Clinical Evaluation of Absolute Biological Effectiveness Dose in Boron Neutron Capture Therapy

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ABSTRACT

Boron neutron capture therapy (**BNCT**) delivers biologically complex, multi-component doses. Conventional dose evaluation commonly relies on fixed **CBE/RBE-weighted equivalent dose**, which may not fully reflect **patient-specific tumor biological sensitivity**. This study evaluated pathology-informed **Absolute Biological Effectiveness (ABE) dose** as a prognostic biological dose index for **malignant brain tumor patients** undergoing BNCT. Seventeen patients were eligible for ABE dose calculation; nine met the nuclear-count and RANO criteria for the main response analysis. Tumor-specific **nucleocytoplasmic (N/C) ratios** were quantified from histopathological images and used to calculate ABE dose. Treatment response was classified as **progressive disease (PD)** or **non-progressive disease (non-PD)** according to RANO criteria.
Conventional mean equivalent dose did **not distinguish PD from non-PD patients**, whereas **ABE-based dose metrics showed greater separation between response groups**, particularly in **glioblastoma cases**. These results suggest that ABE dose may support **individualized biological dose evaluation** in BNCT.

KEY FINDING

In an exploratory GBM subgroup (n = 6), mean ABE dose was significantly different between PD and non-PD groups (p = 0.02).

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Purpose

Current BNCT dose evaluation commonly relies on fixed CBE/RBE-weighted equivalent dose, which may not fully represent patient-specific tumor biological sensitivity.

This study aimed to calculate pathology-informed Absolute Biological Effectiveness (ABE) dose using tumor-specific nucleocytoplasmic (N/C) ratios.

We further evaluated whether ABE-based dose metrics improve treatment response discrimination in malignant brain tumor patients undergoing BNCT.

METHODS AND MATERIALS

This retrospective study included **malignant brain tumor patients** treated with BNCT between **March 2017 and June 2023**. Patients were eligible if they were diagnosed with malignant brain tumors, had undergone prior conventional treatment, were unsuitable for surgical resection, and had available **histopathological slide data for N/C ratio analysis**.

Physical dose information was obtained **from BNCT treatment planning**. Conventional clinical dose evaluation was based on fixed **CBE/RBE-weighted equivalent dose**, while the proposed biological dose evaluation used pathology-informed **Absolute Biological Effectiveness (ABE) dose**.

Tumor-specific **nucleocytoplasmic (N/C) ratios** were quantified from **histopathological images**. Nuclear area and cytoplasmic area were estimated using image-based segmentation, and the **N/C ratio** was used to derive the **ABE factor** based on **Ono's formulation.**

ABE dose = ABE factor × physical boron dose

$$\text{ABE factor} = D_0^{-1}$$

$$D_0 = 0.1341(N/C)^{-1.586}$$

Treatment response at 4 months after BNCT was classified as **progressive disease (PD) or non-progressive disease (non-PD)**. For the main ABE analysis, cases with more than **1500 quantified nuclei** were selected to improve measurement reliability. Subgroup analysis was further performed for glioblastoma cases. Between-group comparisons were performed using the Mann–Whitney U test, with a two-sided $p < 0.05$ considered statistically significant.

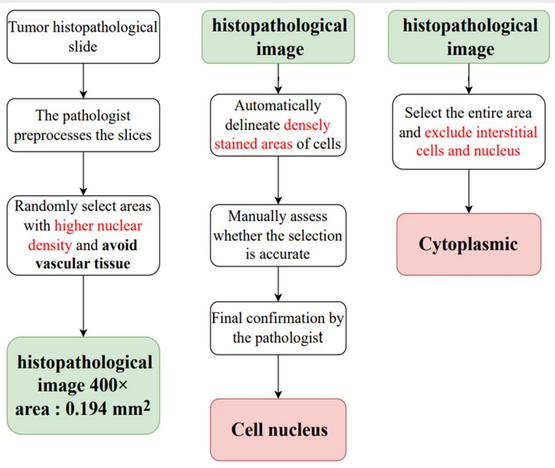

Figure 1. Pathology-informed workflow for nucleocytoplasmic (N/C) ratio quantification.

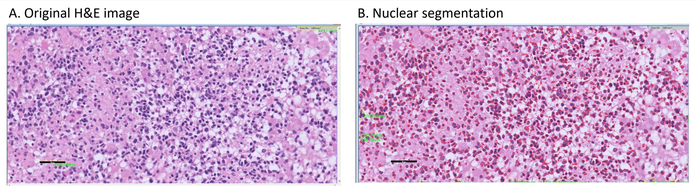

Figure 2. Representative histopathological image and nuclear segmentation for N/C ratio quantification.

Table 1. Patient characteristics for ABE dose analysis.

