Otolaryngology: Open Access

Aihara et al., Otolaryngol (Sunnyvale) 2016, 6:6
DOI: 10.4172/2161-119X.1000277

Mini Review OMICS International

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

Teruhito Aihara[1,2*], Jyunichi Hiratsuka[3], Nobuyoshi Fukumitsu[1], Hitoshi Ishikawa[1], Norimasa Morita[2], Hiroaki Kumada[1], Nobuhiko Kamitani[3], Kayoko Ohnishi[1], Minoru Suzuki[4], Hideyuki Sakurai[1] and Tamotsu Harada[2]

[1]*Proton Medical Research Centre, University of Tsukuba, Tsukuba, Japan*

[2]*Department of Otolaryngology Head and Neck Surgery, Kawasaki Medical School, Kurashiki, Japan*

[3]*Department of Radiation Oncology, Kawasaki Medical School, Kurashiki, Japan*

[4]*Radiation Oncology Research Laboratory, Research Reactor Institute, Kyoto University, Osaka, Japan*

[*]**Corresponding author:** Teruhito Aihara, M.D., Proton Medical Research Centre, University of Tsukuba, Tennodai 1-1-1, Tsukuba, Ibaraki, 305-8575, Japan, Tel: (+81)29-853-7100; Fax: (+81)29-853-7102; E-mail: aiteru@med.email.ne.jp

Received date: October 25, 2016; **Accepted date:** November 03, 2016; **Published date:** November 10, 2016

Abstract

Introduction: A role for fluoride-18-labeled boronophenylalanine positron emission tomography (^{18}FBPA-PET) in boron neutron capture therapy (BNCT) has not been fully elucidated. We investigated the role of ^{18}FBPA-PET in BNCT for recurrent head and neck squamous cell carcinoma (HNSCC) patients.

Materials and methods: ^{18}FBPA-PET images were obtained from 10 histologically verified recurrent HNSCC patients who received BNCT. The intratumoral accumulation of ^{18}FBPA was calculated as the ratio of maximum and minimum radioactivity counts to that of normal tissue (T_{max}/N and T_{min}/N ratios, respectively). The percentage volume at which the radioactivity count ratio was >2.5 compared to normal tissue was also calculated (Vo2.5). Moreover, mean and minimum irradiation dose to the tumor was calculated. We investigated which parameters could predict the treatment effect of BNCT.

Results: Treatment effects of local lesions were as follows: complete remission (CR) in 5 cases and non-CR in 5 cases. Only T_{min}/N ratio showed a significant difference between the CR and non-CR groups (P=0.008).

Conclusion: The T_{min}/N ratio of ^{18}FBPA-PET can predict the treatment effect of BNCT for recurrent HNSCC.

Keywords Recurrence head and neck SCC; BNCT; ^{18}FBPA-PET; T/N ratio; ^{10}B

Introduction

Boron neutron capture therapy (BNCT) is a type of high linear energy transfer radiation therapy. High irradiation doses can be selectively delivered to tumor cells without causing serious damage to surrounding normal tissue, due to high accumulation of ^{10}B in the tumor compared to adjacent normal tissue. The results of clinical trials of BNCT that used L-^{10}B-para-boronophenylalanine (L-BPA) as a boron delivery agent have been reported for the treatment of recurrent head and neck cancers [1-4].

The actual irradiation dose to the tumor during BNCT is determined by the intratumoral ^{10}B concentration and the neutron flux to the tumor [5,6]. Since a fairly constant neutron flux is achieved in the irradiation field, the tumor irradiation dose can be largely determined from the intratumoral ^{10}B concentration. Thus, estimation of ^{10}B concentrations is required. Less invasive methods for measuring ^{10}B concentration did not exist 2 decades ago. Therefore, using surgical specimens from malignant melanomas, Mishima and Fukuda et al. measured ^{10}B concentrations directly to estimate the tumor/normal tissue ratio (T/N ratio) [7,8].

