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Analysis of boron neutron capture reaction sensitivity using Monte Carlo simulation and proposal of a new dosimetry index in boron neutron capture therapy

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ABSTRACT

Boron neutron capture therapy is a cellular-scale heavy-particle therapy. The factor determining the biological effects in the boron neutron capture reaction (BNCR) is the value of α_{boron}, which is the alpha component in the Linear Quadratic (LQ) model. Recently, the factor determining the value of α_{boron} has been revealed to correspond to the structural features of the tumor tissue. However, the relationship and mechanism have yet to be thoroughly studied. In this study, we simulated BNCR in tissues using the Monte Carlo simulation technique and examined the factors that determine the value of α_{boron}. According to this simulation, the nuclear-cytoplasmic (N/C) ratio, nuclear diameter and heterogeneity of the distribution of boron in the tissue have been suggested to determine the value of α_{boron}. Moreover, we proposed Biological Effectivity (BE) as a new dosimetry index based on the surviving fraction (SF), extending the concept of absolute biological effectiveness (ABE) in a previous report.

Keywords: boron neutron capture therapy (BNCT); dosimetry index; compound biological effectiveness (CBE); absolute biological effectiveness (ABE); Monte Carlo simulation

INTRODUCTION

Boron neutron capture therapy (BNCT) is a cellular-scale particle therapy in which boron compounds are incorporated into tumor cells. The tumor cells are irradiated with thermal neutrons to produce a boron neutron capture reaction (BNCR) within the tumor cells, generating a high-linear energy transfer (LET) particle beam with a range shorter than that of a single cell, which destroys the tumor cells [1]. Although conventional radiation therapy deposits energy to the entire treatment region, BNCT deposits energy only to the cells which take up the boron compounds. This means that if the tumor cells specifically take up the boron compounds, the tumor cells are exclusively destroyed by the high-LET particles and the normal cells surrounding the tumor are not damaged.

In BNCT dose evaluation, the compound biological effectiveness (CBE) factor is commonly used as an index to convert the boron neutron dose to the X-ray equivalent dose [2]. The CBE factor is similar to relative biological effectiveness (BE). However, it depends on the boron compound, tissue type and the predetermined endpoint. Although the sensitivity of tumor cells may differ across tumor types, the commonly used value for tumor cells is constant at 3.8 regardless of the type of tumor [3]. Moreover, it is already known that the value of the CBE factor varies with the boron neutron dose as well [4–6]. Therefore, applying a constant value as the tumor CBE factor may not allow for the proper evaluation of the biological tumor dose. It is already known that in clinical practice, when the X-ray equivalent dose is calculated using the CBE factor, a significant relationship between

the dose and treatment result is not obtained [7]. Therefore, a new dosimetry index for BNCT is required.

Ono *et al.* proposed the concept of absolute biological effectiveness (ABE) as a new dosimetry index [8]. Accordingly, the ABE factor is defined as:

$$ABE\,factor = Gy/D_0, \tag{1}$$

where D_0 denotes the average lethal dose. Using the ABE factor, the ABE dose is defined as:

$$ABE\,dose = ABE\,factor \times physical\,dose. \tag{2}$$

In other words, the value of the ABE dose is an indicator of the magnification of the absorbed dose in relation to the D_0 dose. Here, the ABE factor is defined as a unitless number, and the unit of ABE is Gy. According to this definition, the surviving fraction (SF) is as follows:

$$SF = e^{-ABE\ dose/Gy} = e^{-(ABE\ factor \times physical\ dose)/Gy}. \tag{3}$$

The ABE factor in equation (3) corresponds to the α-component of BNCR (α_{boron}) in the Linear Quadratic (LQ) model, depicting sensitivity to BNCR. As the LQ model is a more common concept than the ABE factor, we used the term α_{boron} instead of the term ABE factor in this article.

As BNCT is a high-LET particle therapy, radiation sensitivity depends on the tissue's structural features rather than the tumor microenvironment such as oxygen conditions. Therefore, the value of α_{boron} may be determined by the structural features of the tissue. Ono *et al.* reported that the D_0 dose strongly correlates with the nuclear-cytoplasmic (N/C) ratio in BNCT using p-boron-L-phenylalanine (BPA: $C_9H_{12}BNO_4$) as the boron compound [8]. In that report, the relationship between the N/C ratio (NC) and D_0 or α_{boron} was expressed as:

$$D_0 = 0.1341/NC^{1.586} \tag{4}$$

$$\alpha_{boron} = NC^{1.586}/0.1341. \tag{5}$$

Equation (4) is called Ono's equation. In the examination of BNCT in clinical practice, ABE dose has been shown to be an excellent indicator of therapeutic outcome [9]. However, it is still not clear whether Ono's equation is always true in all ranges of the N/C ratio, and whether the N/C ratio is the only factor determining the value of α_{boron}. Therefore, in this study, we investigated the factors that determine the value of α_{boron} by examining how the cell SF changes when the cell structural features such as N/C ratio and nuclear diameter are changed, using Monte Carlo simulation to reproduce the BNCR in tissues.

MATERIALS AND METHODS

Monte Carlo simulation

Construction of virtual tissue

We built a 1000-pixel square 3D space (0.177696 μm/pixel) using Python 3.7.9 and OpenCV 4.2.0, and employed this space as the simulation field. We then evenly distributed spherical cell nuclei of arbitrary diameter and N/C ratio in the field in a hexagonal close-packed structure. In this simulation, only the nuclear structures of each cell were defined, and the rest of the area was defined as the cytoplasm. Because the effect of cytoplasmic damage on the SF was assumed to be minor, the cytoplasm was not divided into individual cells; this helped in simplifying the model.

Generation of boron neutron capture reaction positions in the virtual tissue

The BNCR positions were distributed in the simulation field according to the density determined by the boron neutron dose. During this process, we assumed that BPA was present only in the cytoplasm. We discuss this assumption in the Discussion section.

Furthermore, BPA uptake into cells is cell cycle-dependent, with higher BPA uptake in the G2/M phase than in the G0/G1 phase. BNCR positions were randomly placed in the cytoplasm to reflect this heterogeneity. Cells in the G2/M phase take up a large amount of BPA early and the uptake reaches a plateau quickly, whereas cells in the G0/G1 phase take up BPA slowly. Therefore, the difference between cells in these two phases is more pronounced immediately after BPA administration [10]. We extrapolated published data and assumed a value of 10 for the BPA uptake ratio in the G2/M and G0/G1 phases at three hours after administration. Here, it is generally accepted that a very low percentage of the total number of cells is in the G0 phase, especially in xenograft tumors in the stable growth phase, though specific data are unavailable. Therefore, the percentage of the cells in G0 phase was assumed to be 25%, meaning the percentage of the cells actively within the cell cycle (G1/S/G2/M phase) was 75% (i.e. Ki-67 index is 75%). An additional study showed that of all the cells that have entered the cell cycle, approximately 20% are in the G2/M phase [11]. As a result, the cells in the G2/M phase comprise 15% of the total number of cells (G1/S/G2/M/G0). The G2/M phase cells were assumed to be spherical to simplify the model.

Generation of alpha particles and recoiled lithium nuclei

We generated alpha particles in a three-dimensionally random direction and a recoiled lithium nucleus in the opposite direction. The particle ranges were estimated as the ranges in which the LET reduced to half of its maximum LET in water. The ranges of the alpha particle and recoiled lithium nucleus were set to 7.72 μm and 3.98 μm, respectively [12].

