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Comparison of lifetime attributable risk of post-irradiation secondary cancer of boron neutron capture therapy, proton beam therapy, and X-ray therapy for pediatric and adolescent and young adult patients

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ABSTRACT

Background and purpose: This study aimed to compare the post-irradiation secondary cancer rates of boron neutron capture therapy (BNCT), proton beam therapy (PBT), and X-ray therapy (XT) in pediatric and Adolescent and Young Adult (AYA) patients with intracranial lesions.
Materials and methods: BNCT, PBT, and XT plans were optimized for nine pediatric and AYA patients with intracranial lesions. The BNCT dose calculation results were biologically effective dose converted. Lifetime attributable risk (LAR) was calculated using a calculation model proposed by Schneider *et al.* Statistical analysis was performed using log-linear model with mixed effects. Organs included in the radiation field were the brain, bones, and soft tissue. The difference in LAR between the three treatments for each organ and the number needed to treat (NNT), as an indicator of the number of cases required to achieve the effect of suppressing the occurrence of secondary cancers, was calculated and evaluated.
Results: Statistically significant differences between BNCT vs PBT and XT were confirmed for the brain, bone, soft tissue, and cumulative ($P < 0.0001$). Significant differences were also observed in PBT and XT, with $P < 0.0001$ for brain and cumulative, $P = 0.0002$ for bone, and $P = 0.0281$ for soft tissue. The cumulative NNT for BNCT vs. PBT, BNCT vs. XT, and PBT vs. XT were 162, 78.6, and 153, respectively.
Conclusion: BNCT had a significantly lower LAR compared to PBT and XT. These findings suggest the usefulness of BNCT in pediatric and AYA patients with brain tumors from the perspective of post-irradiation secondary cancer.

Introduction

In cancer treatment, patients aged 0–14 are called pediatric patients, and those aged 15–39 are identified as the Adolescent and Young Adult (AYA) generation [1]. Long-term survivors of childhood cancer who receive radiation therapy have a significantly higher risk of developing secondary cancers than adults [2]. Therefore, it is important to consider secondary cancer when performing radiotherapy in young patients such as pediatric and AYA patients. Follow-up and cohort studies have been conducted on cancer incidence after radiation exposure in children [3,4]. However, it takes a long time, at least 30 years, to evaluate secondary cancer incidence from these studies. Therefore, as surrogate markers of secondary cancer incidence, the lifetime attributable risk (LAR) of each organ has been calculated using the method described by Schneider et al. [5]. LAR calculations using this method have been used to compare different irradiation methods [6–9]. Proton beam therapy (PBT) has been reported that it has a lower incidence of secondary cancers compared to intensity-modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy of X-ray therapy (XT) [6,7,10]. Additionally, PBT studies evaluating proton craniospinal irradiation with vertebral body sparing and a comparative evaluation of scattering and scanning proton beam therapy have been reported [8,9].

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Boron Neutron Capture Therapy (BNCT) is a type of radiation therapy conducted by exposing tumors, which selectively absorb ^{10}B, to thermal neutrons and treating them with ^{7}Li and α particles produced in the neutron capture reaction (^{10}B (n, α) ^{7}Li). The generated ^{7}Li and α particles have ranges of 9–10 μm and 4–5 μm, respectively, which are less than 10 μm, corresponding to the cell size. These particles have the high linear energy transfer and more cell-killing than X-ray and PBT. Therefore, it is possible to administer a high dose to the tumor while minimizing the dose to the surrounding normal tissue, and treatment can be completed in one session [11]. BNCT for brain tumors in pediatric patients has been performed previously, and their study have suggested the possibility of applying BNCT to pediatric patients [12–14]. Regarding to post-irradiation secondary cancer, Zhang et al. has reported a study on the secondary cancer risk in pediatric patients treated with BNCT for brain tumors in China using a phantom [15].

Reports have compared the doses of BNCT, PBT, and XT in patients with brain tumors, previously [16]. However, no comparative evaluation of the three treatments (BNCT, PBT, and XT) has been reported regarding the post-irradiation secondary cancer rate, which should be considered in radiation therapy for pediatric and AYA patients. Therefore, this study aimed to compare and evaluate the rates of post-irradiation secondary cancer among BNCT, PBT, and XT and clarify their differences.