In 1998, Imahori et al. reported a less invasive method for estimating intratumoral ^{10}B concentrations using positron emission tomography (PET) [9] and calculation of the T/N ratio of ^{10}B-containing compounds using PET has since become the standard BNCT planning method. The tumor irradiation dose is calculated from the neutron flux and the T/N ratio of ^{18}FBPA-PET (Figure 1). Clinically, a ^{18}FBPA-PET T/N ratio of ≥ 2.5 is generally considered a requirement for use of BNCT in head and neck cancer [2,10]. This value was established to ensure that tumors with a depth ≥ 6 cm will receive >20 Gray equivalent (GyE), which is necessary for tumor control, while surrounding normal tissue (primarily skin) receives a tolerable irradiation dose [11].

Although the utility of the T/N ratio has been comprehensively reported in some clinical studies, actual intratumoral accumulation of ^{18}FBPA can fluctuate depending on cell density and tumor cell activity [12] and this value is inhomogeneous in tumor tissue. Moreover, radiosensitivity differs for each pathologic tumor type. In this study, we investigated whether ^{18}FBPA accumulation that has potentially inhomogeneous distribution in tumors can predict the treatment effect of BNCT for head and neck squamous cell carcinoma (HNSCC).

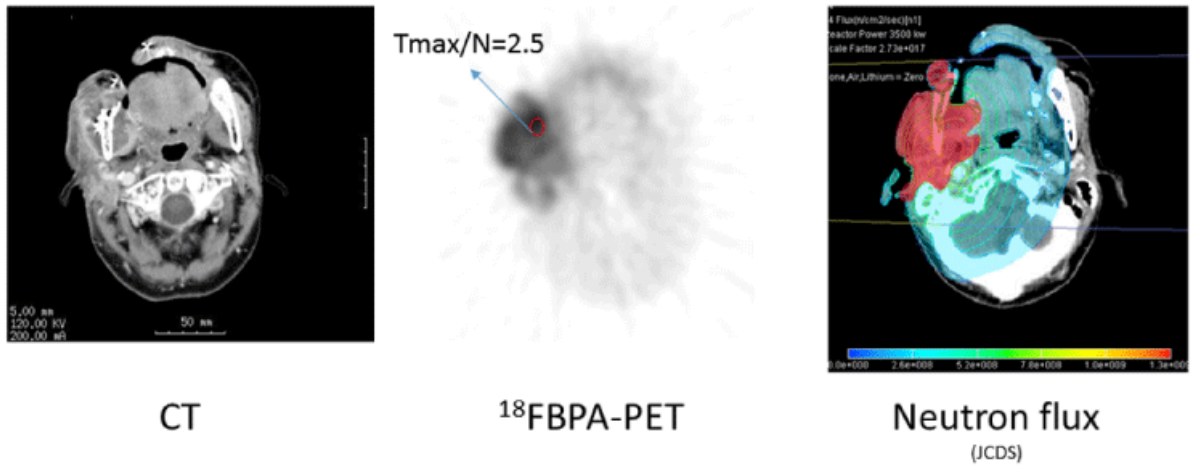

Figure 1: A schematic diagram of BNCT dose planning, Left: CT before BNCT, Middle: ^{18}FBPA-PET, Right: Neutron flux calculated by the dose planning software (JCDS), Blue: normal tissue. Red: tumor.

Patients and Methods

Study design

This study was a retrospective, single-institution review of HNSCC patients treated with BNCT.

Patients

We previously reported 20 recurrent head and neck cancer patients treated with BNCT [2]. We selected 10 of these 20 patients with squamous cell carcinoma for the present analysis; the remaining 10 patients with other pathologies were excluded, as their tumors had different degrees of radiosensitivity. Characteristics of the selected 10 cases are presented in Table 1. Patients included 8 men and 2 women, with a median age at time of treatment of 62.5 years (range, 39 to 77 years). Primary lesion sites were the oropharynx in 5 cases, tongue in 2 cases, and nasal ala, oral floor and larynx in 1 case each. All patients were undergoing third-line or later treatment, and had already received 40-66 Gy (median, 62.5 Gy) of radiotherapy prior to BNCT. The clinical stage was rN2a in 5 cases, rT4 in 3 cases and rT2 in 2 cases at the time of treatment based on the Union for International Cancer Control Disease Stage Classification (VIIth Edition).