Estimation of absorbed energy for each cell nucleus

The LETs of the alpha particles and recoiled lithium nuclei were set to 163 keV/μm and 210 keV/μm, respectively. The absorbed energy of each cell nucleus was then calculated by multiplying the particle ranges in the nucleus and LET. If the cell nucleus volume increases X times, the density of chromosomes in the nucleus decreases by 1/X.

Therefore, when considering damage to the cell nucleus, we need to consider the specific energy, which is the absorbed energy of the cell nucleus corrected by its mass. The specific energy (z) of the cell nucleus is described as:

$$z = \left(total\ absorbed\ energy\right) / \left(nucleus\ volume\right), \tag{6}$$

when the specific gravity of tissue is 1 g/cm^3.

Estimation of cell surviving fraction

In this simulation, cell death due to BNCR was assumed to be primarily caused by nuclear damage. Van Vliet-Vroegindeweij *et al.* reported the survival rate of a cell (S) as:

$$S = e^{-N\int f(\varepsilon)\cdot EF(\varepsilon)d\varepsilon}, \tag{7}$$

where N is the number of energy deposition events, ε is the energy deposited from a single event, f(ε) is the distribution of the imparted energy, and EF(ε) is the effectiveness function for the energy deposited in the nucleus [13]. Here, EF(ε) is considered to be a sigmoid curve, described as:

$$EF\left(\varepsilon\right) = \frac{1}{1+e^{-b(\varepsilon-a)}}, \tag{8}$$

where a and b are two arbitrary constants [13, 14]. Although van Vliet-Vroegindeweij *et al.* considered the energy micro-distribution for each energy deposition event, for simplification, we considered the energy distribution for the sum of all energy deposition events in each nucleus and assumed a uniform energy distribution. Based on this assumption, the survival rate of a cell can be described as:

$$S = e^{-c\cdot EF(z)\cdot z}, \tag{9}$$

where c is an arbitrary constant, and z is the specific energy in the nucleus. This equation can be described as:

$$S = e^{-\alpha_0(z)\cdot z}\left(\alpha_0(z) = \frac{c}{1+e^{-b(z-a)}}\right). \tag{10}$$

The constants a, b and c were determined to best explain the actual measurements. The survival rate of each cell was estimated from equation (10) using the specific energy calculated from equation (6). The average survival rate of all the cells in the tissue was determined as the SF in the tissue.

Comparison of the simulation result to literature data

Ono *et al.* have shown the relationship between structural properties such as N/C ratio and nuclear diameter and D_0 dose (i.e. the value of α_{boron}) for five different cell types (EL4, B16BL6, SAS/neo, SAS/mp53 and SCCVII) [8]. We simulated the SF of the five cell types for boron neutron doses at 0.5 Gy, 1.0 Gy, 1.5 Gy, 2.0 Gy, 3.0 Gy and 4.0 Gy. As BNCT is a high-LET particle therapy, the β-component from BNCR in the LQ model can be assumed to be zero [15]. Therefore, the relationship between the boron neutron dose (D_{boron}) and SF is given by the following:

$$SF = e^{-\alpha_{boron}\cdot D_{boron}} \tag{11}$$

based on the LQ model. We determined the constants a, b and c in equation (10) so as to match the value of α_{boron} to the literature data. In this process, the values of a, b and c which were not consistent with the relationship between the dose (D_{boron}) and the SF in equation (11) were excluded.

Moreover, we simulated the SF of each cell in a 0.5 Gy boron neutron dose (a relatively low dose) using the parameters determined here. The rationale for adopting 0.5 Gy in this simulation is explained below. In this simulation, a small region with extremely high specific energy can exist in the nucleus at high boron neutron doses. However, the effect of the small region is not always the same as in other regions because of the overkill effect. This may lead to simulation errors because our simulation model used the average absorbed energy. Therefore, a relatively low dose was adopted for the simulation to minimize this error.

Simulation of the surviving fraction with various N/C ratios and nucleus diameters, and heterogeneity of p-boron-L-phenylalanine distribution

Using the parameters determined above, we simulated the effects of the N/C ratio, nucleus diameter and heterogeneity of BPA distribution. First, we prepared virtual tissue with a N/C ratio of 0.1 to 0.5 and a fixed nucleus diameter (12 μm). We simulated the SF in heterogeneous and homogeneous BPA distributions for a 0.5 Gy boron neutron dose. Then, we prepared virtual tissue with nucleus diameters ranging from 4 to 20 μm and a fixed N/C ratio (0.4). The simulations were performed again in the same manner.

The surviving fraction of the cells in normal liver tissue

Ono *et al.* reported that the N/C ratio of normal liver tissue is 0.123 and its D_0 dose is 2.29 Gy; thus, the value of α_{boron} is 0.437 [5]. We also simulated the SF of normal liver tissue using the above mentioned simulation with a boron neutron dose of 0.5 Gy and compared them with literature data and estimation from Ono's equation. As there were no data on the diameter of a nucleus, we varied it from 4.0 μm to 6.0 μm in the simulation. BPA distribution was set as homogeneous because normal liver tissue does not proliferate actively.

RESULTS

Comparison of the simulation result to literature data

We determined that when the values of parameters a, b and c were 0.8, 12 and 1.2, respectively. The simulated value of α_{boron} in each cell type matched the literature value. The relationship between the N/C ratio and the value of α_{boron} is shown in Fig. 1. The relationship between the dose and the SF calculated using this simulation is shown in Fig. 2. According to this figure, the simulated cell SF was slightly lower than that expected at high doses. This gap could be due to the overkill effect,

Table 1. The SF and the value of α_{boron} and D_0 dose

		Surviving fraction at 0.5 Gy	α_{boron}	D_0 dose
Literature data (Ono *et al.*) [5]		0.804	0.436	2.29
Simulation data	Nucleus diameter 4.0 μm	0.781	0.494	2.02
	Nucleus diameter 5.0 μm	0.687	0.750	1.33
	Nucleus diameter 6.0 μm	0.599	1.02	0.976
Prediction from Ono's equation [8]		0.874	0.269	3.71

The literature data is from Ono *et al.* [5] and the simulation data is the simulation result assuming nucleus diameter values from 4.0 – 6.0. The data from Ono's equation [8] is the estimated value using equation (4).

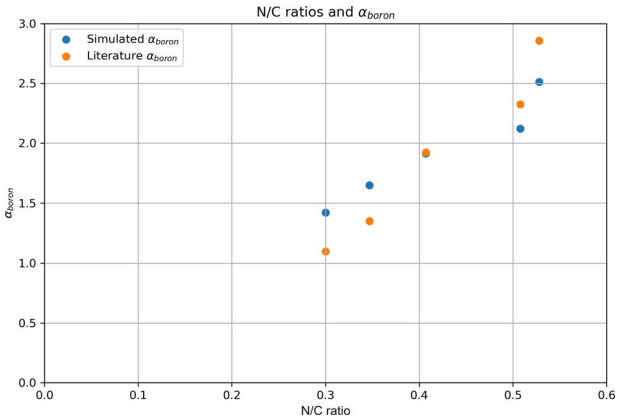

Fig. 1. The relationship between the N/C ratio and the value of α_{boron}. The values of α_{boron} were simulated at boron neutron doses of 0.5Gy, 1.0 Gy, 1.5 Gy, 2.0 Gy, 3.0 Gy and 4.0 Gy. The blue dots show the simulation value and orange dots show the value reported from Ono *et al.* [8].

