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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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Keywords: *boron neutron capture therapy,compound biological effectiveness, borono-phenyl-alanine, tumor, $^{10}B(n,\alpha)^{7}$ li,sigmoid function.*

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Shintaro Ishiyama [α], Yoshio Imahori [σ], Jun Itami [ρ] & Hanna Koivunoro [ω]

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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}.

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

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.

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

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 eq.(2) as;

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

And the calculated *CBE* factor values obtained from eq. (1), with N_{th}/N_{max}.

Keywords: *boron neutron capture therapy, compound biological effectiveness, borono-phenyl-alanine, tumor, $^{10}B(n,\alpha)^{7}$ li, sigmoid function.*

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I. Introduction

Many types of pilot innovative accelerator-based neutron source for neutron capture therapy with lithium target were designed [1][2][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) is accomplished in 2014 in National Cancer Center, of which system was designed with the production of neutrons via threshold ^{7}Li (p, n) ^{7}Be reaction at 25kW 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-bononphenylalaine (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 was 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 $^{10}B(p,\alpha)^{7}Li$ 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 = [(X-rayED_{50}) - (thermal beam component of $ED_{50}\times RBE$]/ $^{10}B(p,\alpha)^{7}Li$ component of ED_{50}.

The *CBE* factors concerning to tumor, skin lung, liver [10][11], heart [12] and oral mucosal tissues [13] were 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 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.

II. Materials and Methods

a) ^{10}B concentration measurement of BPA by dynamic PET technique

A brain tumor patient (grade IV) was given low dose (approximately~100μg/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.

b) Mathematical analysis model for the ^{10}B concentration data

After ^{10}BPA 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 ^{10}BPA begins to rapidly up-taken into cancer cell group at the injection initial and eventually suppressed increase with increasing ^{10}BPA-containing population.

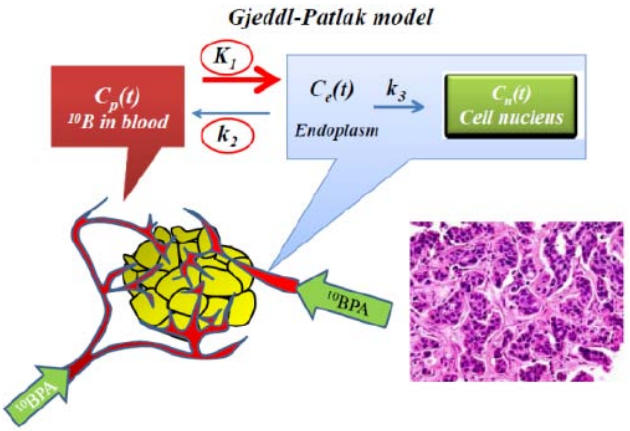

Figure 1: Gjeddle-Patlak model using three-compartment rate constanta *(k_1, k_2 and k_3)*

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:

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

Where $D_{bnormal}$ and D_{btumor} are ^{10}B concentrations in tumor, normal tissues and time-dependent function. A, a and t_0 in eq. (1) are constants, respectively.

III. Results and Discussions

a) Dynamic PET measurement for normal tissues and tumor

Typical changes in ^{10}B concentration in normal tissue, tumor and blood are illustrated in the figure by ^{10}BPA administration by intravenous and drip injection methods (Figure 2).

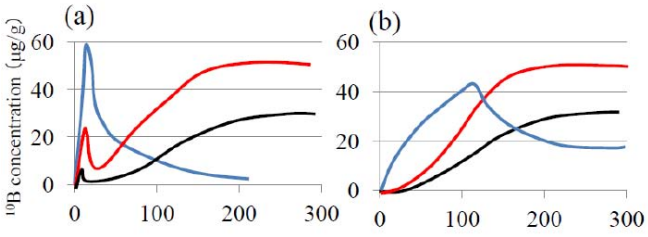

Figure 2 : Typical change in ^{10}B concentration in tumor, normal tissues and blood measured by Dynamic PET technique with ^{10}BPA administration by (a) Intraveous injection and (b) Drip injection methods

