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Impacts of multiple-field irradiation and boron concentration on the treatment of boron neutron capture therapy for non-small cell lung cancer

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► ***Original Article***

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ABSTRACT

Background*:** Boron neutron capture therapy (BNCT) is a radiotherapy that combines biological targeting and high linear energy transfer. A potential therapeutic approach for non-small cell lung cancer (NSCLC) is considered. However, dose in lung tumor is not homogeneous, and it will reduce the effect of BNCT treatment. In order to improve the dose distribution of BNCT, the multi-field irradiation strategy and its effects need to be explored. ***Materials and Methods*:** Common NSCLC model was defined in Chinese hybrid reference phantom and the boron concentration in skin and tumor varied from 6 to 18 ppm and from 30 to 65 ppm, respectively. Monte Carlo method for dose distribution calculation was used. Accelerator-based neutron source called "Neuboron source" was used and multi-field source irradiation plans were designed to optimize the dose distribution. ***Results: Under one-field irradiation, it was not feasible to perform BNCT, because the skin dose is unlikely to meet its dose limit. Under two- and three-field irradiation, the uniformity of tumor dose was improved and the maximum dose to organs at risk (OARs) decreased. If boron concentration in skin was between 6-18 ppm, BNCT was feasible with the boron concentration in tumor reaching about 57-60 ppm for two-field irradiation and 41-45 ppm for three-field irradiation, respectively. ***Conclusion:*** The multi-field irradiation plan could improve the dose distribution and the feasibility of BNCT for NSCLC. Theoretical distributions of Boron-10 were obtained to meet the treatable requirement of BNCT, which could provide a reference for NSCLC using BNCT in future multiple-field irradiation.

Keywords: *Multiple-field irradiation, BNCT, non-small cell lung cancer, radiation dose, Monte Carlo.*

INTRODUCTION

Local non-small cell lung cancer (NSCLC), a common cause of cancer deaths, presents limited therapeutic options because of tumor location, which is mostly near the trachea [1]. Cancer cells in this region require timely treatment, which have diffused into the lung but not diffused to the whole body. Boron neutron capture therapy (BNCT) combines biological targeting and high linear energy transfer (LET) radiation. At present, the study on BNCT includes the developments of neutron sources [2-3], boron drugs, radiation measurement [4] and

radiobiological effect, etc. As the exploited reaction ^{10}B (n, alpha) ^{7}Li is the neutron capture with ^{10}B, which has a cross section of 3837 b at thermal energies, and the neutron capture gives rise to high LET radiation, generating an alpha particle and a ^{7}Li nucleus with ranges in tissues comparable to a cell diameter. Therefore, dose delivery in BNCT is selective at the cellular level. The BNCT has been commonly used for treatment of melanoma and malignant glioma. Recently, some scholars have proposed BNCT for the NSCLC [5], and the feasibility of applying BNCT to treat local lung cancer had been explored [6]. This therapy can avoid the inaccurate treatment caused by the motions of cancerous lung tissues during radiotherapy, as the major effect depends on boron localization. Moreover, the treatment may be delivered in a single-fraction through BNCT.

In BNCT treatment, since the well-known phenomena of self-shielding and neutron flux depression [2], the dose distribution in tumor is not homogeneous; the dose in the front of the tumor is always higher than that in the tumor latter part [7]. It will reduce the curative effect of BNCT treatment because the deeply buried cancer cell dose not be killed. Meanwhile, the skin dose rate often exceeds its dose limitation and it limits the irradiation time [5]. In order to improve the dose distribution of BNCT, some researchers have made efforts to develop the boracic drugs to improve its specificity and homogeneous enrichment in tumor [8]. While its usage range is limited to the specific type of tumor, and it will have different responding in different individuals. The other approach was using a skin-shielding layer during the treatment [9] to improve the dose distribution, for example, Li_2CO_3 pad. The use of skin-shielding layer results in a slight reduction of skin dose, but it also leads to much longer irradiation time, which does not seem to introduce a real benefit to the treatment. Meanwhile, both of the above approaches also need a neutron beam with good beam characteristics to improve dose distribution. Thus, designing optimized beam shaping assembly [10] to improve treatment beam characteristics has been paid much attention to, while it is difficult to improve the dose distribution using mixed energy neutron beam. In 2003, the multi-field neutron source irradiation was proposed to improve the dose distribution of BNCT for brain tumor [11-12]. However, for NSCLC using BNCT, an in-depth study on improving the dose uniformity has not been conducted. Thus, multi-field irradiation will be studied in BNCT for NSCLC in this study. Moreover, the overdose problem of the skin may also be solved by multi-field irradiation, because it can reduce the maximum dose to skin by sharing the dose to other areas of skin. Furthermore, different multi-field irradiation plans may require different ^{10}B distributions for treatment. Thus, in order to improve the dose distribution, the boron distributions that meet the demands of treatment need to be explored in different multi-field irradiations.

The impacts of multi-field irradiation condition and the boron distribution on the curative effect were studied. This study aimed to compare the dose distributions of BNCT under single-, double- and three-field irradiations, and determine the theoretical Boron-10 distribution under multi-field irradiations in BNCT for lung cancer treatment.