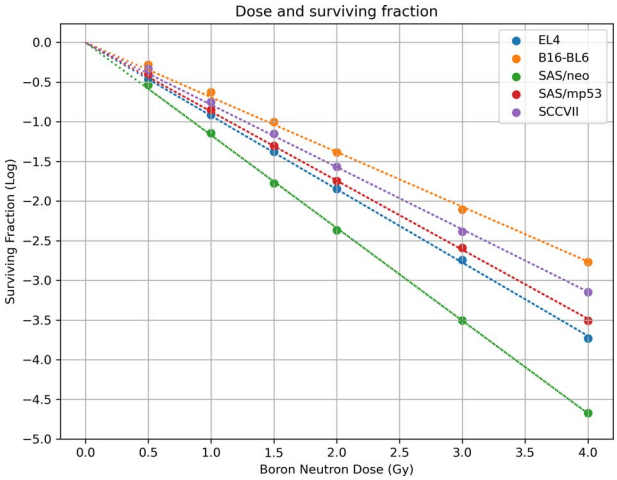

Fig. 2. The relationship between boron neutron dose and SF estimated using the simulation. The SFs of each of the cell types (EL4, B16-BL6, SAS/neo, SAS/mp53 and SCCVII) were simulated at the boron neutron doses of 0.5Gy, 1.0 Gy, 1.5 Gy, 2.0 Gy, 3.0 Gy and 4.0Gy. The dotted lines show survival curves fitted to these SFs.

which was not reflected in this simulation. The relationships between the N/C ratio, nucleus diameter and SF at a boron neutron dose of 0.5 Gy are shown in Figs 3A and B. The value of α_{boron} calculated based on the SF at 0.5 Gy is shown in Fig. 3C. These results indicate that the present simulation reproduces the actual survival rate and value of α_{boron} in the literature.

Contribution of the N/C ratio and nuclear diameter to cell survival

For a nucleus diameter of 12 μm, the relationship between the N/C ratio from 0.1 to 0.5 and the corresponding SF is shown in Fig. 4. Here, we show the case of heterogeneous and homogeneous boron distributions and Ono's equation for comparison. When the boron distribution is heterogeneous, the impact of the N/C ratio on the SF is more significant. If the N/C ratio is approximately 0.4, the simulated SF is similar to the value calculated using Ono's equation. However, the smaller the N/C ratio, the larger is the deviation from Ono's equation.

The relationship between the diameter of the nucleus and the corresponding SF is shown in Fig. 5. When the diameter ranges from 8 to 14 μm in the case of a heterogeneous boron distribution, the impact of the diameter on the SF is minimal. However, when the diameter is below or above that range, the effect of the nucleus diameter becomes non-negligible and prominent, especially for smaller diameters. The impact of the nucleus diameter is larger with a heterogeneous boron distribution than that with a homogeneous distribution.

Simulation of the value of α_{boron} in normal liver tissue

According to a previous report, the N/C ratio of the liver is 0.123, and the D_0 dose and the value of α_{boron} of the liver are 2.29 Gy and 0.437, respectively [5]. In this simulation, the simulated values of α_{boron} corresponding to nucleus diameters of 4.0, 5.0 and 6.0 μm were 0.487, 0.730 and 1.02, respectively. The simulated value with a nucleus diameter of 4.0 μm was similar to the literature data. In contrast, the value of α_{boron} calculated using Ono's equation was 0.269, indicating underestimation (Table 1).

DISCUSSION

Distribution of p-boron-L-phenylalanine in a cell

The simulation in this study assumed that the BPA was distributed only in the cytoplasm and was not taken up by the nucleus. In this

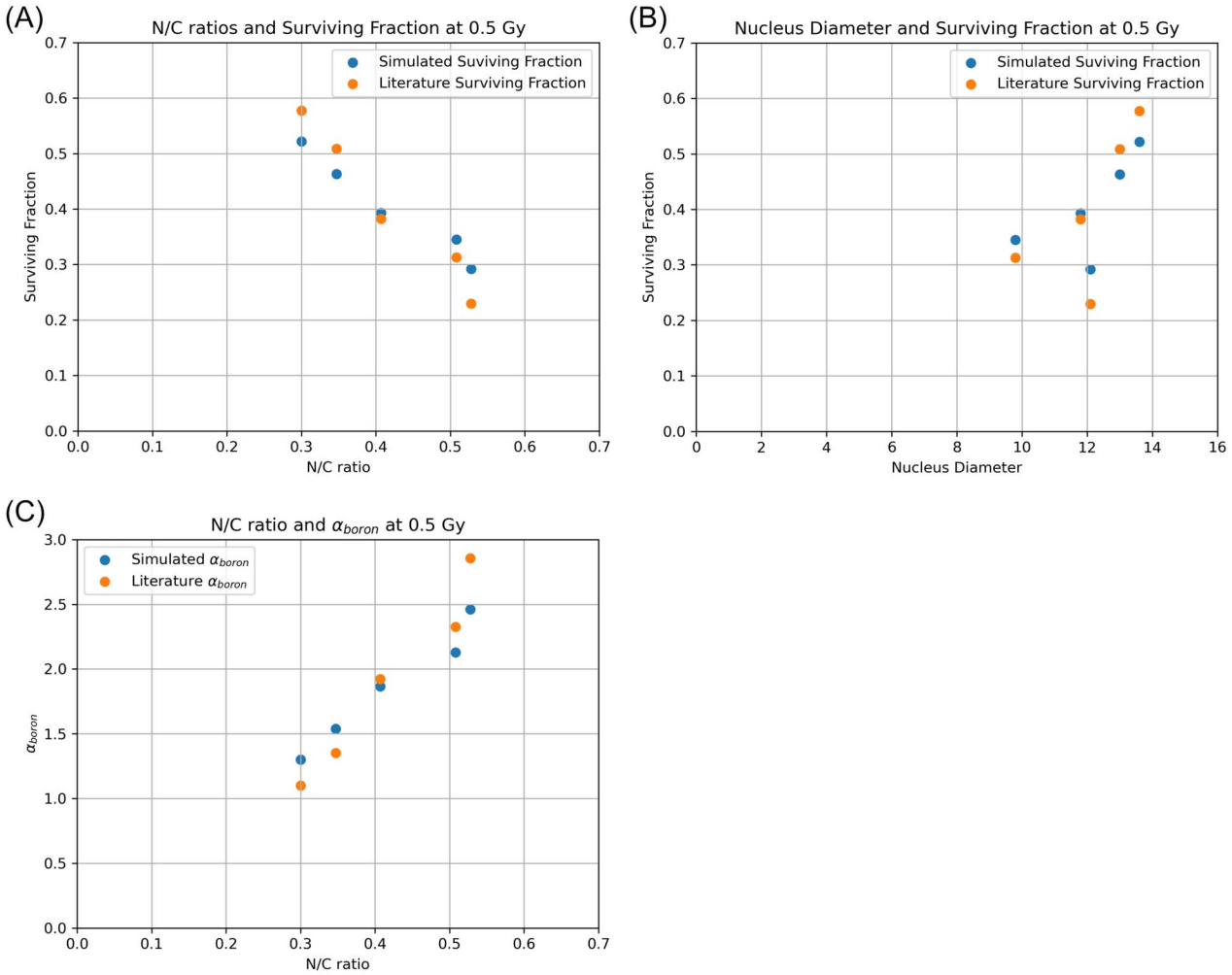

Fig. 3. The simulated SF and the value of α_{boron} at a boron neutron dose of 0.5 Gy. As the simulation may not reflect the overkill effect at high boron neutron doses, we analyzed at a relatively low dose. (A) Graph shows the relationship between the N/C ratio and the SF. (B) Graph shows the relationship between the nucleus diameter and the SF. (C) Graph shows the relationship between the N/C ratio and the value of α_{boron}. In graphs (A)–(C), the orange dots represent the simulated values, and the blue dots represent the reported values from Ono *et al.* [8].

