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Determination of the Compound Biological Effectiveness (CBE) Factors Based on the *ISHIYAMA-IMAHORI* Deterministic Parsing Model with the Dynamic PET Technique

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Abstract

Purpose: In defining the biological effects of the ^{10}B$(n, \alpha)^7$Li neutron capture reaction, we have proposed a deterministic parsing model (*ISHIYAMA-IMAHORI* model) to determine the Compound Biological Effectiveness (*CBE*) factor in Borono-Phenyl-Alanine (*BPA*)-mediated Boron Neutron Capture Therapy (*BNCT*). In present paper, we demonstrate a specific method of how the application of the case of application to actual patient data, which is founded on this model for tissues and tumor. Method: To determine the CBE factor, we derived the following new calculation formula founded on the deterministic parsing model with three constants, CBE_0, F, n and the eigen value N_{th}/N_{max}.

$$CBE = CBE_0 + \frac{F}{2}\left(1-\left(\frac{N_{th}}{N_{max}}\right)^{\frac{1}{n}}\right)\left\{2-\left(\frac{N_{th}}{N_{max}}\right)^{\frac{2}{n}}+\left(\frac{N_{th}}{N_{max}}\right)^{\frac{1}{n}}\right\}, 0 < \frac{N_{th}}{N_{max}} < 1 \quad \text{(1)},$$

where, N_{th} and N_{max} are the threshold value of boron concentration of N and saturation boron density and CBE_0, F and n are given as 0.5, 8 and 3, respectively. In order to determine N_{th} and N_{max} in the formula, sigmoid logistic function was employed for ^{10}B concentration data, $D_b(t)$ obtained by dynamic PET technique.

$$D_b(t) = \frac{A}{\left(1+\mathrm{e}^{-a(t-t_0)}\right)} \quad \text{(2)},$$

where, A, a and t_0 are constants. Results and Conclusion: From the application of sigmoid function to dynamic PET data, it is concluded that the N_{th} and N_{max} for tissue and tumor are identified with the parameter constants in the sigmoid function in Equa-

tion (2) as: $N_{th} = D_b$ at $t = 0$ and $N_{max} = A$ (3). And the calculated *CBE* factor values obtained from Equation (1), with N_{th}/N_{max}.

Keywords

Boron Neutron Capture Therapy, Compound Biological Effectiveness, Borono-Phenyl-Alanine, Tumor, $^{10}B(n, \alpha)^7Li$, Sigmoid Function

1. Introduction

Many types of pilot innovative accelerator-based neutron source for neutron capture therapy with lithium target were designed [1]-[3] and many inventions for the progressive power run-up were reported [4] [5]. In Japan, implemented deployment of accelerator-driven neutron source for Boron Neutron Capture Therapy (BNCT) was accomplished in 2014 in National Cancer Center, of which system was designed with the production of neutrons via threshold $^7Li\ (p, n)\ ^7Be$ reaction at 25 kW proton beam with energy of 2.5 MeV, which was designed to dovetail the narrow peak band resonance of lithium target and started its installation at middle of 2013. This BNCT device is expected to offer the potential for achieving the objects of which any treatment capable of sterilizing the primary tumor locally will result in a high probability of cure.

BNCT is a targeted radio-therapeutic modality used for the treatment of brain tumors and melanoma and a bimodal approach to cancer therapy. Before BNCT, Boron-10(^{10}B)-enriched compounds are used to deliver ^{10}B to tumors. Once tumor uptake of a given boron delivery agent relative to the surrounding normal tissues and blood has been maximized and then irradiation with low-energy neutron takes place. An alternative boron delivery agent, p-boronophenylalaine (BPA) instead of administration of the boron delivery agent borocaptate sodium (BSH), is being used together with mode deeply penetrating epithermal neutron beam [6]. BNCT is extensively reviewed in two recent articles [7] [8] and the targeting effectiveness of BNCT is dependent upon the preferential delivery of ^{10}B to the primary tumor and its metastatic spread.

In defining the biological effects of the $^{10}B(p, \alpha)^7Li$ neutron capture reaction relative to photons, the term compound biological effectiveness (*CBE*) factor was used as an alternative to *RBE*. Calculation of the *CBE* factor is similar to that of the *RBE* factor [9]. Equating the X-ray ED_{50} dose with a BNC dose (beam + BSH) that gives the same end point of a 50% incident of ulceration produces the following equation:

The *CBE* factor

$$= \left[(\text{X-ray } ED_{50}) - (\text{thermal beam component of } ED_{50} \times RBE) \right] \Big/ {}^{10}B(p, \alpha)\ {}^7Li \text{ component of } ED_{50}.$$

The *CBE* factors concerning to tumor, skin lung, liver [10]-[12] and oral mucosal tissues [13] are reported and prospect of actually using BNCT for the patients has been developing under the right circumstances. However, there is no theoretical unified explanation of the *CBE* factors for normal tissues and tumor, despite the fact that significance of high precision of the *CBE* factor evaluation is requested for the patients.