MATERIAL AND METHODS

CHRP-M30 Phantom implementation

A dose calculation model was established based on a Chinese hybrid radiation phantom of 30-year-old male (CHRP-Male 30 phantom) [13] (figure 1). The high-precision male phantom was built using Rhinoceros 5.0 [14] and voxelizer series tools were employed to transform the phantom into a voxel-based model. Considering the geometry construction precision and the calculation speed in the Monte Carlo code used in this study, the phantom was voxelized with a resolution of 0.4 × 0.4 × 0.4 cm^3. Tissue or organ compositions were from the data in ICRU-46 [15] and ICRP-89 [16]. Details of the construction procedure for the phantom geometry and materials have been described in a previous publication [15]. Based on CHRP-Male 30 phantom, the tumor (depth of 7 cm) was

established (figure 1) according to the common NSCLC [1]. The gross tumor volume (GTV) was about 7 × 4 × 3 cm^3 and the cancerous lung was divided into the healthy lungs (black) and the gross tumor volume (GTV) (purple).

The initial concentrations of Boron-10 in tumor and skin were assumed as 30 ppm and 9 ppm [12], respectively. The ratio of boron in skin to that in other healthy tissues was 1.5:1. Here, Boron-10 concentration was considered a constant.

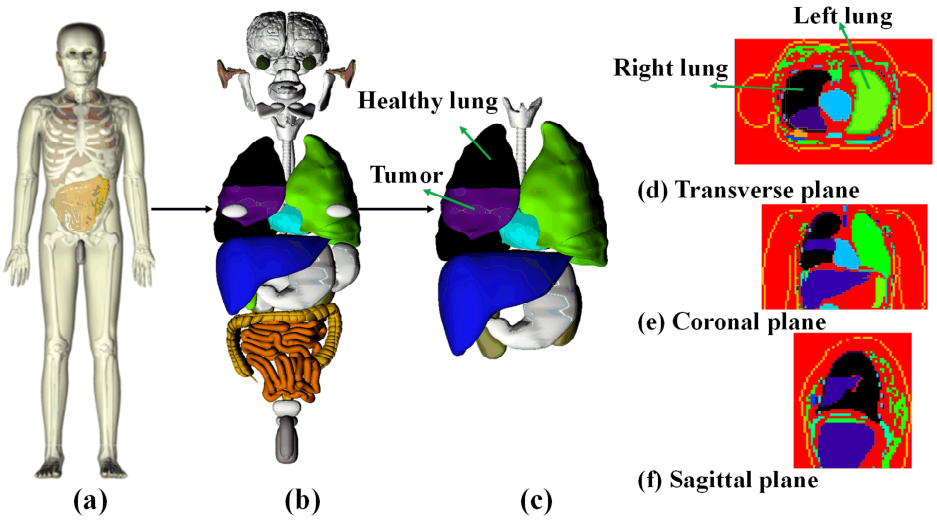

Figure 1. The implementation of lung cancer NSCLC model in the CHRP-Male 30 phantom, and the three views of NSCLC model.

Neutron source

Neutron beam is produced from reactions of 2.5-MeV protons and the 93.1-mm-thick lithium target for accelerator-based boron neutron capture therapy (AB-BNCT) [17]. The total neutron yield of the $^7Li(p, n)^7Be$ reaction is 1.5×10^{12} neutrons per millicoulomb of 20-mA, 2.5-MeV protons (standard error of the neutron yield was < 0.1 %). It is called "Neuboron source", which is under the construction by Neuboron Medtech Ltd. in China. Neuboron source is in accordance with the recommended criteria by International Atomic Energy Agency (IAEA) [18], and its neutron and photon energy spectra were shown in figure 2.

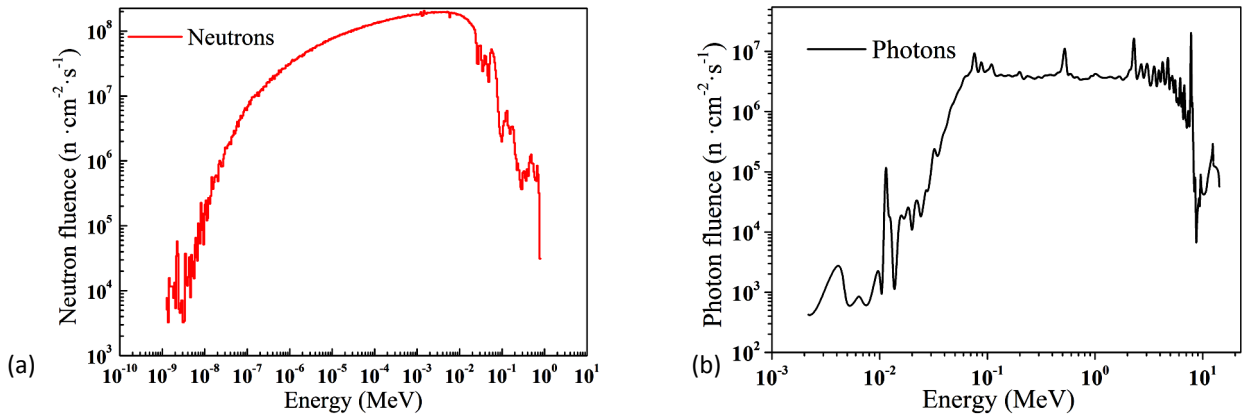

Figure 2. (a) Neutron and (b) photon fluence rate per unit of lethargy as a function of energy for the Neuboron source based on accelerator-based neutron source [15].

Neuboron source was set as disc non-point source. The diameter of the source was 20 cm. It completely encompassed the tumor volume. In addition, its angel distributing was considered as cosine law distribution (cosine=0.67) after being collimated. The epithermal neutron fluence rate of the beam is 1.3×10^9 n/ (cm^2•s). The neutron beam quality was evaluated based on a tissue equivalent material cuboid model. Treatable depth (TD) (the depth at which the tumor dose falls below twice the maximum dose of the normal tissue) and advantageous depth (AD) (the depth at which the dose in the tumor equals the maximum dose in healthy tissue) were calculated. In tissue equivalent material, the maximum dose rate of 4.4 Gy/min was obtained in the depth of 3 cm and the TD and AD were 7.6 cm and 10 cm, respectively (Figure 3). Therefore, Neuboron source could be applied to treat the NSCLC (depth of 7 cm) as defined in part of "CHRP-M30 Phantom implementation".