Patient characteristics	Case	Result
Diagnosis	N = 17	GBM / Meningioma / AA / A = 9 / 3 / 4 / 1
Gender	N = 17	M/F = 9/8
Age	N = 17	50.2 ± 18.9
Tumor volume (ml)	N = 17	63.2 ± 46.0
T/N ratio	N = 14	4.8 ± 2.5
Blood boron concentration (ppm)	N = 17	33.1 ± 7.9

Continuous variables are shown as the mean, standard deviation (SD) or median with interquartile range
AA: anaplastic astrocytoma, A:astrocytoma

RESULTS

Of the 17 ABE-eligible patients, 10 had more than 1500 quantified nuclei, and 9 patients with available RANO information were included in the main analysis.

In the main cohort, conventional mean equivalent dose did not differentiate PD from non-PD outcomes (**p = 0.878**), whereas mean ABE dose showed a trend toward greater separation between response groups (**p = 0.09**). This finding suggests that incorporating tumor-specific biological characteristics may provide information beyond conventional fixed-CBE dose evaluation.

In the exploratory GBM subgroup (n = 6), mean ABE dose significantly differed between PD and non-PD groups (**p = 0.02**), while ABE $D_{50\%}$ showed a trend toward separation (**p = 0.07**). These subgroup findings indicate that pathology-informed ABE metrics may be particularly informative in GBM, although confirmation in a larger cohort is required.

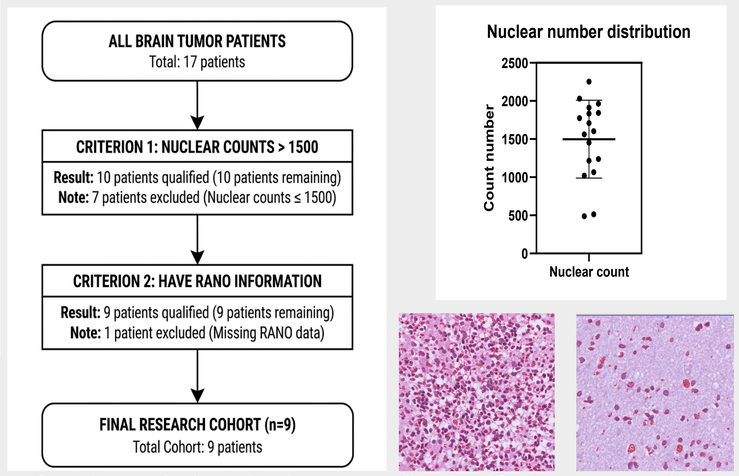

Figure 3. Case selection and nuclear-count quality control for ABE response analysis.

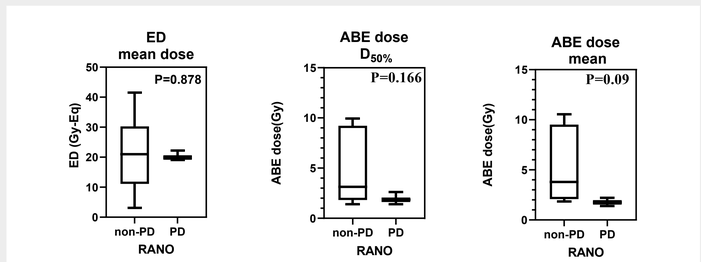

Figure 4. ED and ABE dose metrics between RANO response groups (n = 9).

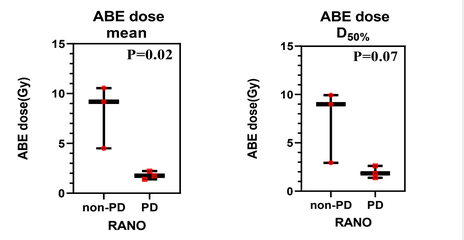

Figure 5. ABE dose metrics between RANO response groups in the GBM subgroup (n = 6).

DISCUSSION

Conventional BNCT equivalent dose relies on fixed **CBE/RBE weighting factors** and may not fully account for **inter-patient variation in tumor cellular characteristics**. The lack of differentiation between **PD and non-PD groups** using mean equivalent dose suggests that conventional physical dose weighting alone may be insufficient to describe treatment response in this cohort.

In contrast, **ABE dose** incorporates the tumor-specific **N/C ratio** and provides a **pathology-informed estimate of biological sensitivity**. The improved **response-group separation** observed with ABE-based metrics suggests that **microscopic cellular morphology** may provide clinically relevant information beyond conventional dose evaluation. The clearer separation in the **GBM subgroup** may indicate that ABE dose is particularly informative for **high-grade tumors** with prominent nuclear characteristics.

These exploratory findings are limited by the small cohort and uncertainties in tumor-region selection, nuclear segmentation, intratumoral heterogeneity, and the nuclear-count threshold. Larger diagnosis-specific studies with standardized image analysis are needed.

CONCLUSIONS

Pathology-informed Absolute Biological Effectiveness (ABE) dose incorporates **tumor-specific nucleocytoplasmic (N/C) ratios** into BNCT dose evaluation and may provide biological information beyond conventional fixed-CBE equivalent dose.

ABE-based dose metrics showed **improved separation** between progressive disease and non-progressive disease outcomes, with clearer separation observed in the **glioblastoma subgroup**.

These preliminary findings support the potential of ABE dose as an individualized biological dose indicator for BNCT. Larger diagnosis-specific cohorts with standardized histopathological image analysis are required to further validate its clinical utility.

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