Materials and methods

Patient selection

Nine patients diagnosed with brain tumors aged 7–38 years who underwent PBT or IMRT at the Shonan Kamakura General Hospital between 2011 and 2024 were enrolled in this study. The selected patients included those treated with re-irradiation. The institutional review board approved this study (no. TGE02071-024). Table 1 shows patient information.

Irradiation was performed in the supine position with the head fixed to a thermoplastic shell. Computed tomography (CT) was used to obtain images of the head with a slice thickness of 2 mm for treatment planning.

Treatment planning

Precision version 3.3.1.3 (Accuray, Sunnyvale, CA, USA) was used as the treatment planning system (TPS) for the XT plans. The dose calculations were performed using the VOLO-Ultra algorithm [17]. Tomo-Helical was selected as the plan delivery mode, IMRT as the plan mode, and the dynamic mode as the jaw mode. The field width and pitch of the plans depend on the patient. At the end of each optimization round, a final dose with a high-resolution grid and a rescaled dose of 50 % of the planning target volume (PTV) was obtained. Treatment planning was performed such that 95 % of the PTV would meet more than 95 % of the prescribed dose ($D_{95\%}$) while reducing the dose to the organs at risk (OAR) as much as possible.

VQA version 6.1.5 (Hitachi, Tokyo, Japan) was used as the TPS for the PBT plans. Intensity-modulated proton therapy was used as the irradiation method. Using Clinical tumor volume (CTV)-based treatment planning, plans were optimized robustly with 3 mm setup uncertainty and 3.5 % range uncertainty. The dose was prescribed at $D_{50\%}$ of the CTV, and the Pencil Beam Convolution method was used as the calculation algorithm.

For the BNCT plans, we used RayStation version 2023B (RaySearch Lab, Stockholm, Sweden) and nuBeam Dose Engine version 1.00 (Neutron Therapeutics LLC., Danvers, MA, USA) as the calculation engines for dose calculation. The current version of the nuBeam Dose Engine uses the GEANT4 version 11.1.1 [18] for particle transport. The BNCT dose was calculated using the simulated neutron and γ ray fluxes and the corresponding KERMA and dose conversion factors provided vendor. ENDF/B-VIII.0 and JEFF-3.3 were used for the nuclear data [19,20]. The relative biological effectiveness (RBE) and compound biological effectiveness (CBE) of each dose component for each organ were determined based on the previous literature [21–25] and vendor recommendations (Table 2). Dose calculations were performed to satisfy the dose constraints of 5 GyE to 5 % volume of the eye ($D_{5\%}$) and 9 GyE for $D_{1\%}$ of the normal brain.

Two radiation oncologists assessed the appropriates of treatment plan.

When comparing BNCT doses with PBT and XT doses, a biological effective dose (BED) conversion is required. Therefore, using the MIM software (MIM Software Inc. 25,800 Science Park Drive – Suite 180 Cleveland, OH 44122), BED conversion was performed to match the BNCT dose calculation results with PBT and XT [26]. α/β was set to 10 for tumors and 3 for normal tissue.

LAR calculation

The LAR was calculated based on the concept proposed by Schneider et al. [5] using the formula and parameters from the previous study [6,8]. Three organs were analyzed: the brain, bone, and soft tissue. Dose data were transferred from each TPS to the MIM software, and the dose-volume histogram (DVH) data used for calculations were output from the MIM software.

Table 2
The CBE and RBE parameters used for the dose calculation of BNCT.

Tissue type	CBE	RBE_N	RBE_H	RBE_γ	Tissue to blood ratio
Tumor	3.8	3.2	3.2	1	3.5
Skin	2.5	3.3	3.2	1	1
Bone	1	3.2	3.2	1	1
Brain	1.35	3.2	3.2	1	1
Soft tissue	1.35	3.2	3.2	1	1
Water	1	0	3.2	1	1
Air	0	0	0	0	0

CBE: Compound Biological Effectiveness.
RBE_N : Relative Biological Effectiveness of Nitrogen dose.
RBE_H : Relative Biological Effectiveness of Hydrogen dose.
RBE_γ : Relative Biological Effectiveness of Gamma-ray dose.

Table 1
Patient characteristics.

