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Boron Neutron Capture Therapy for Breast Cancer during Pregnancy: A Feasibility Study

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ARTICLEINFO	ABSTRACT
<i>Article type:</i> Original Paper	<i>Introduction:</i> the present study aimed to evaluate the feasibility of boron neutron capture therapy (BNCT) for breast cancer (BC) incidence during pregnancy.
Article history: Received: Aug 24, 2019 Accepted: Dec 12, 2019	Material and Methods: Computational models of pregnant women at 3- and 6- month gestational ages were used with two different simulated tumors in their left breasts. The Monte Carlo simulation of tumor irradiation by thermal and epithermal output beams of in-hospital neutron irradiator was performed in five directions. The optimum treatment plans as a combination of the irradiation directions and output beams
<i>Keywords:</i> Boron Neutron Capture Therapy Breast Cancer Pregnancy	were then assessed using an optimization code. Results: Based on the findings of the present study, the total irradiation time of ≤ 10 min was needed to deliver a prescribed dose of $R_x = 24.4$ Gy-Eq to gross tumor volume (GTV) in a BNCT single fraction. The dosimetric properties and volume metrics of the optimized treatment plans were obtained and the dose- volume histogram (DVH)-based metrics, were compared to those from conventional radiotherapy. It has been shown that the dose to both target volume and organs at risk (OARs) were within clinically acceptable dose constraints throughout the course of a single- fraction BNCT. Moreover, the fetal dose (~4.8 mGy-Eq) was well below the threshold for secondary cancer incidence (10 mGy) in the first trimester of pregnancy, while for the second trimester of pregnancy, it was much higher (~35.5 mGy-Eq). Conclusion: Regarding the DVH metrics for GTV, maternal OARs, and the fetus, the studied treatment modality was an appropriate alternative treatment, especially for BC incidence in the first trimester of pregnancy.

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Introduction

Cancer and pregnancy coincidence is a completely challenging condition because saving both the mother and her unborn child is of prime importance. The incidence of cancer during pregnancy is approximately within 17-100 in 100,000 pregnancies [1]. Breast cancer (BC) is one of the most common malignancies occurring during pregnancy and as more women delay childbearing, the incidence of BC in pregnancy is expected to increase [2]. When treating BC during pregnancy, it is recommended to adhere to standard treatment of the non-pregnant patients [1] which may have detrimental effects on the fetus. Moreover, treatment should not be delayed unless the woman is within 2-4 weeks of delivery. Therefore, the physician may be forced to complete the treatment after premature delivery (or pregnancy termination) to save the mother [1]. The major therapeutic options for BC include surgery, chemotherapy, using trastuzumab, and radiotherapy (RT). Each of these treatments could be used alone as monotherapy or in combination with other treatments. For most BC cases, adjuvant treatments are used post-operatively. However pre-operative treatments are currently considered a possible and effective option for patients with early, locally advanced, or inflammatory BC [3]. The pre-operative treatment strategy would be a highly cost-effective choice if targeted RT is used instead of conventional RT in the near future [4, 5]. Nowadays, the main and the only safe treatment during pregnancy is surgery. However, it does not effectively remove all microscopic cancerous cells. Therefore, a debate exists over the fact that whether there is any safe adjuvant treatment to surgery for pregnant patients. The chemotherapy regimen is not allowed in the first trimester and only allowed in the second and third trimester of pregnancy. Common targeted therapy using trastuzumab is forbidden, as Both of these treatments well [1]. using pharmaceuticals that are not limited to the maternal tissues and could transfer through the placenta to the fetus. In addition, RT is not suggested due to the high fetal dose and recommended to be postponed until after the delivery [6]. Carcinogenic effects of radiation are including, the incidence of childhood cancer and