(Kawasaki Medical School IRB approval number 40).

No.	Primary site	Age	Sex	Histology	TNM (Recurrence)	TNM (Initial)	Initial treatment	Salvage treatment
1	Oropharynx	73	M	SCC	rT2	T1N2M0	CCRT	Chemo
2	Lingual	39	F	SCC	rT4	T2N0M0	CCRT	Op
3	Nasal ala	71	M	SCC	rN2a	T2N0M0	OP	CCRT, Chemo
4	Oropharynx	77	M	SCC	rT2	T1N2bM0	CCRT	Op
5	Oropharynx	73	M	SCC	rT4	T4aN2bM0	CCRT	Op
6	Larynx	64	M	SCC	rN2a	T2N0M0	CCRT	OP, Chemo
7	Oral floor	57	M	SCC	rT4	T1N0M0	OP+RT	Chemo
8	Oropharynx	39	F	SCC	rN2a	T2N2bM0	CCRT	Chemo, 3DRT
9	Lingual	45	M	SCC	rN2a	T2N1M0	Op+RT	Chemo
10	Oropharynx	61	M	SCC	rN2a	T2N2bM0	CCRT	Chemo
Abbreviations:	SCC: Squamous Cell Carcinoma; CCRT: Concurrent Chemoradiotherapy; Op: Operation; Chemo: Chemotherapy; 3DRT: Three Dimensionsradiotherapy							

Table 1: Patient and tumor characteristics.

Quantitative measurement of PET data

^{18}FBPA-PET scans were performed at Nishijin Hospital, Kyoto, Japan. BPA was synthesized as described previously [13,14]; the protocol for PET measurements using a HEADTOME III (Shimadzu Co., Kyoto, Japan) has also been described elsewhere [8,15,16]. We used PETViewer 2.0 (software.informer.com) and Amide software (SourceForge, Inc.) for data analysis.

Parameters

We placed a rectangular region of interest (ROI) (size: 4 pixels, 1 pixel=2 × 2 mm) on tumor and normal tissue. The left ventricle was designated as normal tissue. The contralateral cervical artery was also substituted for normal tissue in patients whose PET scans only evaluated the head and neck regions. The highest ROI count was defined as the T_{max}, while the lowest was defined as the T_{min}. The ratios of the T_{max} or T_{min} to the ROI count of normal tissue were calculated as the T_{max}/N and T_{min}/N ratios, respectively. The percentage intratumor volume with a T/N ratio ≥ 2.5 was defined as Vo2.5. All ROIs were drawn by the same physician, who has >13 years of experience in PET analysis.

Mean and minimum irradiation doses to the tumor were calculated by the BNCT planning system (mean tumor dose and minimum tumor dose, respectively).

Examinations

Patients were divided into two groups based on local treatment effect: the complete remission (CR) and the non-CR groups. The T_{max}/N ratio, T_{min}/N ratio, Vo2.5, mean tumor dose and minimum tumor dose were compared between the CR and non-CR groups.

Statistical analysis

Student's t test was used for statistical analysis. A P-value <0.05 was considered statistically significant.

Results

All results are shown in Table 2. Of the 10 patients, recurrences consisted of local recurrence in 5 patients (2 of whom also had distant metastasis), regional recurrence in 2 patients and distant metastasis in 1 patient. Based on local treatment effect, 5 patients were assigned to the CR group and the remaining 5 were assigned to the non-CR group. Survival times ranged from 3 to 20 months; all patients died within 20 months. The 1 year survival rate was 20% and median survival was 10.5 months. Causes of death were local recurrence in 5 cases, distant metastasis in 3 cases and other (carotid blowout syndrome [CBS]) in 2 cases. (We have previously reported these 2 CBS deaths [17]).