section, we discuss this assumption in detail. If we assume that the concentration of BPA is the same at any location in a cell including the cytoplasm and nucleus, the density of BNCR is the same at any location in the tissue (where the tissue is simplified by omitting the consideration of stroma). Because the distance between adjacent nuclei does not contribute to the cell SF, the N/C ratio is not related to the cell SF (Fig. 6A). On the other hand, if we assume that the BPA is distributed only in the cytoplasm, the volume of the cytoplasm becomes small in a cell with a high N/C ratio, resulting in a higher BNCR density surrounding the nucleus (Fig. 6B). This means that the higher the N/C ratio, the higher the number of particles that reach the nucleus, and lower the SF. Ono *et al.* reported that the N/C ratio correlated strongly with the SF [8], supporting this assumption.

BPA is actively taken up by cells via L-type amino acid transporter 1 (LAT1) [16] and diffuses into the nucleus via nuclear pores. As the number of nuclear pores is limited, the active uptake into the cytoplasm from out of the cell can be much faster than passive uptake into the nucleus from the cytoplasm. Therefore, the concentration of BPA in the cytoplasm is assumed to be much higher than that in the nucleus. Hence, the assumption that BPA is homogeneously distributed only in the cytoplasm seems reasonable, and simplifies reality. In reality, it is also assumed that BPA concentration is graduated in the cytoplasm and nucleus (see Supplementary Fig. S1). According to this mechanism, a longer exposure time of a cell to BPA is assumed to lead to more BPA flowing into the cell nucleus; thus, the intracellular boron distribution is expected to be closer to uniform.

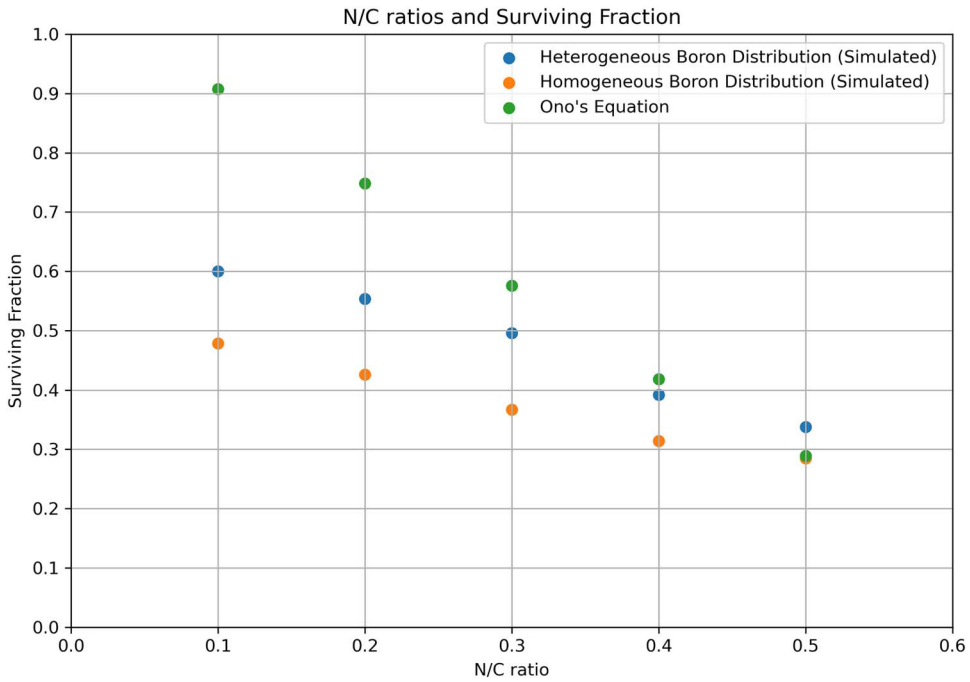

Fig. 4. The relationship between the N/C ratios ranging from 0.1 to 0.5 and the corresponding SF in the virtual cells. The SF is compared with Ono's equation [8]. In this graph, the cell diameter is fixed to 12 μm.

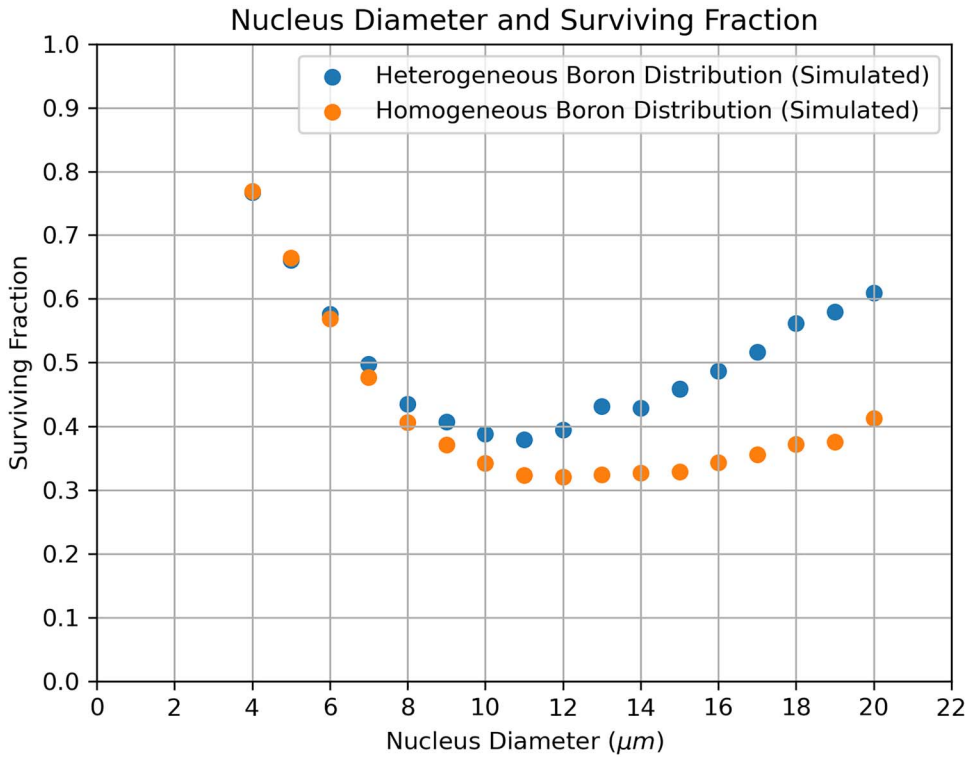

Fig. 5. The relationship between the nucleus diameters ranging from 4 to 20 μm and the corresponding SF in the virtual cells. In this graph, the N/C ratio is fixed to 0.4.