Multi-field irradiation configurations

In order to study the influence of multi-field neutron source on the dose distribution of lung tumor treatment, three irradiation fields were set as follows: beam 1 ("1"): 30° left anterior of the tumor; beam 2 ("2"): front of the tumor; beam 3("3"): 30° right anterior of the tumor (Figure 4). Multiple-field irradiation (a b c) was adopted and "a", "b", and "c" represented the irradiation time proportions for beam "1", "2", and "3".

First, 1-field and 2-field radiation plans were compared based on treatment time and dose uniformity of tumor. Best plans of 1-field and 2-field were chosen. Second, in order to improve the dose distribution, based on the chosen best irradiation plan, three-field irradiation plans were optimized by adjusting the irradiation time proportions for each beam. Third, to assess the effect of multi-fields, the organs at risk (OARs) dose distributions of 1-field, 2-field and 3-field irradiation plans were simulated.

Dose calculations

The dose of BNCT includes boron dose (D_B), thermal neutron dose (D_{th}), fast neutron dose (D_f), and gamma dose (D_y). The boron dose stems from the interaction of thermal neutrons with ^{10}B atoms in the tissue and goes through the ^{10}B (n, alpha) ^{7}Li reaction. The thermal neutron dose arises primarily from the thermal neutron capture reaction of ^{14}N (n, p) ^{14}C. The fast neutron dose comes from fast neutrons with energies above 10 keV delivering the dose through elastic collisions with hydrogen nuclei in the tissue. The gamma dose is generated from an unavoidable gamma contamination of the beam and the induced gamma dose in the tissues.

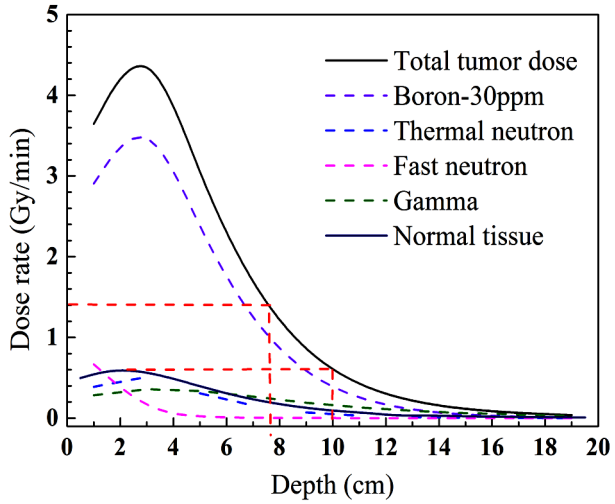

Figure 3. Considering 30/9 ppm of Boron-10 concentration in tumor/skin, depth-dose distribution of tumor and normal tissue in tissue equivalent material.

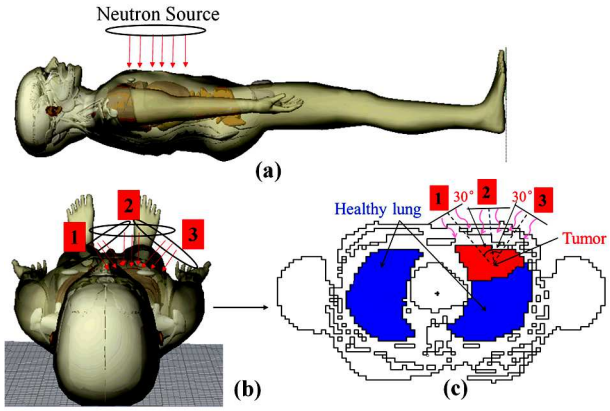

Figure 4. The neutron irradiation planning, including (a) lateral view, (b) vertical view, and (c) the cross section of lung cancer irradiation. Three irradiation fields include beam 1: 30° left anterior of tumor; beam 2: front of tumor; beam 3: 30° right anterior of tumor. Here, healthy lungs (blue) and the GTV (red) were marked.

Photon-equivalent dose HT (Gy) [19] is the photon equivalent dose of the BNCT dose. It was computed by multiplying each absorbed dose component by the relative biological effectiveness (RBE) or the compound biological effectiveness (CBE) factors listed in table 1. Calculation has been done according to equation 1 as follows:

$$HT = \omega_B \times D_B + \omega_{th} \times D_{th} + \omega_f \times D_f + D_y \quad (1)$$

Where ω_B is the radiation weighting factor of dose components (D_B, D_{th}, D_f and D_y) in a particular tissue (table 1).

Monte Carlo configurations

The general-purpose Monte Carlo particle transport code MCNP5 was used to perform the dose calculations [20] in this study. The universe/lattice card was employed in the construction of the human voxel phantom. Each combination of multi-field neutron source and ^{10}B distribution was modeled separately to calculate the dose values. The SDEF card defined disc non-point source for thermal neutrons and different concentrations of ^{10}B were added in Material Cards of tumor and OARs. In addition, the MT card was used to fix the thermal reaction cross section.

The doses in the tumor and organs at risk were calculated using MCNP5 tally F4 combined DE/DF cards. For the dose conversion, point wise KERMA factors and energy mass absorption coefficients from the reference [21] were input with DE and DF cards directly. Tally FM4 card was adopted to convert the normalized dose (Gy/s) to photon-equivalent dose (Gy/min). The number of simulated source particles was set to 1×10^9 in all simulations to make the statistical uncertainty below 2 % for the dose results in all the organs of interest.