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leukemia, with the chance of 0.2-0.3% at low doses and 1.4% at 10 mGy fetal dose (up to 15-year-old). Based on the available data in the literature, conventional RT leads to fetal doses quite higher than 10 mGy. This issue makes it prohibited to prescribe RT during pregnancy. This issue brings the question to the fore whether an RT with a high dose gradient outside the target could be proposed to deliver the prescribed dose to the clinical target volume and keep the fetal dose below 10 mGy. Among the RT modalities. it is reported that interstitial brachytherapy, proton therapy, and BNCT are able to produce, such a high dose gradient. More importantly, BNCT is regarded as a targeted therapy that could wipe out the malignancy in one single fraction. Consequently, focusing on the BNCT as a preoperative RT, as well as its benefits and risks is the scope of the current study. The BNCT is an external RT that uses a combination of neutron irradiation and perfusion of ¹⁰B into the tumor cells to treat cancer. Using this technique, the ¹⁰B (n, α) ⁷Li reaction with its lethal effect occurs selectively in cancerous cells and kills them [7]. This selectivity leads to improved therapeutic efficiency and confines the destructive effects of radiation to boron-containing cells. Moreover, several studies investigated BNCT as a treatment option for different cases of BC [8-11]. However, the feasibility of BNCT during pregnancy was not yet studied; therefore, the present research was aimed to evaluate this feasibility. In this respect, two different tumors were placed at two different locations separately inside the breasts of pregnant patient models. The pregnant phantoms were at two gestational ages and then were simulated under the irradiation of in-hospital neutron irradiator (IHNI), a new, small (30 kW) reactor, specifically designed for BNCT near a hospital site in Beijing, China. The optimum treatment approach was then obtained using an optimization code. Consequently, the current research attempted to show the great potential of BNCT for the sensitive group of pregnant patients and its superiority over conventional RT.

Materials and Methods

Monte Carlo simulations

Geometry of computational phantoms

Our previously developed 3- and 6-month pregnant phantoms were used (Figure 1). These pregnant phantoms are reference models developed on the basis of adult female *International Commission on Radiological Protection* reference phantom [12, 13]. The fetal models include 20 different organs and tissues. The information about the elemental composition of fetal tissues can be found in previous studies [12, 13]. The two first trimesters of pregnancy were selected due to the following considerations. Firstly, undesired irradiation of embryo (fetal ages<8 weeks) generally leads to spontaneous abortion [13]; therefore, there is no need to consider those early fetal ages. Therefore, the fetus at 13 weeks' gestation (3-month) is an appropriate candidate for our simulation. Secondly, for ages ≥ 28 weeks, premature delivery could be prescribed [14, 15]. As a result, 26 weeks was considered an upper age limit in the simulations.

Simulated breast tumors

The tumors were considered to be simple 3 cmdiameter spheres in two breast locations, including the upper outer quadrant (Quad) and near nipple (Nipp). The tumor size was chosen based on cancer stage II [16,17] and the tumor location was selected where the probability of tumor occurrence was higher [18]. The researchers simulated the tumors within the left breast, as the BC occurs equally in both sides and the left breast irradiation presents a higher risk of cardiac involvement.

Boron compound uptakes

Different values of boron uptake are reported for the two common available boron delivery agents, namely Boronophenylalanine (BPA) and Sodium Borocaptate [19]. The ratio of tumor to healthy tissue boron uptake (T: H) ranges from 2:1 to 8:1 for the mentioned boron agents [10,20]. Although there are some reports of obtained 12:1 and 35:1 ratios of oligomeric phosphate diesters boron agent uptake for HER2+ BC in animal studies [10], there are no reports on the human tissues. For the BPA-f compound in glioblastoma multiforme treatment, a boron concentration in the tumor is commonly assumed to be 3.5 times higher than that in blood [21]. Therefore, a uniform boron concentration of 72 ppm ¹⁰B was assumed to be in the tumor. Since drug uptake from blood is different in various tissues, a boron concentration of 16.8 ppm, 24 ppm, and 28 ppm uptake was considered in bone, soft, and skin tissues, respectively [22]. As a result, a conservative T: H ratio (i.e., tumor to healthy soft tissue) of 3:1 was assumed. To the best of the researchers' knowledge, there is no research or published report on boron uptake by the fetus. Therefore, the boron uptake of soft tissue (24 ppm) was considered for the fetus. Further studies are necessary in this regard to estimate the exact fetal uptake.