Patient	Primary pathology	Lesion site	Diameter of the PTV (cm)	Sex	Age	Fractional dose (Gy)	No. of fractions	Prescribed dose (Gy)
A	Glioma	Left frontal lobe	6.5	M	11	1.8	33	59.4
B	Glioblastoma	Left temporal lobe	9.6	M	7	1.8	33	59.4
C	Glioma	Left frontal lobe	7.4	F	35	2.0	30	60
D	Ependymoma	Right temporal lobe	5.3	M	10	1.8	30	54
E	Gliosarcoma	Left frontal lobe	8.0	F	38	2.0	30	60
F	Glioma	Right frontal lobe	12.2	M	36	2.0	30	60
G	Glioblastoma	Left frontal lobe	7.1	M	30	2.0	30	60
H	Astrocytoma	Cerebellum	6.5	F	16	1.8	28	50.4
I	Glioma	Left frontal lobe	8.5	M	36	2.0	30	60

Statistical analysis

The LAR for BNCT, PBT, and XT were transformed using common logarithms to homogenize the variance, and parallel box plots were used to visualize the distribution. Additionally, the analysis was conducted using the mixed-effects model, incorporating individual differences as random-effect factors. The statistical software 'EZR' was utilized for the statistical analysis [27] and two-tailed tests were performed.

The following model (a log-linear model with mixed effects) was set with the common logarithmic value of the LAR as the objective variable and individual differences as random variable factors, and an analysis of variance was performed.

$$log(LAR_{ij}) = \begin{cases} \mu + \delta_i + \varepsilon_{i0}(BNCT) : j = 0 \\ \mu + \beta_1 + \delta_i + \varepsilon_{i1}(PBT) : j = 1 \\ \mu + \beta_2 + \delta_i + \varepsilon_{i2}(XT) : j = 2 \end{cases} \quad (1)$$

Here, μ, β_1, β_2 are unknown parameters (regression coefficient with fixed effects), δ_i is a random effect variable that follows a normal distribution with mean zero and variance φ^2 independently for patient i, (i = 1–9), and ε_{ij} (j = 0, 1, 2, i = 1–9) is a random term that represents the residual variation σ^2 with mean zero and variance (unknown) independently.

Furthermore, to directly compare the LAR values of PBT and XT, the following statistical model was set up and evaluated (i = 1–9):

$$log(LAR_{ij}) = \begin{cases} \mu + \delta_i + \varepsilon_{i1}(PBT) : j = 1 \\ \mu + \beta + \delta_i + \varepsilon_{i2}(XT) : j = 2 \end{cases} \quad (2)$$

The number needed to treat (NNT) was then calculated. The NNT is the inverse of the LAR difference (%) divided by 100, indicating the number of patients required for treatment to prevent one additional incidence of post-irradiation cancer.

Results

Fig. 1 shows an example of the dose distribution for patient A in XT, PBT, and BNCT. The central issue of this paper is the evaluation of LAR calculated from irradiated normal tissue. Therefore, in BNCT, the dose distribution of normal tissue is shown. XT uses TomoHelical and irradiates from a 360° direction, so the dose spreads to the normal brain. On the other hand, PBT irradiates with two fields at 0° and 50°, and it can be seen that the spread of the dose to the normal brain is suppressed compared to XT. Furthermore, BNCT sets the $D_{5\%}$ of the left eyeball at 5 GyE or less, which further suppresses the dose to the normal brain.

Table 3 shows LAR differences (%) between each treatment and the NNT for each organ. In all comparisons, the difference was larger for the brain than for bone and soft tissue, resulting in a smaller NNT. The NNT of cumulative for BNCT vs. PBT, BNCT vs. XT, and PBT vs. XT were 162, 78.6, and 153, respectively. Therefore, the NNT for BNCT vs. XT was the smallest and LAR difference was the largest.

Fig. 2 shows boxplots of the log-transformed LAR for each organ in the BNCT, PBT, and XT. The cumulative risk of post-irradiation secondary cancer was calculated as the sum of the LAR of all organs in the same patient. When comparing BNCT with PBT and XT, LAR was significantly lower in the brain, bone, soft tissue, and cumulative ($P < 0.001$). In addition, when comparing the LAR of the PBT and XT, the P-values for the brain, soft tissue, and cumulative were less than 0.001, and the P-value for the bone was less than 0.05, confirming statistical significance.

Table 3
LAR differences between each treatment and the NNT for each organ at risk.