Table 1. RBE and CBE factors (radiation weighting factor ω_1) used to convert physical dose (Gy) into photon equivalent dose (Gy)[5].

BNCT dose components	Normal tissues	Tumor	Skin
$^{10}B(n, alpha)^7Li$ (CBE)	1.4	3.8	2.5
Thermal neutron (RBE)	3.2	3.2	3.2
Fast neutron (RBE)	3.2	3.2	3.2
Photon	1	1	1

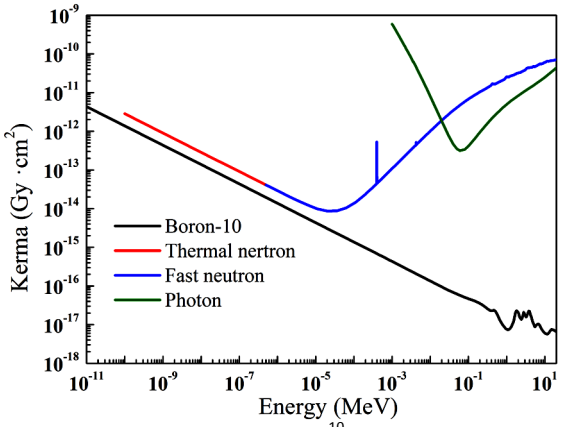

Figure 5. Energy-dependent kerma factors based on 1-ppm ^{10}B for neutron reactions with ^{10}B, thermal neutron, fast neutron, and photon [18].

Treatment assessment

The doses to OARs (including skin and right healthy lung, esophagus, heart, liver, breast, and trachea) are relative higher than any other tissues or organs. Thus, they were selected to characterize dose distribution and estimate the efficacy of BNCT treatment, according to their maximum dose, minimum dose, average dose, and treatment time. In addition, to compare the dose distribution of tumor or OARs, dose volume curves (DVCs) were depicted. Here, in order to obtain the DVCs, software of MATLAB 2013a and

Origin 8.5 were used to process and analyze the dose results based on MCNP calculation.

The minimum dose of GTV should be at least 60 Gy [22]. In addition, homogeneity index (HI) [23] of tumor is defined as equation 2:

$$HI = (HT_{1\%} - HT_{99\%}) / HT_{50\%} \quad (2)$$

Where, $HT_{a\%}$ stands for the photon equivalent dose level corresponding to the a % volume in the DVCs. A smaller HI value indicates a better dose uniformity.

The dose to OARs should meet the following two limitations according to the National Comprehensive Cancer Network (NCCN) [24]. First, more than 1,000 cm^3 of the volume of the healthy lung should receive less than 7.5 Gy to prevent pneumonia. Second, the maximum dose to the heart, spinal cord, skin, esophagus, trachea, ribs, and breast should be less than 22, 14, 26.0, 15.4, 20.2, 30, and 30 Gy, respectively.

RESULTS

The tumor and OARs doses were calculated to compare the dose distributions of BNCT under one-, two- and three-field irradiations. The required boron concentration distributions were simulated in different irradiation conditions.

Influence of multi-field irradiation on tumor dose

One-field irradiation

One-field irradiation (100), (010), and (001) respectively represent the "1", "2", and "3" neutron beam irradiated alone. When it was irradiated by plan (100), the treatment time under the minimum dose in tumor of 60 Gy was 148 min and the dose uniformity of tumor was poor (HI was 1.12). When it was irradiated by plan (010), the dose uniformity in tumor (HI was 0.75) was better than that by the plan (100), and the treatment time was the shortest (70.6 min) (table 2). For the neutron transport of irradiation (010) was directly facing the tumor, thus, it could deliver the dose to the more volume of tumor than (100) and (001) plans at the same depth. With the purpose of shorter treatment time and good tumor dose uniformity, plan (010) was considered as the most advantage plan of the one-field irradiation. In the one-field irradiation, the dose uniformity of tumor was unsatisfactory. This problem also existed in Yen-Wan Hsueh Liu's [9] research, when the one-field neutron source was used to treat the brain tumor, the HI of tumor only reached 0.75-1.14.

Two-field irradiation

Multiple-field irradiation (a b c) was adopted and "a", "b", and "c" represented the irradiation time proportions for beam "1", "2", and "3". Irradiation (011), (110), (101) were used in 2-field irradiation. When it was irradiated by two-field plan, the dose uniformity in tumor was improved (table 3). For the neutrons in two-field irradiation has a better transport in the tumor than one-field irradiation plans. To be specific, the two-field irradiation combines two angles of neutron beams to deliver the different depth doses in the tumor, which could increase the dose uniformity in tumor. Although the dose uniformity of plan (101) was better, considering that in the clinical treatment, too long irradiation time could cause inconvenience and deviations, the plan (011) was superior for the shorter treatment time, whose irradiation plan: the irradiation times of "2" and "3" beams were 38.2 min and 38.2 min.

Three-field irradiation

The above results showed that the plan (010) and (011) had the better dose uniformity in tumor and cost shorter treatment time. Therefore, based on plan (010), the irradiation time ratio of the beam "2" was increased in 3-field irradiation, irradiation plans were set as follows: (132), (142), (152), and (162). Based on plan (011), treatment time proportions of beam "2" and "3" were increased in 3-field irradiation, irradiation plans were set as follows: (122), (133), (144), and (155).