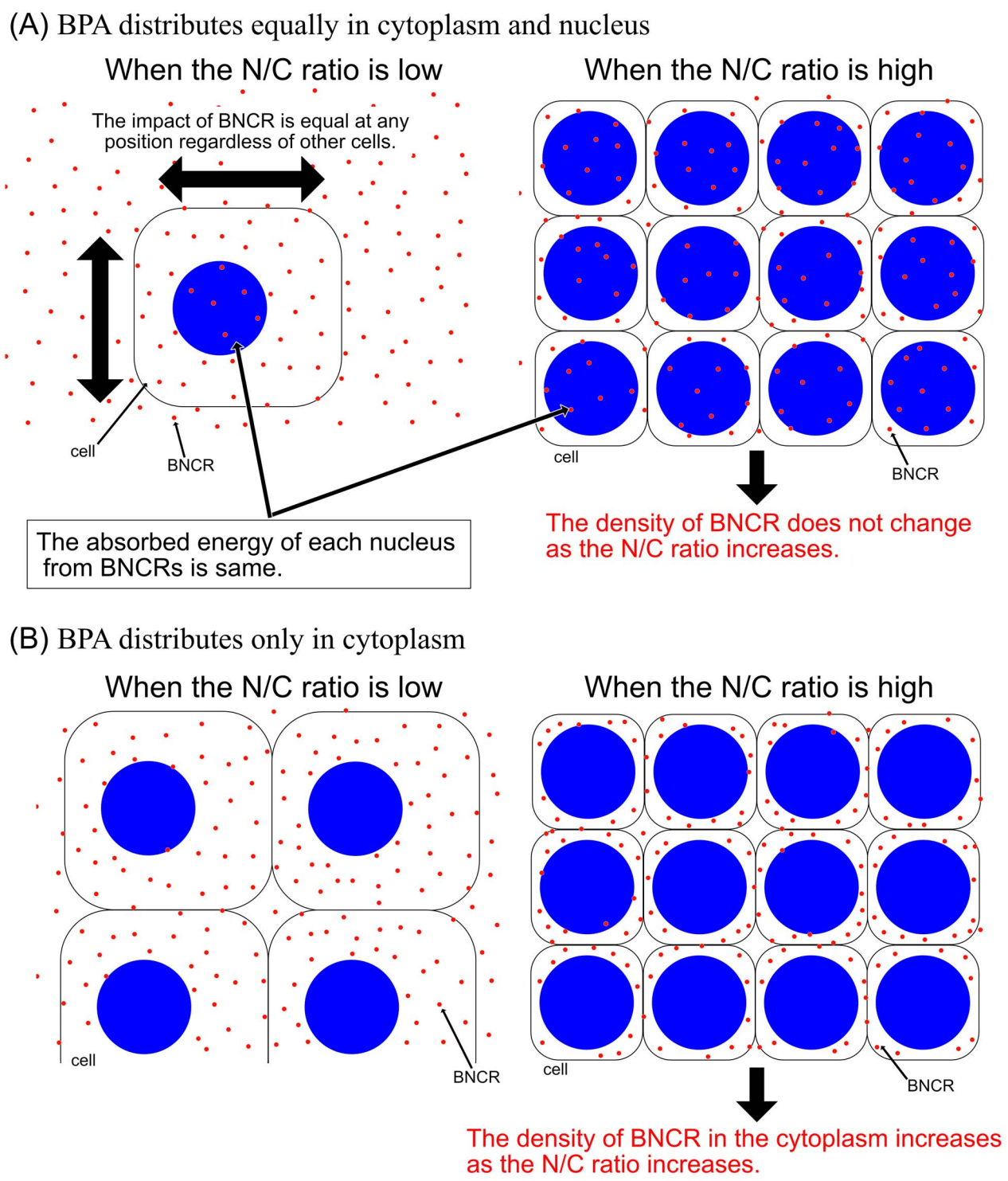

Fig. 6. The distribution of p-boron-L-phenylalanine (BPA) in the cell. (A) If the BPA distributes equally in cytoplasm and nucleus, the distribution of BNCRs is also homogeneous. This means that the impact of BNCRs throughout the cell is the same regardless of the position in the cell. Thus, the survival probability of each cell is the same regardless of the N/C ratio. In other words, the N/C ratio does not affect the SF. (B) If the BPA distributes only in the cytoplasm, the density of BNCRs in the cytoplasm increases with an increase in the volume of the nucleus. In the other words, the N/C ratio does affect to the SF.

Determinants of boron neutron capture reaction sensitivity

N/C ratio

As discussed in the previous section, a higher N/C ratio corresponds to a higher boron density in the cytoplasm under the assumption that the BPA is distributed only in the cytoplasm, thus reducing the cell SF. On the other hand, a higher N/C ratio leads to closer proximity of adjacent cell nuclei where boron is not distributed; this in turn leads to an increased cell SF. The cell SF is determined by the combination of these two opposing effects.

The diameter of the cell nucleus

If the diameter of the cell nucleus is small, a small amount of absorbed energy from the particle leads to significant specific energy, which exceeds that required for cell death. The excess energy does not contribute to cell death. Thus, the smaller the cell nucleus, the lesser is the energy that contributes to cell death, and the higher the SF (Fig. 7A). However, there is also an opposite relationship between the cell nucleus size and the SF. Because the BPA is assumed to exist only in the cytoplasm in this simulation, the specific energy of a cell nucleus is proportional to the surface area of the nucleus, and it is inversely proportional to the volume of the nucleus. Therefore, a larger nucleus corresponds to lower specific energy, and thus a higher cell SF (Fig. 7C).

According to the simulation results, when the diameter of the nucleus is less than 8 μm, a larger nucleus corresponds to a smaller SF, showing the dominant effect of the former mechanism (Fig. 7A). In the diameter range of 8–14 μm, especially in cells with a heterogeneous boron distribution, the two opposite effects on the SF are antagonistic (Fig. 7B). For cell diameters larger than 14 μm, the latter effect on the SF becomes dominant, and a larger cell nucleus corresponds to a higher SF (Fig. 7C).

Heterogeneity of boron distribution

It has already been reported that a heterogeneous boron distribution can lead to regions of lower boron concentration; thus results in a higher SF compared to those with a homogeneous boron distribution [4]. The same tendency was observed in this simulation (Figs 4 and 5). It is also clear that heterogeneous boron distribution can amplify the effect of the N/C ratio and the nucleus diameter on the SF.

In this simulation, the ratio of cells with a high boron accumulation (G2/M phase) was fixed at 15%. However, the ratio in actual cancer tissue may not always be 15%. The ratio of cells in the proliferative phase can be estimated using the Ki-67 index, which can help to estimate the number of cells with high boron accumulation.

The relationship between the simulation in this study and Ono's equation

According to Ono's equation, the SF of cells in the tissue is determined by the N/C ratio in BPA-BNCT. On the other hand, the simulation in this study revealed that the factors that determine the SF include a combination of the N/C ratio, the diameter of the nucleus and the heterogeneity of boron distribution. At the same time, this simulation has also identified that for nucleus diameters ranging from 8 to 14 μm with heterogeneous boron distribution, the primary factor in determining the SF is the N/C ratio. Because Ono's equation is built using experimental data from tumors with nucleus diameters in the range of 9.8–13.6 μm, Ono's equation is a good approximate model under the conditions that the nucleus diameter is 8–14 μm and the boron concentration is heterogeneous.