No.	T_{max}/N	T_{min}/N	Vo2.5 (%)	GTV (cm3)	Tumor mean dose (Gy-Eq)	Tumor minimum dose (Gy-Eq)	Tumor Response	Follow up (M)	Failure	Cause of death
1	2.5	1.9	83	12	18.9	12.4	NC	19	Local	Local
2	5	1.2	92	52	45.9	32.7	PR	11	Local+Distant	Distant
3	2.6	2.2	95	7	21.6	13.4	NC	12	Local+Distant	Distant
4	4	2.6	100	15	52	25.3	CR	20	Distant	Distant
5	5	1.9	97	24	54.6	25.6	PR	11	Local	Local
6	3.8	3.5	100	25	38.2	20.1	CR	7	(-)	CBS
7	2.5	2.1	73	43	55.2	36.5	PR	10	Local	Local
8	2.9	2.3	87	16	53.6	25	CR	7	Local(out of field)	Local
9	4.2	3.5	100	23	62.9	29.3	CR	6	Local(out of field)	Local
10	2.6	2.3	78	36	54.3	25.3	CR	3	(-)	CBS
Abbreviations:	CR: Complete Remission; PR: Partial Remission; NC: No Change; CBS: Carotid Blowout Syndrome									

Table 2: Dose evaluation after BNCT and Clinical results of all patients.

In the CR group, the T_{max}/N ratio ranged from 2.6 to 4.2 (median, 3.8) and the T_{min}/N ratio ranged from 2.3 to 3.5 (median, 2.6). Vo2.5 ranged from 78% to 100% (median, 100%). Mean tumor dose ranged from 38.2 to 62.9 (median, 53.6) GyE and minimum tumor dose ranged from 20.1 to 29.3 (median, 25.3) GyE.

In the non-CR group, the T_{max}/N ratio ranged from 2.5 to 5 (median, 2.6) and the T_{min}/N ratio ranged from 1.2 to 2.2 (median, 1.9). Vo2.5 ranged from 73% to 97% (median, 92%). Mean tumor dose ranged from 18.9 to 55.2 (median, 45.9) GyE and minimum tumor dose ranged from 12.4 to 36.5 (median, 25.6) GyE.

Of these five parameters, a statistically significant difference between the CR and non-CR groups was only noted for the T_{min}/N ratio (Figure 2, P=0.008).

Discussion

In our institute, the BNCT irradiation dose for head and neck cancers is determined using the T/N ratio of ^{18}FBPA-PET in the following manner: (1) skin dose ≤ 18 GyE and (2) tumor dose ≥ 20 GyE. Biologically, the effect of the boron neutron capture reaction does

not differ much in normal tissue between individuals [18], but largely differs in tumor tissues. As shown in this manuscript, the only parameter that predicted treatment effect was the T_{min}/N ratio (P=0.008); none of the other parameters appeared to be associated with treatment effect. We consider that in patients with high T_{min}/N ratios, a sufficient dose could be administered to the large tumor volume, so satisfactory local treatment effect was achieved. In contrast, in patients with low T_{min}/N ratios, the volume to which a sufficient irradiation dose was not delivered was large, residual tumor cells survived and the patients failed to achieve a CR. For example, the tumor disappeared 10 weeks after BNCT in a patient with a high T_{min}/N ratio (3.5) and a high T_{max}/N ratio (5; Case 9, Figure 3). In contrast, the tumor remained 12 weeks after BNCT in a patient with a low T_{min}/N ratio (1.2). The tumor irradiation dose was calculated as 32.7 GyE based on the T_{max}/N value of 5 at the actual BNCT planning and ^{18}FBPA accumulation varied largely in the tumor in this patient (Case 2, Figure 4).