Organ at risk	BNCT vs. PBT		BNCT vs. XT		PBT vs. XT	
	LAR diff (%)	NNT	LAR diff (%)	NNT	LAR diff (%)	NNT
Brain	0.54 ± 0.26	185	1.15 ± 0.35	87.1	0.61 ± 0.16	165
Bone	0.05 ± 0.04	2.04 × 10^3	0.08 ± 0.05	1.22 × 10^3	0.03 ± 0.02	3.05 × 10^3
Soft tissue	0.03 ± 0.02	3.61 × 10^3	0.04 ± 0.03	2.40 × 10^3	0.01 ± 0.02	7.18 × 10^3
Cumulative	0.62 ± 0.30	162	1.27 ± 0.41	78.6	0.65 ± 0.17	153

LAR diff (%): Lifetime Attributable Risk difference, expressed in percentage.

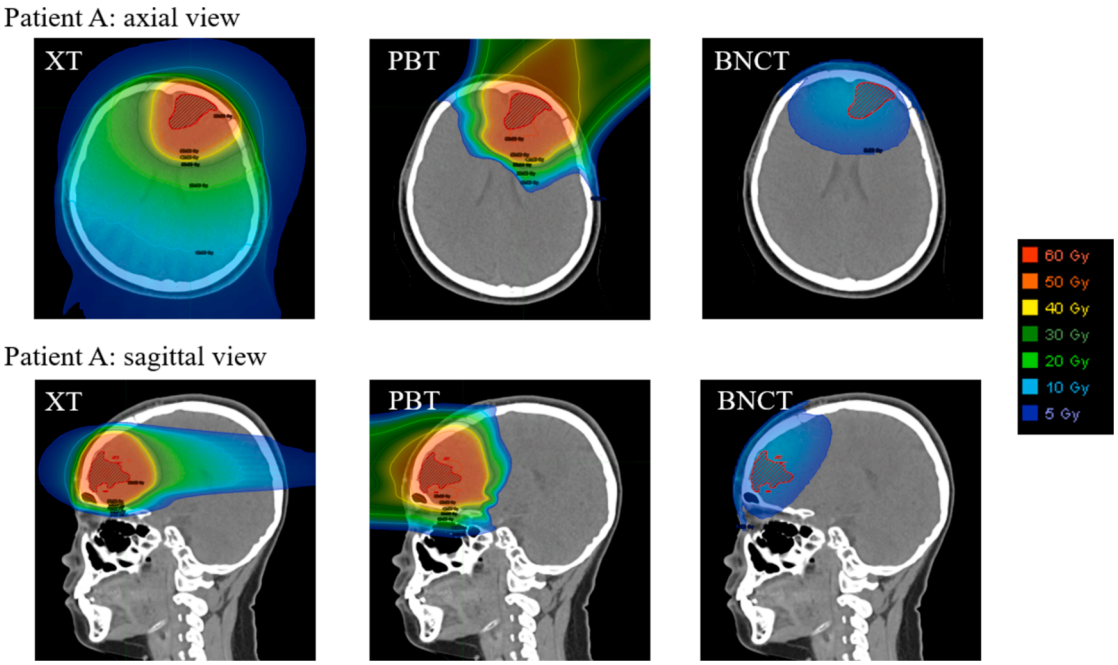

Fig. 1. Dose distribution of transversal (upper) and sagittal (lower) views for patient A. Doses above 5 GyE are shown with dose color wash (scale as right). GTV is shown in red diagonal lines. Dose distributions for XT (left), PBT (middle), and BNCT (right) are shown, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

