ppm	26.012 ppm
Patient 15	N/A	28.97 ppm	N/A

N/A: not applicable.

Table 3. Post-treatment results after Boron Neutron Capture Therapy (BNCT).

Patient	Date of BNCT	Irradiation time (min)	Tumor average dose (GyE)	Brain maximum dose (GyE)	Tumor response	Complications CTCAE v4.03 †	Outcome/ Last follow up
2	2017/5/26	22.35	27.10	9.08	PR	Skin hyperpigmentation Grade 1	PD, tumor recurrence 2018/11/14
10	2017/10/13	20.65	11.82	7.82	PR	Skin hyperpigmentation Grade 1	PD, tumor recurrence 2018/8/20
15	2017/11/29	16.3 (1^{st}) 16.02 (2^{nd})	27.75 (cerebellar) 29.02 (frontal)	6.53 (combined)	PD	Headache Grade 1	PD, tumor progression 2018/4/8

GyE: Gray-equivalent; PR: partial response; PD: progressive disease; CTCAE: Common Terminology Criteria for Adverse Events.

† The adverse effects, including skin damage and neurological deficit after radiation, were graded according to the CTCAE.

1. BNCT is effective for malignant brain tumors, including high grade gliomas.
2. BNCT is able to benefit quality of life for brain tumor patients, and potentially increase their survival time.
3. BNCT has relatively low adverse effect, while able to control tumor progression.

The authors declare no conflict of interest.