The total treatment time and the dose uniformity in tumor of 3-field irradiation was similar with that of two-field irradiation (table 4). In addition, the dose uniformity in tumor of 3 -field irradiation was better than that of the one-field irradiation. The treatment time of plan

(162) was the shortest among the 3-field irradiation plans, and its tumor dose uniformity was 14.6 % better than that of plan (010). Besides, the tumor dose uniformity of plan (155) was the best among the 3-field irradiation and the radiation time of it was relatively shorter in 3-field irradiation plans. Thus, the (162) and (155) plans were the better irradiation plans among the 3-field irradiations.

The optimized irradiation plan (162) cost the shortest treatment time and irradiation times of beam "1", "2", and "3" were respectively 7.9 min, 47.0 min, and 15.7 min. The optimized irradiation plan (155) showed the better dose uniformity in tumor, and irradiation times of beam "1", "2", and "3" were respectively 6.7 min, 33.3 min, and 33.3 min.

Table 2. Considering 30/9 ppm of ^{10}B concentration in tumor/skin, the tumor dose in one-field irradiation condition.

Source irradiation	1-field irradiation		
	100	010	001
Max(Gy)	189.93	122.86	136.36
Min(Gy)	60.00	60.00	60.00
$H_{50\%}$ (Gy)	114.27	83.29	87.20
Time (min)	148.40	70.60	82.26
HI	1.12	0.75	0.88

Table 3. Considering 30/9 ppm of ^{10}B concentration in tumor/skin, the tumor dose in 2-field irradiation condition.

Source irradiation	2-field irradiation		
	011	110	101
Max (Gy)	108.54	115.38	101.73
Min (Gy)	60.00	60.00	60.00
$H_{50\%}$ (Gy)	81.55	94.63	74.83
Total time for all fields (min)	76.44	97.04	81.66
HI	0.56	0.58	0.51

Table 4. Considering 30/9 ppm of ^{10}B concentration in tumor/skin, the tumor dose in 3-field irradiation condition.

Source irradiation	3-field irradiation				3-field irradiation			
	132	142	152	162	122	133	144	155
Max (Gy)	108.10	108.90	109.89	110.77	107.00	107.14	107.28	107.49
Min (Gy)	60.00	60.00	60.00	60.00	60.00	60.00	60.00	60.00
$H_{50\%}$ (Gy)	77.78	77.34	77.67	78.21	78.26	79.20	79.90	80.04
Total time for all fields (min)	72.36	71.06	70.69	70.60	74.35	73.8	73.71	73.32
HI	0.61	0.63	0.64	0.64	0.60	0.59	0.59	0.58

Influence of multi-field irradiation on OARs dose

One-field and two-field irradiation

According to above results, (010) and (011) irradiation plans were better than other plans of 1-field and 2-field irradiations. Here, to compare the effect of one-field and two-field irradiations, OARs doses were calculated under these two irradiation plans.

The dose to the healthy lung was evaluated to assess physiological impact to the lung. The irradiation dose of the plan (010) was larger than that of the plan (011), because the (011) irradiation plan could reduce the maximum dose to the healthy lung by sharing the dose to other areas of the lung. The maximum dose in right healthy lung and left lung were 16.5 Gy and 10.1 Gy under the irradiation of plan (010). Under the

irradiation plan (011), the maximum dose in right healthy lung and left lung were 15.1 Gy and 6.5 Gy, respectively (figure 6). In this study, the volume of lung was 3177 cm^3, when was irradiated by the plan (010), only 22.5 % of the volume of right healthy lung received more than 7.5 Gy, and 2.5 % of the volume of left lung received more than 7.5 Gy, which achieved the requirement of NCCN guidelines [24]. When it was irradiated by the plan (011), only 3.5 % of the volume of right healthy lung received more than 7.5 Gy, and 0.5 % of the volume of left lung received more than 7.5 Gy. In this way, it fully met the requirements in NCCN guidelines [24] when irradiated with both of these irradiation plans.

There were similarities between 1-field and 2-field irradiation plans. Some OARs (including esophagus, trachea, spinal cord) were far away from the neutron beam, thus their doses were far less than their dose limits. The breast doses were high, but it were still slightly lower than its maximum dose limits (Table 5). However, the skin doses were both higher than its dose limit. There was differences between 1-field and 2-field irradiation plans. Treatment time of the plan (010) was shorter, but its OARs doses were higher than that of the plan (011), and the breast dose and skin dose of the plan (010) were respectively 20.5 % and 20 % higher than that of the plan (011). Therefore, in order to decrease the radiation risk, irradiation plan (011) was better.

In the 1-field and 2-field irradiations, the skin overdose problem also existed, and in the previous study of BNCT, the skin dose exceeded it dose limitation in some conditions [5]. Thus, three-field irradiation need to be further study and it probably decreases the skin dose.

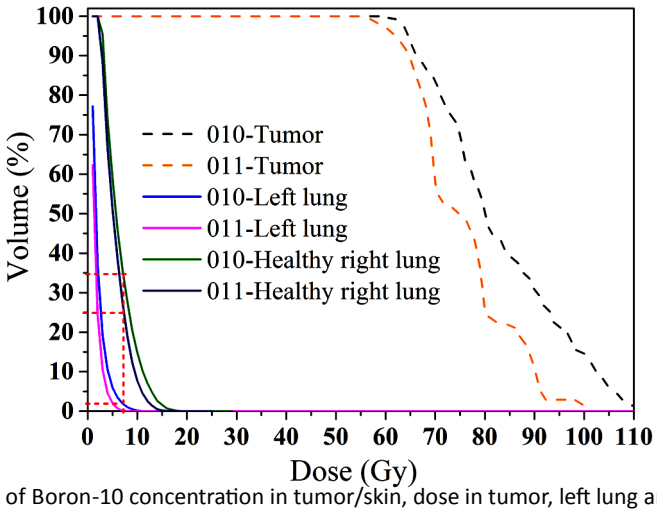

Figure 6. Considering 30/9 ppm of Boron-10 concentration in tumor/skin, dose in tumor, left lung and right healthy lung irradiated with plan (010) and plan (011).