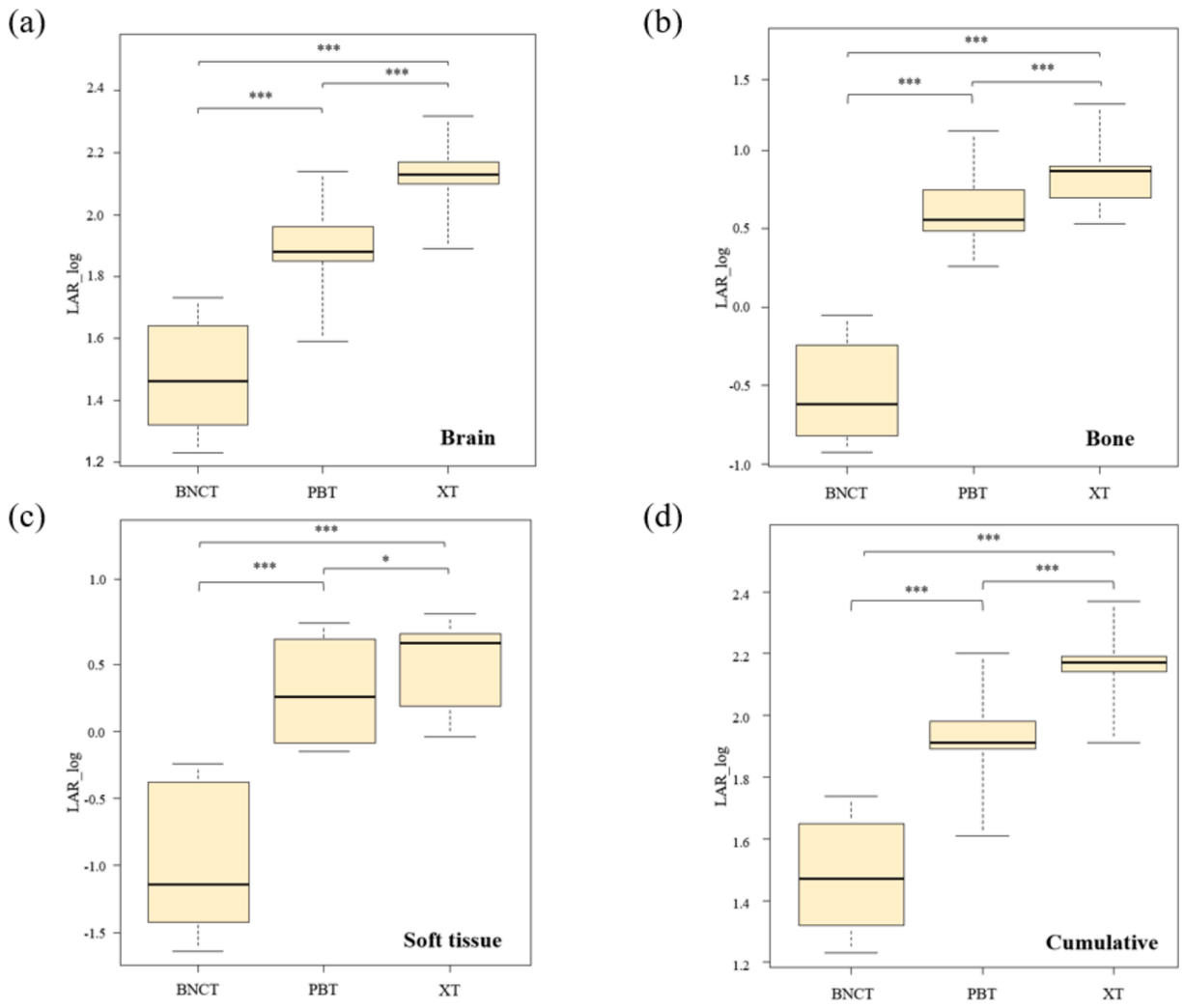

Fig. 2. Boxplots of log-transformed LAR for each organ in BNCT, PBT, and XT, (a) Brain, (b) Bone, (c) Soft tissue, (d) Cumulative. ***P-value < 0.001, **P-value < 0.01, and *P-value < 0.05.

Discussion

We evaluated and compared the risks of secondary cancers after BNCT, PBT, and XT in pediatric and AYA patients with brain tumors. We found that BNCT can reduce the risk of post-irradiation secondary cancer incidence compared to PBT and XT.

A LAR comparison of XT and PBT for pediatric brain tumors has been previously reported [6], and the results of this study, in accordance with those of the past, showed that the LAR of PBT was significantly lower. This is thought to be because PBT has a Bragg peak and is more focused than XT in terms of both lateral penumbra and depth distribution, thereby reducing the dose to nearby normal organs. In BNCT, boron uptake varies between tumors and surrounding healthy organs, such as the brain, and is considered in dose calculations as CBE for each tissue. Therefore, the difference in CBE and boron uptake between the tumor and adjacent brain tissue enhances the dose gradient. Consequently, the dose administered to healthy tissues in BNCT is reduced compared to PBT and XT, and the LAR is believed to be smaller.

The subjects of this study were patients with brain tumors, whose tumors were located relatively close to the skin. It is thought that the difference in post-irradiation cancer rates between each treatment will also vary depending on whether the tumor is central or peripheral, and whether it is infratentorial or supratentorial. Additionally, it has been reported that irradiation of the chest and abdomen yields greater differences in LAR when compared to brain tumors for PBT and XT [6]. Therefore, if BNCT is applied to the chest or abdomen, it is estimated that the LAR disparity will be more pronounced, and the NNT will be smaller than observed in this study. However, many parameters remain uncertain, such as the RBE and CBE of the abdominal organs. Therefore, addressing these issues could facilitate comparisons of LAR for tumors in these regions.