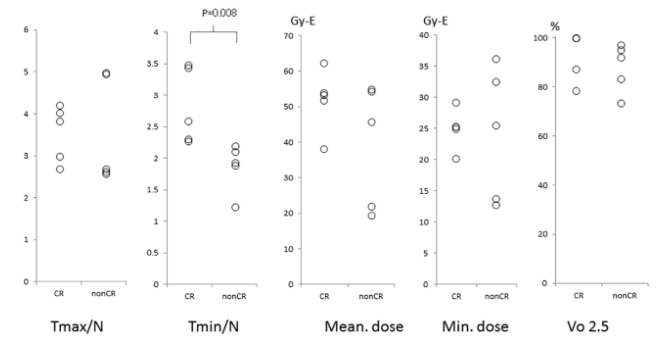

Figure 2: T_{max}/N, T_{min}/N ratios, mean and minimum tumor dose and Vo2.5 between the CR and non-CR groups.

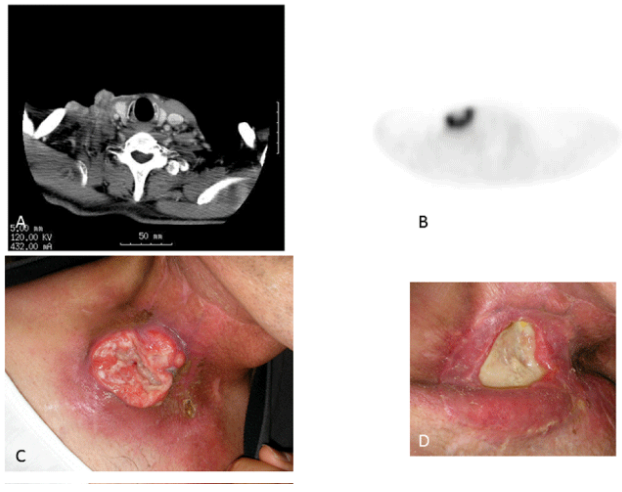

Figure 3: 45 year old man with lingual carcinoma (Case 9), A: CT before treatment, B: ^{18}FBPA-PET, C: Macroscopic findings before BNCT, D: Macroscopic findings 10 weeks after BNCT.

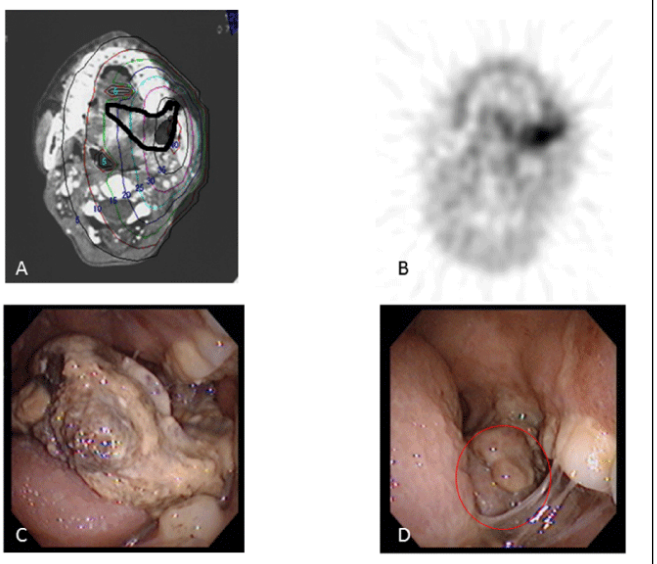

Figure 4: 77 year old man with oropharyngeal carcinoma (Case 2), A: Neutron flux image. Black line: tumor, B: ^{18}FBPA-PET, C: Macroscopic findings before BNCT, D: Macroscopic findings 12 weeks after BNCT.