Recently, the authors proposed deterministic parsing model of CBE factors (*ISHIYAMA-IMAHORI* model) and applied to human tumor brain cases and derived good results dovetailed with empirical facts [14] [15].

The purpose of the present investigation was to demonstrate the unified methodology for the evaluation of the *CBE* factors for normal tissues and tumor in BNCT.

2. Materials and Methods

2.1. ^{10}B Concentration Measurement of BPA by Dynamic PET Technique

33 brain tumor patients (grade AII (8 patients), AIII (11) and GBM (14)) were given low dose (approximately ~ 100 μg/g) of intravenous radioactively-labeled ^{18}F-BPA before BNCT and diagnosed cancer by Positron-Emission-Tomography (PET) [16]. To obtain ^{10}B concentration in a body, ^{18}F-BPA was administrated to the patient by intravenous drip injection and PET inspection was performed in every 20 minutes to measure a change in ^{10}B concentrations in tumor, normal and blood of the patient, respectively.

2.2. Mathematical Analysis Model for the ¹⁰B Concentration Data

After ¹⁰BPA administration, boron atoms are ingested into the cell model consisted of endoplasm and cell nucleus and Imahori [17] reported the kinetic analysis for brain tumor patients by using three-compartment rate constant (K_1, k_2 and k_3) (**Figure 1**).

This model implied that the body injected ¹⁰BPA begins to rapidly up-taken into cancer cell group at the injection initial and eventually suppressed increase with increasing ¹⁰BPA-containing population.

As a function that can better represent this phenomenon, the sigmoid function are frequently applied as natural population increasing model. Accordingly, logistic function based on the sigmoid function was employed to analyze dynamic PET data. The logistic function in present study was defined as:

$$D_b(t) = \frac{A}{\left(1 + e^{-a(t-t_0)}\right)} \tag{1}$$

where $D_{b\text{normal}}$ and $D_{b\text{tumor}}$ are ¹⁰B concentrations in tumor, normal tissues and time-dependent function. A, a and t_0 in Equation (1) are constants, respectively. Iteration calculation technique was employed to obtain constants A, a and t_0 in Equation (1) for normal tissue and tumor cases, respectively [15].

3. Results

3.1. Dynamic PET Measurement for Normal Tissues and Tumor

Typical changes in ¹⁰B concentration in normal tissue, tumor and blood of a BGM patient are illustrated in the figure by ¹⁰BPA administration by intravenous and drip injection methods (**Figure 2**).

Sudden increase and peak in ¹⁰B concentration in blood, normal tissue and tissue were found just before intravenous injection of BPA administration. Whereas, the changes in ¹⁰BPA concentration after drip injection show modest slow changes in ¹⁰B concentration in normal tissues, tumor and blood, respectively (**Figure 3**).

These typical changes after ¹⁰BPA administration indicate compatibility to define saturation boron concentration, $N_{\max}$ and threshold of boron density, N_{th} for the determination of CBE factors by *ISHIYAMA IMAHORI* model [14] [15] as below:

$$CBE = CBE_0 + \frac{F}{2}\left(1 - \left(\frac{N_{\text{th}}}{N_{\max}}\right)^{\frac{1}{n}}\right)\left\{2 - \left(\frac{N_{\text{th}}}{N_{\max}}\right)^{\frac{2}{n}} + \left(\frac{N_{\text{th}}}{N_{\max}}\right)^{\frac{1}{n}}\right\}, \quad 0 < \frac{N_{\text{th}}}{N_{\max}} < 1 \tag{2}$$