Neutron irradiator properties

The neutron irradiator is the IHNI, an in-hospital reactor operating at 30 kW in Beijing, China, with two separated output beams (i.e., thermal and epithermal beams). The Monte Carlo-based spectra of the beams were validated by measurements [23]. The spectra of the thermal beam mainly consist of thermal neutrons; however, it contains epithermal neutrons, fast neutron, and additional gamma-ray components. The same is true for the epithermal beam. The radius of the beam aperture was measured at 6 cm.





Figure. 1. a) Three-dimensional view of 3- and 6-month fetal models, b) Monte Carlo particle transport code plot of pregnant phantoms

Table 1.	Particle	flux ((cm ⁻²	s ⁻¹)	for	different	in-hospital	neutron	irradiator	outputs
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				Flux $(cm^{-2} s^{-1})$	
IHNI o	NI output	Source particle	Beam aperture (radius 0-6 cm)	Beam leakage (radius 6-10 cm)	Beam leakage (radius 10-15 cm)
Thomas	alhaam	Neutron	1.75E9	8.95E7	1.33E7
Thermal bear	ai beam	Photon	2.10E7	1.49E7	2.36E7
En Manuel I.	Neutron	5.30E8	7.05E7	5.10E6	
Epithe	mai beam	Photon	3.08E7	2.35E7	6.76E6

IHNI: In-hospital neutron irradiator

For the neutron components, the beam radius expands to 10-15 cm to take into account the neutron leakage. Table 1 illustrates the source flux for different components of the IHNI beam. Details of the energy, angular, and spatial distributions of the source were provided by the manufacturer. According to the angular distribution of the source, the maximum flux occurs at 25 degrees relative to the central beam axis.

Dose calculation considerations

The physical dose is assumed to be compromised of several dose components with different biological effects. In order to make a comparison between different techniques of RT, the photon equivalent dose (i.e., the biologically weighted dose) should be calculated. In this respect, all dose components, including γ -ray, recoil proton, nitrogen capture, and ¹⁰B capture doses were scored separately using the Monte Carlo N-Particle extended 2.6.0 code. The simulation for each of the beam orientations was performed with 2×10 ⁹ primary photon histories and 1×10 ⁹ primary neutron histories. The mesh tally (type 1) dose estimator was used by setting the dose keyword MSHMF, including the flux-to-kerma conversion coefficients from [24]. The size of

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the rectangular mesh grid was assumed to be conformed to the size of the phantom's voxel $(1.775 \times 1.775 \times 4.84 \text{ mm}^3)$. Molecular effects and scattering treatment, *S* (α , β), were also considered in our calculations for neutrons with energies below 4 keV (MTm card). The biologically-weighted dose (D_W) is the summation of all dose components multiplied by an experimentally measured weighting factor:

$$D_{W} = (\gamma - ray \ dose) + (recoil \ proton \ dose \cdot RBE_{n}) + (nitrogen \ capture \ dose \cdot RBE_{N}) + (^{10}B \ capture \ dose \cdot CBE)$$
(1)

In which relative biological effectiveness (RBE) and compound biological effectiveness (CBE) factors were used. The common unit used for the biologicallyweighted dose was RBE-Gy or Gy-Eq. Based on the study carried out by Horiguchi et al., the RBE is 2.5 for both recoil proton dose and nitrogen capture dose. The CBE factor is also considered to be 3.8, 2.5, 2.3, 4.25, and 1.35 for tumor, skin, lung, liver, and heart tissue, respectively [22].



Figure 2. Three-dimensional views of simulated tumors in upper outer quadrant (Quad) and nipple neighborhood (Nipp), as well as the schematic directions of irradiation beams for the 3m-Nipp situation

Irradiation configuration

Five irradiation directions were considered to cover all the spatial angles, including straight to the breast (anterior-posterior) and four other directions along 45° rotation with respect to the straight direction (right, left, up, and down). Moreover, Figure 2 illustrates the schematic configuration of irradiation directions. The appropriate beam center was determined based on the tumor location. The distance between the fetal neck and the beam center was 41 cm and 26 cm for 3- and 6month models, respectively.