The actual tumor irradiation dose is less than the calculated dose, based on the value of the T_{max}/N ratio. In particular, in cases in which the difference between the T_{max}/N and T_{min}/N ratios is large, large discrepancies in BNCT treatment effects may exist. In fact, the calculated irradiation dose in the area with the lowest ^{18}FBPA accumulation was 25-85% of the highest in the 5 non-CR cases. Of 5 non-CR patients, the total amount of neutron flux was determined by the normal skin irradiation dose in 1 patient and the tumor irradiation dose in 4 patients. In those 4 patients, the tumor irradiation dose was calculated to be 12.4-32.7 GyE using the T_{max}/N ratio for actual BNCT and the skin irradiation dose was 4-9 GyE. The minimum tumor irradiation dose was only 7.8-11.4 GyE based on our simulation using the T_{min}/N ratio. Considering the skin irradiation dose was much lower than the possible tolerated dose, a higher treatment effect could be obtained if the T_{min}/N ratio had been used for dose calculation.

Some issues regarding the use of ^{18}FBPA results for BNCT planning remain to be resolved. First, whether ^{18}FBPA accumulation correctly reflects BPA distribution during BNCT remains controversial. Mitsuyoshi et al. demonstrated that ^{18}FBPA was taken up into cells via the same amino acid transporter L-system as BPA in human glioblastoma cells [19]. ^{18}FBPA and BPA showed almost identical pharmacokinetics in the body in the experimental study [20]. Thus, we have used ^{18}FBPA-PET in BNCT planning as an indicator of ^{10}B concentration. Second, it is difficult to reflect the inhomogeneous ^{10}B intratumoral concentration with the current BNCT dose planning system (SERA [5] and JCDS [6]). We anticipate the development of a BNCT planning system that can support inhomogeneous ^{18}FBPA accumulation in the tumor. Alternatively, we propose use of the T_{min}/N ratio rather than the T_{max}/N ratio to increase the treatment effect of BNCT.

The source of neutrons in Japan has been the long-employed nuclear reactors; however, BNCT accelerators that can provide an alternative to

nuclear reactors are currently under development [21]. Detailed analysis of previous clinical cases is required to properly administer next-generation BNCT using accelerators. We hope such endeavors will lead to the development of highly effective head and neck cancer treatment. This is the first study in which the results of ^{18}FBPA-PET imaging have been shown to predict a treatment effect of BNCT against recurrent HNSCC.

Conclusion

The T_{min}/N ratio of ^{18}FBPA-PET is a useful parameter for predicting the BNCT treatment effect in patients with recurrent HNSCC.

Acknowledgement

This work was supported by JSPS Grant-in-Aid for Scientific Research (C) Number 15K10797.

Conflicts of Interest

None to declare.