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

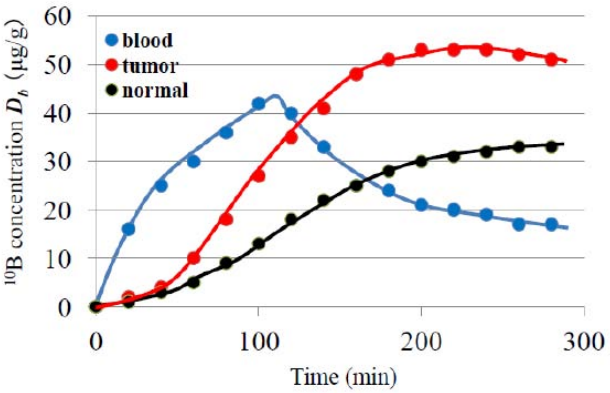

Figure 3 : Change in ^{10}B concentration in blood, tumor and normal tissue measured by Dynamic PET technique

These typical changes after ^{10}BPA 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:

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

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

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 eq. (1) was applied to these data. Compatibility of the function to normal tissue and tumor are provided in the figures **(Figure 4 and 5)**.

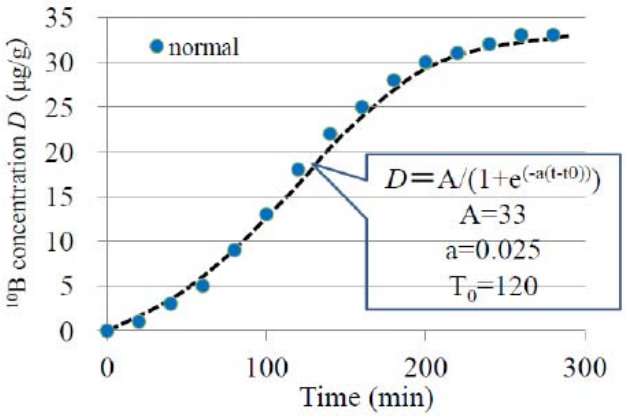

Figure 4 : A change in ^{10}B concentration in normal tissue measured by dynamic PET technique and logistic function

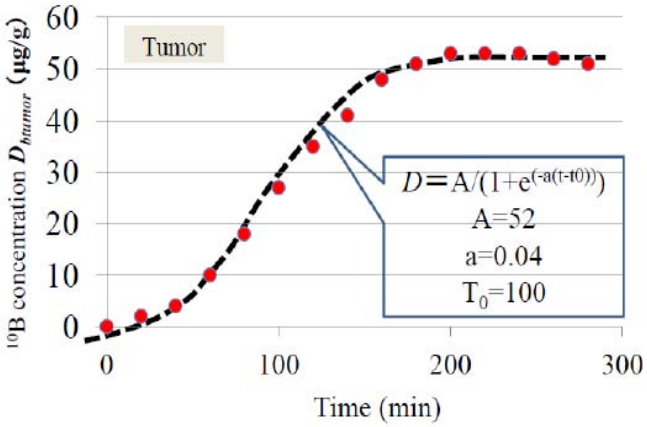

Figure 5 : A change in ^{10}B concentration in tumor measured by dynamic PET technique andlogistic function

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 eq. (1) are obtained in the tumor and normal tissue. These results are listed in the table **(Table 1)**.

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

	A	a	t_0
Tumor	52	0.04	100
Normal	33	0.025	120

$$D = A/(1+e^{(-a(t-t0))})$$

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

	N_{th}	N_{max}	N_{th}/N_{max}
Tumor	0.935	52	55.62
Normal	1.565	33	21.09

N_{th}=D at t=0
N_{max}= A

b) *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 eq.(1), we defined N_{th} and N_{max} as follows:

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

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

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

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

	N_{th}/N_{max}	*CBE*
Tumor	0.018	5.43
Normal	0.047	4.35

c) *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, ie 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.

IV. 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

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

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

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

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

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