Optimization phase

There were several dosimetric indices which were considered to estimate a well-defined treatment plan. First of all, the tumor to normal tissue dose ratio (TNR) was defined as the ratio of average tumor dose to the maximum dose received by a single mesh element of normal tissues. In the optimization phase, it was attempted to maximize the TNR as one of the most important dosimetric indices in the treatment plan. In addition, the tumor dose rate was another important feature. It was attempted to keep the average tumor dose rate high enough to prevent prolonged treatment time. The dose uniformity inside the tumor was the other important factor, as well. In this respect, the coefficient of variation (CV) was introduced as a uniformity index and should be minimized in the optimization process. The CV is calculated as follows:

$$CV = \frac{\sqrt{\frac{1}{N} \sum_{i=1}^{N} (d_i - \bar{d})^2}}{\bar{d}}$$
(2)

where the d_i is the ith mesh volume of the tumor receiving a dose, d is the average receiving dose by the tumor, and N is the total number of points considered inside the tumor. The authors evaluated all possible treatment plans as combinations of different output beams (i.e., thermal or epithermal), and different irradiation directions (straight, up, down, left, and right). They used the forward method to optimize the dosimetric indices following below constraints:

- The TNR should not be lower than 90% of the maximum TNR.
- The average tumor dose rate should not be lower than 85% of the maximum value obtained for the average tumor dose rate.
- The CV of the tumor dose distribution should be minimized.
- The fetal dose must be kept minimized.

where the last constraint was substantially important to be satisfied. Considering these constraints, the 10 most favorable combinations were obtained for each tumor location and gestational age. These combinations have little differences in dosimetric values. Therefore, it is desirable to select the most convenient combination which should not be consisted of many different directions or irradiator outputs. Moreover, simpler combinations lead to patients' comfort and more accurate results.

Prescribed dose to gross tumor volume in a boron neutron capture therapy single fraction

According to the protocols for BC patients treated with pre-operative RT, a complete local control would be achieved by a fractionated dose of 60 Gy [5]. However, BNCT could be prescribed in a single fraction without exceeding the organs at risk (OARs) constraints. To evaluate the corresponding single dose, the biologically effective dose (*BED*) is used:

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) \tag{3}$$

where *n* is the number of fractions, *d* is the dose per fraction, and the product (*nd*) is the total physical dose delivered to the target volume. The α and β are radiobiological parameters (linear-quadratic parameters) related to the irradiated tissue/organ. For any given α/β , treatment schedules that produce identical BEDs are said to be radiobiologically isoeffective. It is common to assume 10 Gy for the α/β ratio of tumors. However, for breast tumors, this ratio may be much lower than the usual assumption. In vitro experiments in human breast



carcinoma cell lines suggested an α/β ratio of about 4 Gy [25]. Therefore, equation (3) yields that a dose of 60 Gy in a 2 Gy/ fraction scheme corresponds to a single dose of about 17 Gy using the $\alpha/\beta = 4$ Gy. Furthermore, a single fraction dose of 24.4 Gy is biologically equivalent if we use the $\alpha/\beta = 10$ Gy. The later one was assumed as an upper extreme to be confident about tumor local control.

Dose-volume histogram metrics

In order to depict the figure of merit of a treatment plan and also make a comparison between various treatment techniques, it is required to report the dosevolume histogram (DVH), as well as a set of related parameters. The parameter VX% is defined as the percent of volume receiving at least X% of the prescribed dose. The V100% is commonly used in the treatment planning systems and is often tried to be > 90% of the target volume. In addition, V95% is considered to be > 95% of the target volume. For the OARs, the common parameters of DMAX, D10cm³, V10Gy, V5Gy, and V2Gy were used to determine the eligibility of BNCT for BC pregnant cases and to easily compare the results of the current study with conventional RT. The DMAX/DMIN was assumed to be the min/max dose to the 0.015 cm^3 volume of the organ receiving the highest/lowest doses. The D10 cm³ was determined as the min dose to the 10 cm³ of the organ that receives the highest doses. The Vx Gy was also considered as the volume receiving more than x Gy.