References

1. Kato I, Ono K, Sakurai Y, Ohmae M, Maruhashi A, et al. (2004) Effectiveness of BNCT for recurrent head and neck malignancies. Appl Radiat Isot 61: 1069-1073.
2. Aihara T, Morita N, Kamitani N, Kumada H, Ono K, et al. (2014) Boron neutron capture therapy for advanced salivary gland carcinoma in head and neck. Int J Clin Oncol 19: 437-444.
3. Kankaanranta L, Koivunoro H, Seppälä T, Saarilahti K, Atula T, et al. (2007) Boron neutron capture therapy in the treatment of locally recurred head and neck cancer. Int J Radiat Oncol Biol Phys 69: 475-482.
4. Haapaniemi A, Kankaanranta L, Saat R, Koivunoro H, Saarilahti K, et al. (2016) Boron neutron capture therapy in the treatment of recurrent laryngeal cancer. Int J Radiat Oncol Biol Phys 95: 404-410.
5. Nigg DW, Wessol DE, Wemple CA, Wheeler FJ (1999) SERA an advanced treatment planning system for neutron therapy and BNCT. Trans ANS 80: 66-68.
6. Kumada H, Yamamoto K, Yamamoto T, Nakai K, Nakagawa Y, et al. (2004) Improvement of dose calculation accuracy for BNCT dosimetry by the multi-voxel method in JCDS. Appl Radiat Isot 61: 1045-1050.
7. Mishima Y (1973) Neutron capture treatment of malignant melanoma using ^{10}B-chlorpromazine. Pigment Cell Res 1: 215-221.
8. Fukuda H, Honda C, Wadabayashi N, Kobayashi T, Yoshino K, et al. (1999) Pharmacokinetics of ^{10}B -p-boronophenylalanine in tumours, skin and blood of melanoma patients: A study of boron neutron capture therapy for malignant melanoma. Melanoma Res 9: 75-83.
9. Imahori Y, Ueda S, Ohmori Y, Kusuki T, Ono K, et al. (1998) Fluorine-18-labeled fluoroboronophenylalanine PET in patients with glioma. J Nucl Med 39: 325-333.
10. Aihara T, Morita N, Kamitani N, Kumada H, Ono K, et al. (2014) Boron neutron capture therapy for advanced salivary gland carcinoma in head and neck. Int J Clin Oncol 19: 437-444.
11. Aihara T, Hiratsuka J, Morita N, Uno M, Sakurai Y, et al. (2006) First clinical case of boron neutron capture therapy for head and neck malignancies using 18F-BPA PET. Head Neck 28: 850-855.
12. Tani H, Kurihara H, Hiroi K, Honda N, Yoshimoto M, et al. (2014) Correlation of (18)F-BPA and (18)F-FDG uptake in head and neck cancers. Radiother Oncol 113: 193-197.
13. Ishiwata K, Ido T, Mejia AA, Ichihashi M, Mishima Y (1991) Synthesis and radiation dosimetry of 4-borono-2-[18F]fluoro-DL-phenylalanine: a target compound for PET and boron neutron capture therapy. Int J Rad Appl Instrum 42: 325-328.
14. Mishima Y, Imahori Y, Honda C, Hiratsuka J, Ueda S, et al. (1997) In vivo diagnosis of human malignant melanoma with positron emission tomography using specific melanoma-seeking 18F-DOPA analogue. J Neurooncol 33: 163-169.
15. Takahashi Y, Imahori Y, Mineura K (2003) Prognostic and therapeutic indicator of fluoroboronophenylalanine positron emission tomography in patients with gliomas. Clin Cancer Res 9: 5888-5895.
16. Miyashita M, Miyatake S, Imahori Y, Yokoyama K, Kawabata S, et al. (2008) Evaluation of fluoride-labeled boronophenylalanine-PET imaging for the study of radiation effects in patients with glioblastomas. J Neurooncol 89: 239-246.
17. Aihara T, Hiratsuka J, Ishikawa H, Kumada H, Ohnishi K, et al. (2015) Fatal carotid blowout syndrome after BNCT for head and neck cancers. Appl Radiat Isot 106: 202-206.
18. Ono K (2016) An analysis of the structure of the compound biological effectiveness factor. J Radiat Res 57 Suppl 1: i83-83i89.
19. Yoshimoito M, Kirihata H, Honda N, Kawai K, Ohe K, et al. (2013) Predominant contribution of L-type amino acid transporter to 4-borono-2-18F-fluoro-phenylalanine uptake in human glioblastoma cells. Nucl Med Biol 40: 625-629.
20. Watanabe T, Hattori Y, Ohta Y, Ishimura M, Nakagawa Y, et al. (2016) Comparison of the pharmacokinetics between L-BPA and L-FBPA using the same administration dose and protocol: A validation study for the theranostic approach using [^{18}F]-L-FBPA positron emission tomography in boron neutron capture therapy. BMC Cancer 16: 859.
21. Kumada H, Kurihara T, Yoshioka M, Kobayashi H, Matsumoto H, et al. (2015) Development of beryllium-based neutron target system with three-layer structure for accelerator-based neutron source for boron neutron capture therapy. Appl Radiat Isot 106: 78-83.