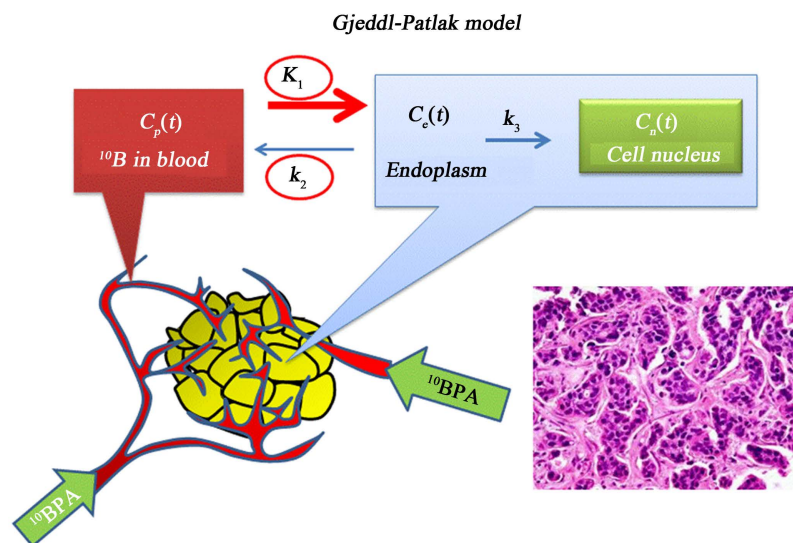and this is because that we chose drip injection in present study.

Gjeddl-Patlak model

Figure 1. Gjeddle-Patlak model using three-compartment rate constants (K_1, k_2 and k_3).
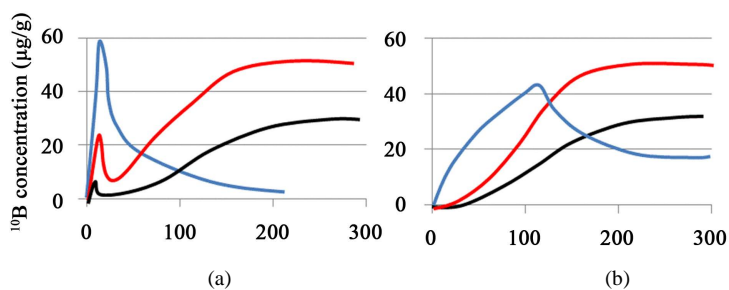
Figure 2. Typical change in ^{10}B concentration in tumor, normal tissues and blood measured by dynamic PET technique with ^{10}BPA administration by (a) intraveous injection and (b) drip injection methods.
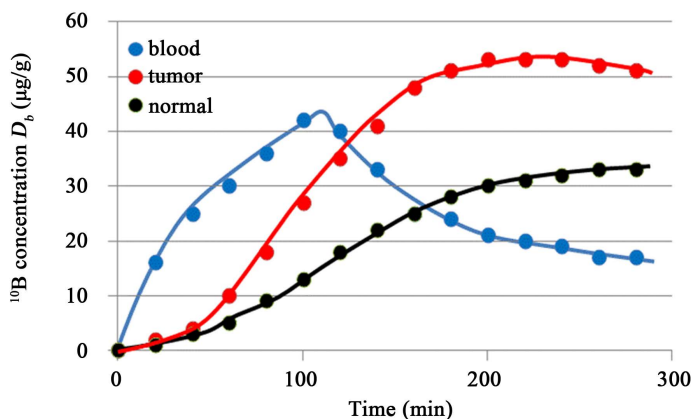

Figure 3. Change in ^{10}B concentration in blood, tumor and normal tissue measured by dynamic PET technique.

As for a typical change in ^{10}B concentration in blood, tumor and normal tissue of a brain tumor patient (Grade IV), logistic function in Equation (1) was applied to these data. Compatibility of the function to normal tissue and tumor are provided in **Figure 4** and **Figure 5**.

From these results, it is clear that very good data fitting curves of the logistic function to dynamic PET data were observed and each constant in Equation (1) are obtained in the tumor and normal tissue. These results are listed in **Table 1**.

3.2. Determination of the *CBE* Factor Depend on Boron Dose Level

To obtained threshold and saturation density of boron, N_{th} and N_{max} in tumor and normal tissue from Equation (1), we defined N_{th} and N_{max} as follows:

$$N_{th} = D_b \text{ at } t = 0 \text{ and } N_{max} = A \tag{3}$$

These values of N_{th}, N_{max} and N_{th}/N_{max} for normal tissue and tumor are listed in **Table 2**.

From these results, The *CBE* factors for normal tissue and tumor in a brain tumor patient were calculated by Equation (2) and these results are given in **Table 3**.