The present dosimetry index in boron neutron capture therapy and its limitation

The biological effects of BNCT are generally assessed using the X-ray equivalent dose, which is the absorbed X-ray energy that results in the same biological effects in the corresponding BNCT conditions. The conversion factor from the boron neutron dose to the X-ray equivalent dose is the CBE factor. Because the CBE factor converts the boron neutron dose to the X-ray dose via the SF (or other endpoints in normal tissue), it includes BNCR sensitivity and X-ray sensitivity (see Supplementary Fig. S2). Therefore, a limitation is encountered when using the X-ray equivalent dose as the only dosimetry index. Although the CBE factor of a tumor is presently a fixed value, it should be determined for each tumor depending on its radiation sensitivity. Considering this, for example, if tumors A and B have the same sensitivity in BNCT but different sensitivities in X-ray therapy, then the X-ray equivalent dose for the same effectiveness in BNCT changes. Thus the dosimetry index for the same biological effect is different because it depends on the sensitivity towards the other modality. However, the dosimetry index for the same biological effect should remain the same without depending on the other treatment modalities. Therefore, a dosimetry index that does not depend on any other modality is needed.

Proposal for a new dosimetry index: 'Biological Effectivity'

The absorbed energy in a specific cell component may be a good candidate for a dosimetry index in BNCT, as in X-ray therapy. However, the absorbed energy does not always correlate with the SF because the effects of the absorbed energy on the nucleus can be saturated depending on the cell structural feature, as shown in Fig. 7A. Therefore, a new dosimetry index that does not depend on the absorbed energy is required.

Ono *et al.* proposed the concept of ABE as a new dosimetry index for BNCT [8]. Accordingly, the ABE factor and ABE dose are defined based on the D_0 dose (equations [1] and [2]), and the ABE dose represents the cell SF in the tissue (equation 3). Moreover, as previously described, the ABE factor corresponds to the α-component of BNCR (α_{boron}) in the LQ model. This index seems to be a good candidate for describing the biological effects of BNCR without depending on the absorbed energy and the traditional X-ray equivalent dose. However, ABE dose is defined as energy since its unit is Gy (equivalent to J/kg), even though the essential meaning of ABE dose is SF (equation 3). Moreover, as the ABE dose is defined based on the D_0 dose, it can be defined only in high-LET particle therapy which has a cell-specific D_0 dose. Here, by defining the index based on the cell SF, we can make the definition clearer in terms of physics and extend the concept of ABE not only for BNCT but also as a universal concept. Therefore, we propose 'BE,' a novel dosimetry index, as an extension of ABE. The definition

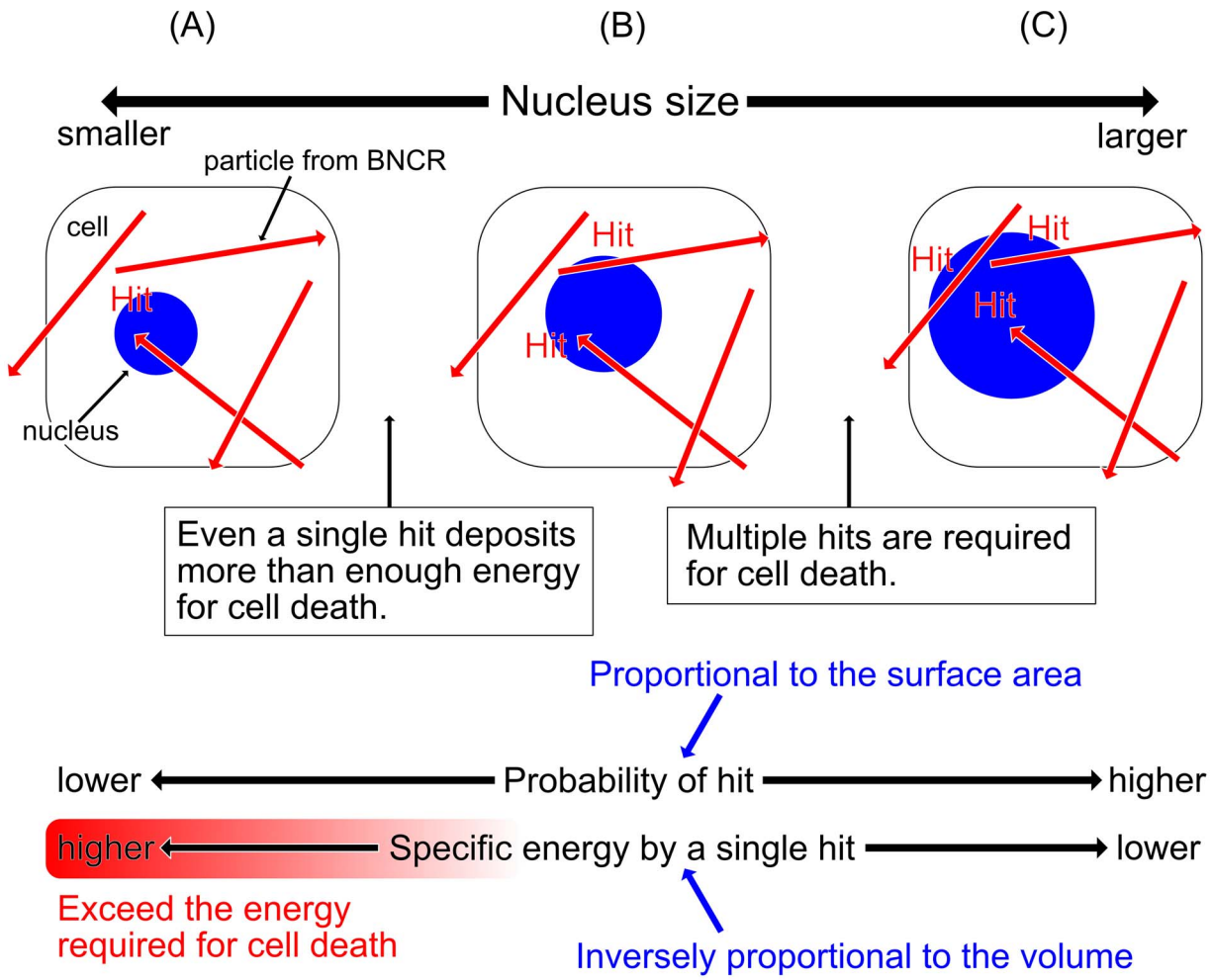

Fig. 7. The impact of the size of the nucleus on the cell SF. (A) If the nucleus is small, the energy absorbed from a single hit is much higher than the energy required for causing cell death. The excess energy does not contribute to cell death and is wasted. (B) If the nucleus size is larger, the wasted energy is low and most of the energy contributes to cell death; this results in a low SF. The probability of a hit is proportional to the nucleus surface area, while the specific energy is inversely proportional to the nucleus volume. Therefore, if the nucleus size becomes even larger (C), the specific energy becomes lower and the SF becomes higher.

of BE is as follows:

$$BE = -\ln(SF), \tag{12}$$

where SF denotes the SF. In this discussion, we consider the BE from BNCR. Using equations (11) and (12), the relationship between BE and α_{boron} can be stated as follows:

$$BE = \alpha_{boron} \cdot D_{boron}, \tag{13}$$

where D_{boron} denotes the boron neutron dose. This equation indicates that α_{boron} is a conversion factor from the physical dose to BE in BNCR. Here, as the D_0 dose is the dose that reduces the SF to 1/e, that is, the dose that lowers BE by 1, BE and α_{boron} are expressed using D_0 dose as:

$$BE = \frac{D_{boron}}{D_0}. \tag{14}$$

Currently, the dosimetry index in several BNCT practices is calculated using the X-ray equivalent dose based on the CBE factor. There is no doubt that the X-ray equivalent dose is an indispensable dosimetry index in BNCT, as it allows for the estimation of the biological effect of BNCT based on the clinical experience in X-ray therapy. Here, the X-ray equivalent dose and CBE factor can be described using BE (Appendix A). The relationship between total dose elements in

BNCT and BE is also shown in Appendix B. The value of α_{boron} can be estimated experimentally (Appendix C). Therefore, BE may become another dosimetry index for BNCT.