Table 5. Considering 30/9ppm of ^{10}B concentration in tumor/skin, the contrasts of the maximum dose to OARs and their dose limits, in condition of irradiation (010), (011).

OARs	Max Dose (Gy)		Dose limits	Differences (%)	
	(010)	(011)	(Gy)	(010)	(011)
Breast	43.50	36.10	50.00	-13.00	-27.80
Heart	16.10	10.60	22.00	-26.80	51.80
Esophagus	4.11	3.80	20.2	-79.60	-81.20
Trachea	6.20	5.10	20.2	-69.30	-74.70
Skin	48.00	40.00	26.00	+84.90	+53.80
Rib	16.23	16.74	30.00	-45.60	-44.20
Spinal cord	2.55	2.12	14.00	-81.70	-84.80
Cartilage	39.33	28.48	/	/	/

Three-field irradiation

The OARs doses of the 3-field irradiation plans (162) and (155) were obviously lower than that of 2-field irradiation plan (011) (Figure 7). As compared with plan (011), when irradiated by plan (162) and plan (155), the maximum dose in skin fell by 5 % and 15.0 %; the maximum dose in breast dropped by 16.9 % and 25.2 %; and the maximum dose in cartilage dropped by 22.8 % and 29.8 %, respectively. In addition, the dose reductions of OARs were more obvious irradiated by plan (155) than that of plan (162). As a whole, the (155) plan was more appropriate for the good dose distributions.

In different cases, the results of multi-field irradiation is various. The healthy organs doses were reduced in our multi-field irradiation. However, the healthy organs doses increased in multi-field irradiation for brain tumor in Fujimoto's research [12]. In this respect, the multi -field irradiation suggests a better effect on the improvement of dose distribution for this type of NSCLC with BNCT.

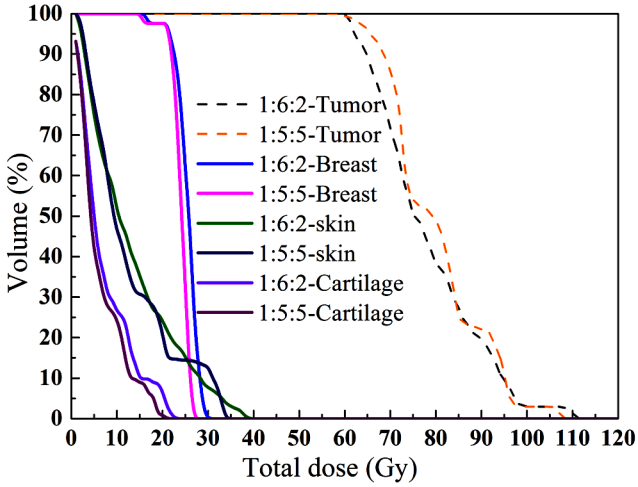

Figure 7. Considering 30/9 ppm of Boron-10 concentration in tumor/skin, the healthy organs doses in (162) and (155) irradiation conditions.

Influence of ^{10}B concentration on dose

The skin dose rate is the largest and the skin has the relatively smaller dose limit than the other OARs, if dose to skin is under the dose limitation of 26 Gy, the dose to other healthy organs will not exceed the NCCN dose limitation [24]. Thus, the skin dose was used to assess the feasibility of the multi-field irradiations. Higher boron concentration will improve the dose deposition. In specific conditions of tumors and neutron sources, the required boron conditions are different. Here, the relationship between skin/tumor dose and their boron concentration was studied to explore theoretical condition of boron concentration for the multi-field irradiations.

One-field irradiation

Under 1-field irradiation (010), as the Boron-10 concentration in tumor/skin increased from 30/6 to 100/18 ppm, tumor dose rate increased significantly, and the treatment time was reduced (figure 8(a)).

When the boron concentration in skin was 18 ppm, skin dose rate was 1.0 Gy/min (Figure 8 (b)); in this case, treatment time should be less than 26 min because of the limit of 26 Gy of skin dose. When treatment time was 26 min, boron concentration in tumor should reach 90 ppm, shown in figure 8(a). Therefore, when boron concentration in skin was 18 ppm, boron concentration in tumor should reach 90 ppm. By analogy, when boron concentration in skin was 6 ppm, boron concentration in tumor should reach 85 ppm. In conclusion, when the boron concentration in skin was between 6-18 ppm, BNCT could be performed with 85-90 ppm of boron concentration in the tumor, which could

ensure the dose in OARs all below dose limit of NCCN. However, it was difficult to achieve this boron concentration requirement in clinic. Therefore, BNCT was not feasible under 1-field irradiation (010) with Neuboron source.