In this study, the BNCT dose was converted to the BED, and the LAR was compared with PBT and XT. The RBE dose is determined by taking into account the physical dose based on X-rays and the RBE value. PBT has been defined as the biological dose obtained by multiplying an RBE of 1.1 with the physical dose. However, the dose calculation for BNCT is more intricate than that for other radiotherapies. BNCT accounts for the RBE in four components: boron dose, nitrogen dose, gamma-ray dose, and hydrogen dose, and incorporates the value of CBE to account for the accumulation of boron compounds. Various studies have been conducted on RBE models for BNCT [28,29]. BNCT is a radiation therapy that is prescribed at the cellular level. Therefore, it is essential to evaluate at the cellular level and to consider the boron concentration in the tumor during treatment to predict the biological effects.

XT and PBT using low-LET radiation are usually treated with low-dose fractionated irradiation, while BNCT is basically performed with a single high-dose irradiation. Fractionated irradiation takes advantage of recovery of sublethal damage (SLD) in normal tissue. However, SLD recovery is not expected with high-LET radiation used in BNCT compared to low-LET radiation. Because of the high cell-killing effect of

high-LET radiation, an antitumor effect can be expected for tumors that are resistant to low-LET radiation. However, high LET radiation also has a significant effect on normal cells, so careful consideration must be given in treatment planning. Linear-Quadratic model is difficult to use when the single prescription dose is very high, and it is difficult to compare doses using EQD2 with other radiotherapy modalities because of the complex biological response in the case of high LET radiation. Therefore, it is crucial to establish the method which can easily and accurately evaluate dose comparisons and sums relative to the dose of conventional radiation therapy.

A limitation of this study is that the RBE of the fast neutron doses was not accurately assessed. In this research, the values employed in nuclear reactors to date were selected based on the literature. However, the neutron energy spectra of the accelerator-based BNCT (AB-BNCT) systems vary from system and the RBE of fast neutrons differs across systems. Therefore, RBE is determined experimentally through cell irradiation [30,31]. The RBE for the fast neutron component is estimated to be below 3.2, based on the evaluations for the instrument employing the same lithium target as the BNCT system [30] used in this study. Thus, the actual LAR of BNCT might be lower than our findings, necessitating cell irradiation with our BNCT system for a more precise assessment.

Another limitation was that the dose outside the irradiation area was not considered. Neutrons emitted from the beam aperture of the AB-BNCT system spread out. The dose outside the irradiation area in the AB-BNCT system, employing a beryllium target, has been assessed through measurements and simulations [32]. Although this contribution is believed to be minor compared to the dose inside the irradiation field, it should still be evaluated in a comprehensive assessment of the secondary cancer risk.

In this study, nine cases were analyzed. From Fig. 2, it can be seen that the brain and the total, especially in BNCT, show more variability compared to PBT and XT. Tumor location in this study varied from case to case. With respect to tumor location, depth from the surface and location in relation to normal tissue may affect DVH and LAR, and we intend to continue our research while increasing the number of cases analyzed in the future.

Additionally, since tumor control and long-term survival are important in clinical radiation therapy, these factors must be kept in mind when selecting a treatment modality. Since there is still no clinical data supporting the secondary cancer incidence after BNCT, further evidence needs to be established in the future.

Conclusion

We compared the post-irradiation secondary cancer rates among BNCT, PBT, and XT. The results revealed that BNCT had a significantly lower LAR compared to either PBT or XT. These findings suggest the usefulness of BNCT in pediatric and AYA patients with brain tumors from the perspective of post-irradiation-induced secondary cancer.

Patient consent statement

This study was approved by the Ethics Committee of Shonan Kamakura General Hospital. (TGE02071-024).

CRediT authorship contribution statement

Shunsuke Suzuki: Writing – original draft, Writing – review & editing, Methodology, Data curation, Funding acquisition, Software, Formal analysis. **Shintaro Shiba:** Writing – review & editing, Methodology, Supervision. **Hiroki Tanaka:** Methodology. **Masashi Yamanaka:** Writing – review & editing, Data curation. **Kazuki Matsumoto:** Data curation. **Koichi Tokuuye:** Supervision. **Motoko Omura:** Writing – review & editing, Supervision.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This study was financially supported by the Gold Ribbon Network.

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