Since BE directly shows SF, it can describe SFs of each cell component such as tumor and normal tissue. Furthermore, in future research, the micro-distribution of boron may be obtained utilizing the autoradiography-based method [12] and the value of α_{boron} may be obtained experimentally or using the Monte-Carlo simulation. It may enable the estimation of BE of each cell component. Therefore, it may be possible to estimate the SF of each cell component, enabling better assessment of therapeutic ratio and potential toxicity.

Considering the definition, the concept of BE can be applied not only to BNCT but also to any therapeutic modality such as X-ray therapy and nuclear medicine. According to the LQ model, this conversion factor from physical dose to BE is constant, especially in high-LET particle therapies such as BNCT.

Limitations of this study and challenges for the future

In this simulation, the intracellular and intercellular distributions of BPA have been simplified. Regarding the intracellular distribution, we hypothesized that BPA exists only in the cytoplasm. This simplified hypothesis seems to be theoretically reasonable considering the intracellular BPA dynamics. However, although some data support our hypothesis [17], other data show a homogeneous distribution of boron intracellularly [18]. This discrepancy may be due to the dynamics of BPA distribution in a cell. In reality, the boron concentration may change gradually from the surface of the cell to the interior (Supplementary Fig. S1). As for intercellular distribution, only the effects of the G2/M and G0/G1 phases were considered. However, other factors related to the microenvironment, e.g. the oxygen status [19] can affect BPA distribution. The distribution of L-type amino acid transporter 1 (LAT1), which is the primary transporter for BPA uptake, can be altered by cancer progression [20] or a nutritional condition [21], also resulting in heterogeneous distribution of BPA. As the intra- and intercellular distribution of BPA is critical for estimating sensitivity to BNCR, further studies on this aspect are warranted.

The simulation presented in this article considers only the fundamental factors to determine the cell-killing effect, and SFs based only on the absorbed specific energy of the cell nucleus. However, because the energy distribution inside the nucleus is not considered, the overkill effect has yet to be considered. Cytoplasmic damage, which was not considered in this simulation, is also known to be involved in cell death [22]. Furthermore, the sensitivity of the cell nucleus to particle radiation may vary depending on the state of the cell. For example, it has been pointed out that the percentage of heterochromatin in the nucleus may cause radioresistance in X-ray and carbon therapy [23], and may also affect the sensitivity to BNCT.

Although our simulation was adequate to identify factors determining the value of α_{boron}, there was a non-negligible discrepancy between the calculated and experimental data while estimating the value of α_{boron}. In future studies, a more accurate simulation model that considers these factors needs to be formulated to estimate the value of α_{boron}. The simulation of the heterogeneous cell component, i.e. the mixture of tumor and normal cell, is also warranted, since it may reveal the dose gradient between the tumor cells and normal cells in BNCT.

In summary, we simulated BCNR in virtual tissue, and showed that the factors that determine the value of α_{boron} include the N/C ratio, nucleus diameter and heterogeneity of distribution of boron in the tissue. Additionally, we proposed a novel dosimetry index based on the SF, termed as BE. As this novel index is based on the SF, it can be applied universally and is not restricted to BNCT. The concepts and results presented here can be applied to increase the accuracy of estimating treatment effect and thus improve clinical outcomes of BNCT.

SUPPLEMENTARY DATA

Supplementary data is available at *RADRES Journal* online.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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REFERENCES

1. Suzuki M. Boron neutron capture therapy (BNCT): a unique role in radiotherapy with a view to entering the accelerator-based BNCT era. *Int J Clin Oncol* 2020;25:43–50.
2. Morris GM, Coderre JA, Hopewell JW et al. Response of rat skin to boron neutron capture therapy with p-boronophenylalanine or borocaptate sodium. *Radiother Oncol* 1994;32:144–53.
3. Coderre JA, Makar MS, Micca PL et al. Derivations of relative biological effectiveness for the high-let radiations produced during boron neutron capture irradiations of the 9l rat gliosarcoma in vitro and in vivo. *Int J Radiat Oncol Biol Phys* 1993;27:1121–9.
4. Sato T, Masunaga SI, Kumada H et al. Microdosimetric Modeling of biological effectiveness for boron neutron capture therapy considering intra- and intercellular heterogeneity in 10B distribution. *Sci Rep* 2018;8:988.
5. Ono K, Tanaka H, Suzuki M. Reevaluation of CBE value of BPA for hepatocytes. *Appl Radiat Isot* 2020;161:109159.
6. Gonzalez SJ, Cruz GAS. The photon-isoeffective dose in boron neutron capture therapy. *Radiat Res* 2012;178:609–21.
7. Aihara T, Hiratsuka J. Evaluation of Fluoride-18-Labeled Boronophenylalanine-positron emission tomography imaging for the assessment of boron neutron capture therapy in patients with recurrent head and neck squamous cell carcinoma. *Otolaryngology* 2016;6:277. https://doi.org/10.4172/2161-119x.1000277.
8. Ono K, Tanaka H, Tamari Y et al. Proposal for determining absolute biological effectiveness of boron neutron capture therapy - the effect of 10B(n,α)7Li dose can be predicted from the nucleocytoplasmic ratio or the cell size. *J Radiat Res* 2019;60:29–36.