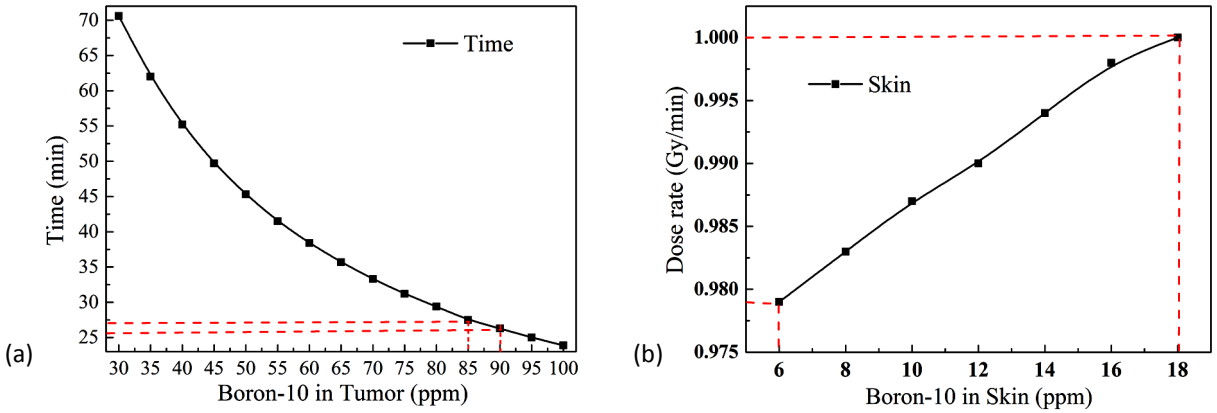

Figure 8. (a) Treatment time of tumor and (b) the maximum dose rates of healthy tissue/organs under 1-field irradiation plan (010) for different boron concentrations.

Two-field irradiation

Under 2-field irradiation (011), the Boron-10 concentration in tumor/skin increased from 30/6 to 65/18 ppm. Treatment time was less than 40 min when the boron concentration in tumor was 60 ppm (Figure 9(a)).

When the boron concentration in skin was 18 ppm, skin dose rate was 0.658 Gy/min (Figure 9 (b)); in this case, treatment time should be less than 39.87 min because of the limit of 26 Gy skin dose limit. When treatment time was 39.87 min, boron concentration in tumor should reach 60 ppm, as shown in figure 9(a). Therefore, when boron concentration in skin was 18 ppm, boron concentration in tumor should reach 60 ppm. By analogy, when boron concentration in skin was 6 ppm, boron concentration in tumor should reach 57 ppm. In conclusion, when the boron concentration in skin was between 6-18 ppm, BNCT could be performed with 57-60 ppm of boron concentration in the tumor, which could ensure the dose in OARs all below dose limit of NCCN.

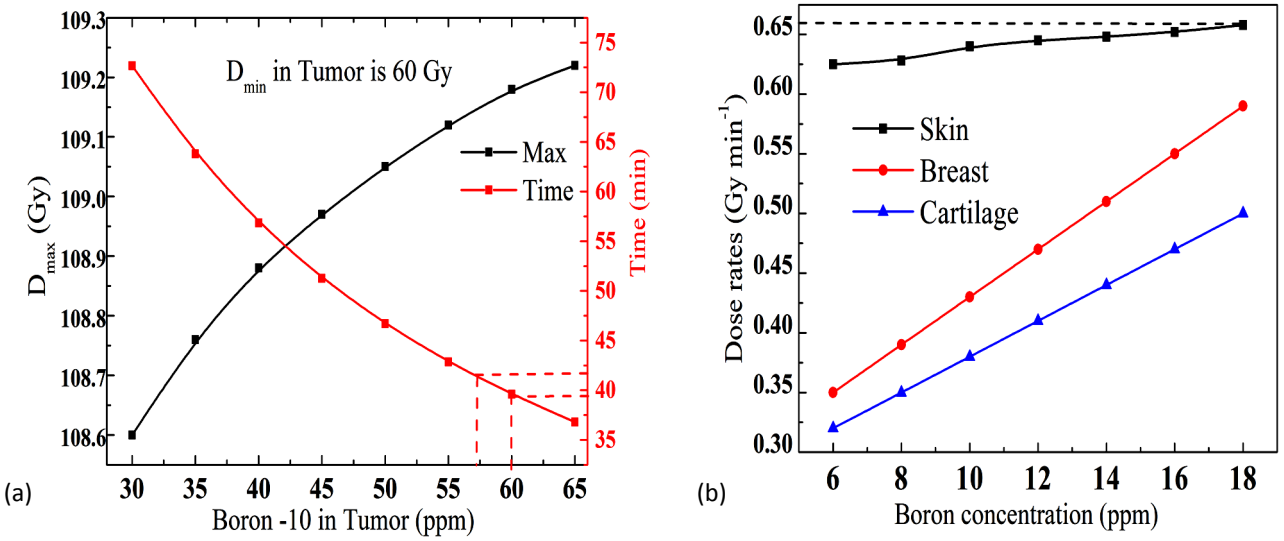

Figure 9. (a) The maximum dose and treatment time of tumor and (b) the maximum dose rates of healthy tissue/organs under 2-field irradiation plan (011) for different boron concentrations.