4. Discussions

4.1. The CBE Factors Estimations by the Severity of the Brain Tumor

The difference between the previous report [15] and this paper mainly lies in the definition of the N_{th} from the dynamic PET curves. From dynamic PET curves of 33 brain tumor patients contained of AII (8 patients), AII (11) and GBM (14) [16], the *CBE* factors were calculated by the ISHIYAMA-IMAHORI model (Equation (2)) with definition of N_{th}/N_{max} by Equations (1) and (3), and plotted in **Figure 6**. From these data, it is clearly
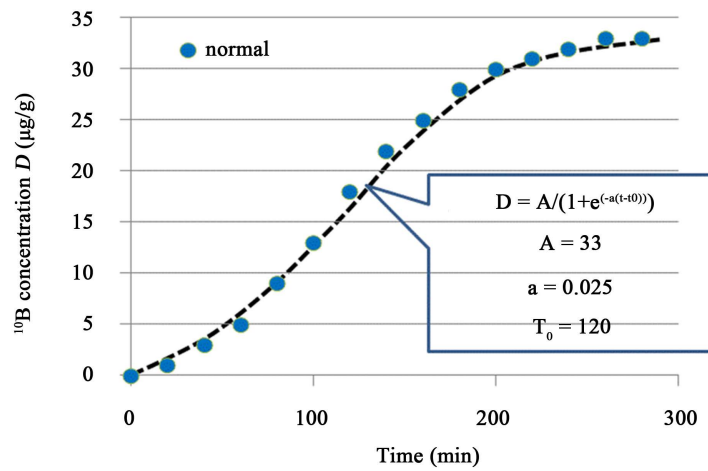
Figure 4. A change in ^{10}B concentration in normal tissue measured by dynamic PET technique and logistic function.
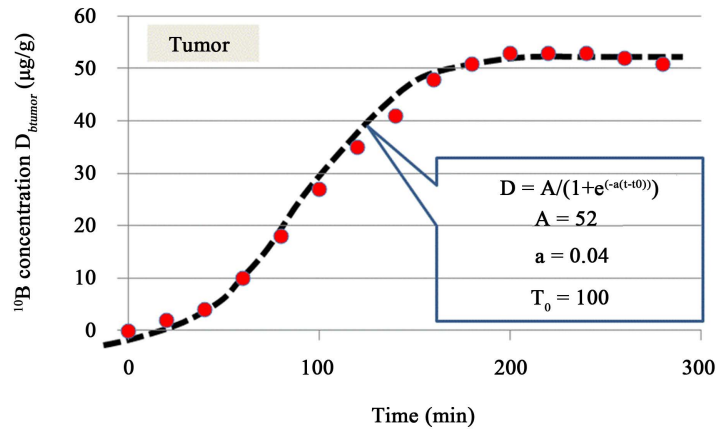

Figure 5. A change in ^{10}B concentration in tuomor measured by dynamic PET technique and logistic function.
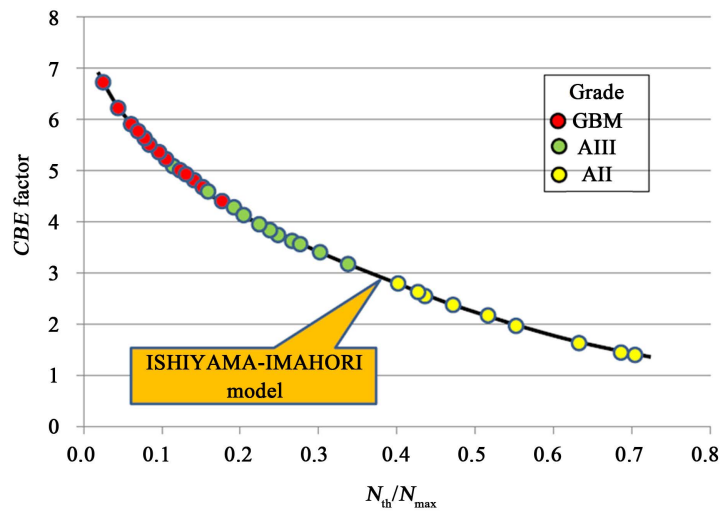

Figure 6. CBE factors calculated by ISHIYAMA-IMAHORI model with for three grade of brain tumor patients as a function of N_{th}/N_{max}.

Table 1. Constants in Equation (1) logistic function obtained for tumor and normal tissue.

	A	a	t_0
Tumor	52	0.04	100
Normal	33	0.025	120

$D = A \big/ \left(1 + \mathrm{e}^{-a(t-t_0)}\right)$.

Table 2. The values of N_{th} and N_{max} defined by Equation (3) for tumor and normal tissue.

	N_{th}	N_{max}
Tumor	0.935	52
Normal	1.565	33

$N_{th} = D$ at $t = 0$; $N_{max} = A$.