9. Aihara T, Hiratsuka J, Kamitani N et al. Boron neutron capture therapy for head and neck cancer: relevance of nuclear-cytoplasmic volume ratio and anti-tumor effect. -a preliminary report. *Appl Radiat Isot* 2020;163:109212.
10. Yoshida F, Matsumura A, Shibata Y et al. Cell cycle dependence of boron uptake from two boron compounds used for clinical neutron capture therapy. *Cancer Lett* 2002;187:135–41.
11. Cooper GM. *The Cell: A Molecular Approach*, 2nd edn. Sunderland (MA): Sinauer Associates, 2000.
12. Takeno S, Tanaka H, Watanabe T et al. Quantitative autoradiography in boron neutron capture therapy considering the particle ranges in the samples. *Phys Med* 2021;82: 306–20.
13. Van Vliet-Vroegindewej C, Wheeler F, Stecher-Rasmussen F et al. Microdosimetry model for boron neutron capture therapy: II. Theoretical estimation of the effectiveness function and surviving fractions. *Radiat Res* 2001;155:498–502.
14. Jul N, Gabel D, Foster S et al. The Monte Carlo simulation of the biological effect of the 10B(n, alpha)7Li reaction in cells and tissue and its implication for boron neutron capture therapy. *Radiat Res* 1987;111:14–25.
15. Ono K, Masunaga SI, Kinashi Y et al. Radiobiological evidence suggesting heterogeneous microdistribution of boron compounds in tumors: its relation to quiescent cell population and tumor cure in neutron capture therapy. *Int J Radiat Oncol Biol Phys* 1996;34:1081–6.
16. Wongthai P, Hagiwara K, Miyoshi Y et al. Boronophenylalanine, a boron delivery agent for boron neutron capture therapy, is transported by ATB0,+, LAT1 and LAT2. *Cancer Sci* 2015; 106:279–86.
17. Chandra S, Lorey DR, Smith DR. Quantitative subcellular secondary ion mass spectrometry (SIMS) imaging of boron-10 and boron-11 isotopes in the same cell delivered by two combined BNCT drugs: in vitro studies on human glioblastoma T98G cells. *Radiat Res* 2002;157:700–10.
18. Hattori Y, Ishimura M, Ohta Y et al. Detection of boronic acid derivatives in cells using a fluorescent sensor. *Org Biomol Chem* 2015;13:6927–30.
19. Wada Y, Hirose K, Harada T et al. Impact of oxygen status on 10B-BPA uptake into human glioblastoma cells, referring to significance in boron neutron capture therapy. *J Radiat Res* 2018;59:122–8.
20. Lu X. The role of large neutral amino acid transporter (LAT1) in cancer. *Curr Cancer Drug Targets* 2019;19:863–76.
21. Taylor PM. Role of amino acid transporters in amino acid sensing. *Am J Clin Nutr* 2014;1:223S–30S. https://doi.org/10.3945/ajcn.113.070086.
22. Zhou H, Hong M, Chai Y et al. Consequences of cytoplasmic irradiation: studies from microbeam. *J Radiat Res* 2009;50: 1–10.
23. Sato K, Imai T, Okayasu R et al. Heterochromatin domain number correlates with X-ray and carbon-ion radiation resistance in cancer cells. *Radiat Res* 2014;182:408–19.
24. Caswell RS, Coyne JJ, Randolph ML. Kerma factors for neutron energies below 30 MeV. *Radiat Res* 1980;83:217–54.

APPENDIX

Appendix A. The relationship between Biological Effectivity and the X-ray equivalent dose

According to equation (12), the SF in the BNCT can be described as:

$$SF = e^{-BE}. \tag{A1}$$

The SF in X-ray therapy at a dose of D_x can be described as:

$$SF = e^{-(\alpha_x D_x + \beta_x D_x^2)} \tag{A2}$$

where α_x and β_x are the coefficients according to the LQ model. If the SFs in equations (A1) and (A2) are equal, the relationship between BE and D_x is as follows:

$$BE = \alpha_x D_x + \beta_x D_x^2. \tag{A3}$$

Solving equation (A3) for D_x, we obtain the following:

$$D_x = \frac{-\alpha_x + \sqrt{{\alpha_x}^2 + 4\beta_x \cdot BE}}{2\beta_x}. \tag{A4}$$

If the boron neutron dose is D_{boron}, D_x can be described as:

$$D_x = \frac{-\alpha_x + \sqrt{{\alpha_x}^2 + 4\beta_x \cdot \alpha_{boron} \cdot D_{boron}}}{2\beta_x}, \tag{A5}$$

using equation (13). Because the *CBE factor* can be calculated by $CBE\ factor = \frac{D_x}{D_{boron}}$, it can be described as:

$$CBE\ factor = \frac{-\alpha_x + \sqrt{{\alpha_x}^2 + 4\beta_x \cdot \alpha_{boron} \cdot D_{boron}}}{2\beta_x \cdot D_{boron}}. \tag{A6}$$

According to equation (A4), BE and the X-ray equivalent dose can be interconverted using the X-ray sensitivity of the tissue. In the same way, according to equation (A6), the values of α_{boron} and *CBE factor* can be interconverted using the X-ray sensitivity and the boron neutron dose.

Appendix B. Biological Effectivity considering all dose elements in boron neutron capture therapy

The dose elements in BNCT consist of the boron neutron dose, proton dose, neutron dose and the γ-ray dose. However, the ABE dose proposed by Ono *et al.* reflects only the boron neutron dose. Here, we discuss extending the BE to all the BNCT dose components. When we divide the total dose components of BNCT into the boron neutron dose and other doses, the BE is also divided as below:

$$BE_{total} = BE_{boron} + BE_{beam} \tag{A7}$$

where BE_{total}, BE_{boron} and BE_{beam} are the BEs of the total BNCT dose, boron neutron dose and the other dose elements, respectively. The dose-effect curve due to beam irradiation alone consists of an α-component and a β-component in the LQ model, but because the effect of the β-component is known to be small in a previous study [15], only the α-component is used for approximation here. Because all the dose elements in BNCT are proportional to the thermal neutron fluence under this assumption, BE_{beam} can be described as:

$$BE_{beam} = {\alpha_{beam}}' \cdot \varphi \tag{A8}$$

where φ is the thermal neutron fluence, and ${\alpha_{beam}}'$ is a coefficient. According to equation (13), BE_{boron} can be described as:

$$BE_{boron} = \alpha_{boron} \times 7.43 \times 10^{-14} \times \left[{}^{10}B\right] \times \varphi, \tag{A9}$$

where 7.43×10^{-14} represents the kerma factor for ^{10}B [24]. According to equations (A7), (A8) and (A9), BE_{total} can be described as:

$$BE_{total} = \left(\alpha_{boron} \times 7.43 \times 10^{-14} \times \left[{}^{10}B\right] + {\alpha_{beam}}'\right) \times \varphi. \tag{A10}$$

When we set $\alpha_{beam} = \frac{{\alpha_{beam}}'}{7.43 \times 10^{-14}}$ for simplification, BE_{total} can be described as:

$$BE_{total} = \left(\alpha_{boron} \times \left[{}^{10}B\right] + \alpha_{beam}\right) \times \varphi \times 7.43 \times 10^{-14}. \tag{A11}$$

According to equations (A1) and (A11), the cell SF (SF_{total}) for all dose components in BNCT can be described as:

$$SF_{total} = e^{-BE_{total}} = e^{-\left(\alpha_{boron} \times \left[{}^{10}B\right] + \alpha_{beam}\right) \times \varphi \times 7.43 \times 10^{-14}}. \tag{A12}$$

The main feature of BE is that the dosimetry index in BNCT directly represents the cell SF.

Appendix C. The method to estimate α_{beam} and α_{boron} experimentally

According to equations (12) and (A7), the relationship between BE_{total}, BE_{beam} and BE_{boron}, the SF of BNCT (SF_{total}), neutron beam only (SF_{beam}), and the boron neutron dose (SF_{boron}) can be described as:

$$BE_{total} = -\ln\left(SF_{total}\right)$$

$$BE_{beam} = -\ln\left(SF_{beam}\right)$$

$$BE_{boron} = -\left(\ln\left(SF_{total}\right) - \ln\left(SF_{beam}\right)\right). \tag{A13}$$

According to equations (A8) and (A13),

$${\alpha_{beam}}' = -\frac{\ln\left(SF_{beam}\right)}{\varphi} \tag{A14},$$

i.e.

$$\alpha_{beam} = -\frac{1}{7.43 \times 10^{-14}} \times \frac{\ln\left(SF_{beam}\right)}{\varphi}. \tag{A15}$$

From equations (A9) and (A13), the value of α_{boron} can be described as

$$\alpha_{boron} = -\frac{1}{7.43 \times 10^{-14} \times \left[{}^{10}B\right]} \times \frac{\ln\left(SF_{total}\right) - \ln\left(SF_{beam}\right)}{\varphi}. \tag{A16}$$

Since we can acquire SF_{total} and SF_{beam} experimentally, we can estimate the value of α_{beam} and α_{boron}.