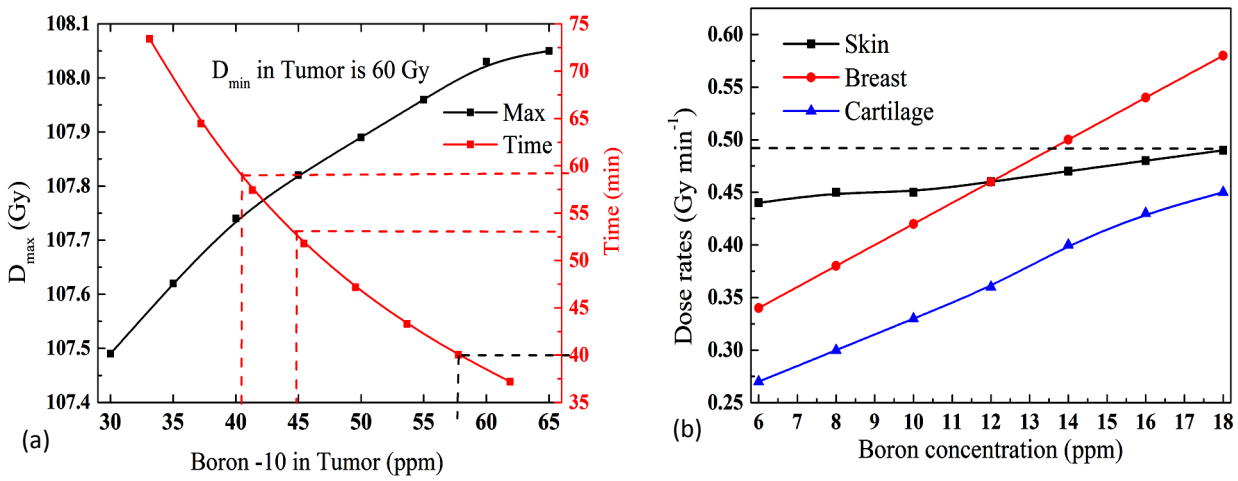

Figure 10. (a) The maximum dose and treatment time of tumor and (b) the maximum dose rates of healthy tissue/organs

Three-field irradiation

Under 3-field irradiation (155), Boron-10 concentration in tumor/skin increased from 30/6 to 65/18 ppm. When the boron concentration in skin was 18 ppm, skin dose rate was 0.49 Gy/min (Figure 10(b)); in this case, treatment time should be less than 53 min because of the limit of 26 Gy of skin dose. When treatment time was 53 min, boron concentration in tumor should reach 45 ppm, as shown in figure 10(a). Therefore, when boron concentration in skin was 18 ppm, boron concentration in tumor should reach 45 ppm. By analogy, when boron concentration in skin was 6 ppm, boron concentration in tumor should reach 41 ppm. In conclusion, when the boron concentration in skin was between 6-18 ppm, BNCT could be performed with 41-45 ppm of boron concentration in the tumor, which could ensure the dose in OARs all below dose limit of NCCN. It was easier to achieve the required boron concentration distribution in clinical under (155) irradiation, as compared with 1-field and 2-field irradiations.

By the above analysis, the boron concentration requirement is high when according as the tumor reaches the prescribed-dose of 60 Gy. Thus, a more suitable prescription criterion should be proposed to decrease the skin dose, and the feasibility of BNCT treatment perhaps could be assessed based on the skin dose limitation [9, 12].

DISCUSSION

The common NSCLC (depth of 7 cm) is treated with BNCT using Neuboron sources. The impacts of multi-field irradiation condition and the boron distribution on the dose distribution were studied. The multi-field irradiations could improve the dose distribution and the feasibility of BNCT for NSCLC. The theoretical distributions of Boron-10 were obtained to meet the treatable requirement of BNCT, which could provide a reference for NSCLC using BNCT with multiple-field irradiation of Neuboron sources in the future.

For one-field irradiation, BNCT was not feasible under one-field irradiation plan (010) with Neuboron source. Because it was difficult to achieve the boron concentration requirement in clinical treatment. Two-field irradiation plan (011), as compared with one-field irradiation, needed a longer treatment time and showed a better tumor dose uniformity. Besides, the maximum dose to OARs decreased obviously. When the boron concentration in skin was 6-18 ppm, BNCT could be performed with 57-60 ppm of boron concentration in tumor. In order to improve the dose distribution, three-field irradiation plans were optimized by adjusting the irradiation time proportions for three beams. Three-field irradiation plan (155) was proposed, and as compared with two-field irradiation, OARs dose decreased and the lower

boron concentration was required. When the boron concentration in skin was 6-18 ppm, BNCT could be performed with 41-45 ppm of boron concentration in tumor.

As compared with the conventional photon radiotherapy—the researches of Cyriac [25] and Qibin [26] on the conformal radiation therapy, the effect of dose improvement in our multi-field irradiation were similar with their effects in conformal radiation therapy, and the healthy organs dose were reduced. In our work, the tumor dose uniformity was improved by multiple-field irradiation, and the HI was reduced from the 0.75 to 0.56. Its effect was similar with the effect of multi-field source in BNCT for brain tumor [12] for whose HI was reduced from the 0.90 to 0.54. Besides, the maximum doses to OARs were decreased under two- and three-field irradiation for NSCLC. Its effect was better than the effect of multi-field BNCT for brain tumor [12], for the OARs dose increased in multi-field for brain tumor. In addition, some advanced neutron beams were designed to improve the tumor dose [2-3, 10-11]. Here, as compared with the dose improvement effects of multi-field irradiation, the neutron beam characteristics improvement suggests a less effective effect on improving dose uniformity of tumor, for their mixed energy neutrons made it difficult to deliver the dose to tumor uniformly in a single direction of irradiation. Furthermore, a more suitable prescription criterion needs to be proposed to decrease the skin dose, and the feasibility of multi-field treatment perhaps could be studied based on the skin dose limitation [9, 12].

Admittedly, some factors including neutron source (for example, beam collimation, beam attenuator, different beam entry angle) and ^{10}B concentration dynamics could affect the dose distribution in clinical application, and here these multi-field irradiation studies were based on an ideal irradiation condition. To realize the application of multi-field irradiation in practice, some factors influencing the treatment effect should be considered. First, multi-field irradiation plans are diverse according to various types of tumors. The implementations of multi-field irradiation need a number of alternative plans and necessary dose verifications. Second, the boron concentration is patient-specific and changed with time. We will study the pharmacokinetic model for ^{10}B concentration, and apply it in our future work to ensure that the treatment planning is coincident with actual condition. In addition, there are some difficulties in multi-field irradiation operation. It is worth looking forward to setting up a rotatable device (such as a gantry) to rotate neutron source for multi-field treatment. Furthermore, the switching time of neutron source should be paid attention to in practice because it may affect the ^{10}B concentration distribution.

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