Table 3. The values of N_{th}/N_{max} and CBE factor defined by Equation (2) for tumor and normal tissue.

	N_{th}/N_{max}	*CBE*
Tumor	0.018	6.97
Normal	0.047	6.20

categorized into three groups corresponding to the severity of the three grades and it can be given as individual numerical values for the individual patient in the same group.

4.2. Application of *ISHIYAMA-IMAHORI* Model to Other Cancer Affected Area Position

The *ISHIYAMA-IMAHORI* model can provide *CBE* factors about not only brain tumors, also cancer affected part of a different site by 18F-BPA dynamic PET measuring technique. Typical lung cancer that can be observed by PET with 18F-BPA was shown in **Figure 7**. There is a ling cancer (adenocarcinoma) in lower right lung field and the diaphragm just above, but no metastasis to the brain in this case.

From dynamic PET curve obtained in this case, N_{th} and N_{max} values can be determined from temporal change in the color intensity of the target diseased part from the Equations (1) and (3), and the *CBE* factor in this case was evaluated as 6.35 from the *ISHIYAMA-IMAHORI* model.

4.3. Application of the Calculation Method and Its Clinical Significance

The charm of the BNCT treatment is that again and again for the same patients and their affected area is capable of irradiation treatment. Therefore, the cure of intractable cancer in a short time by BNCT treatment is not a dream. However, BNCT treatment at this stage is time-consuming due to the following reasons. Normally, cancer patients are given low doses of intravenous radioactively-labelled 18F-BPA before BNCT and diagnosed cancer by Positron-Emission-Tomography (PET). Physicians developed a treatment plan by BNCT based on PET diagnosis and then after administrates high dose of BPA to the patients.

So practical value of present research is that the diagnosis and treatment cycle can be achieved at the same time shorten with high accuracy.

Present research results, *i.e.* by 18F-BPA drip injection administration and dynamic PET measurement method, *ISHIYAMA-IMAHORI* model immediately provides a high-precision *CBE* factor and BNCT treatment for a kind of cancer and its severity in patients individual.

5. Conclusions

ISHIYAMA-IMAHORI model below immediately provides a high-precision CBE factor and BNCT treatment for a kind of cancer and its severity in patients' individual by 18F-BPA drip injection administration and dynamic PET measurement method
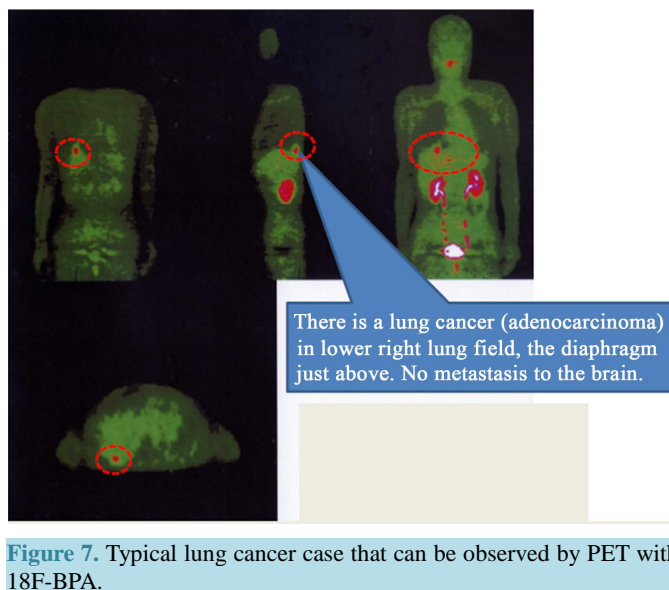
Figure 7. Typical lung cancer case that can be observed by PET with 18F-BPA.

$$CBE = CBE_0 + \frac{F}{2}\left(1 - \left(\frac{N_{\text{th}}}{N_{\text{max}}}\right)^{\frac{1}{n}}\right)\left\{2 - \left(\frac{N_{\text{th}}}{N_{\text{max}}}\right)^{\frac{2}{n}} + \left(\frac{N_{\text{th}}}{N_{\text{max}}}\right)^{\frac{1}{n}}\right\}, \; 0 < \frac{N_{\text{th}}}{N_{\text{max}}} < 1.$$

And $N_{\text{th}}/N_{\text{max}}$ is obtained by the flowing logistic function

$$D_b(t) = \frac{A}{\left(1 + e^{-a(t-t_0)}\right)}$$

where B_b is ^{10}B concentration in tumor and normal tissue, and A, a and t_0 are constants.

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