Results

Optimum treatment plans

The optimum treatment plans are determined for all four situations studied in the present study. The contribution of each output beam and irradiation direction (%) to the optimum treatment plan is demonstrated in Figure 3. As can be seen, the epithermal part of the beam plays a greater role in optimum treatment plans, especially when the tumor is not located deep inside the breast tissue. Moreover, Table 2 depicts the dosimetric indices and treatment times of the proposed treatment plans. As shown, the evaluated TNR for optimum plans were ranged from 2.98 to 3.89, which is satisfying in therapeutic procedures. Furthermore, the CVs of tumor dose are lower than 11.4% except in one situation (17.8%) where the tumor located deep inside the breast (6m-Nipp). Considering the prescribed dose of 24.4 Gy-Eq to the target volume, the total irradiation times were estimated to be from 4.8 to 10.1 min, which seems reasonably practical. Several other dosimetric factors of suggested plans are demonstrated in Table 3.

Target volume (GTV)

Table 3 demonstrates the biological-weighted dose to the target and maternal OARs. The DVH is also provided from the proposed treatment plans (Figure 4). As shown in Table 3 and Figure 4, the GTV dose ranged within 17.3-45.5 Gy-Eq in a single-fraction BNCT. Moreover, the target coverage factors are presented in Table 3. The V100% is greater than 90% for all four studied situations meaning that more than 90% of target volume received 100% of the prescribed dose (Rx=24.4 Gy-Eq). Furthermore, V95% showed that the delivered dose to 95% of the target volume was higher than 95% of Rx. It should be noted that the results were based on the assumption that $\alpha/\beta=10$ Gy. It could be concluded that if α/β was less than this value as previously estimated by several studies [25], even the min dose to the tumor (17.3 Gy-Eq) would be higher than the dose required to completely ablate the tumor. Figure 5 also indicates a two-dimensional view of isodose contours in the unit (Gy-Eq). As can be seen, the target coverage is quite adequate in this slice.



Figure 3. Irradiation combination composed of various output beams and irradiation directions for the proposed treatment plans

Table	2.	The tumor	to normal	tissue	dose ratio,	coefficient	of var	iation,	and in	radiation	time	of the	pro	posed	treatment	plan	ıs

E-t-1	T	Abbreviated	TND	CU(0)	Irradiation time (min)			
Fetal age	Tumor location	name	INK	CV (%)	Total	Thermal	Epithermal	
6-month	Nipple neighborhood	6m-Nipp	3.64	17.77	10.1	1.7	8.4	
6-month	Upper outer quadrant	6m-Quad	3.84	9.20	5.9	0.0	5.9	
3-month	Nipple neighborhood	3m-Nipp	2.98	4.95	4.8	2.2	2.5	
3-month	Upper outer quadrant	3m-Quad	3.77	11.38	6.3	1.3	5.1	

TNR: Tumor to normal tissue dose ratio, CV: coefficient of variation

Table 3. Estimated dose-volume histogram metrics of the tumor and maternal organs at risk for the four simulated situations

	DVII matrice	Gestational age-Tumor location								
	DVH metrics	6m-Nipp	6m-Quad	3m-Nipp	3m-Quad					
	$D_{MAX} (Gy-Eq)^{1}$	45.5	33.4	28.5	35.4					
Tumor	$D_{MIN}(Gy-Eq)^2$	19.7	22.0	21.2	17.3					
Tunior	V100%	94.0%	91.4%	91.1%	93.4%					
	V95%	95.7%	98.2%	97.8%	95.2%					
Q1_:	D _{MAX} (Gy-Eq)	10.0	5.6	8.8	8.3					
SKIN	D10cm ³ (Gy-Eq) ³	5.8	3.9	5.9	5.9					
	D _{MAX} (Gy-Eq)	9.8	7.3	6.3	7.7					
Left breast	V5Gy	47%	25%	14%	23%					
	V10Gy	0%	0%	0%	0%					
Left	D _{MAX} (Gy-Eq)	4.3	5.5	4.5	6.8					
lung	V5Gy	0%	0%	0%	0%					
Heart	D _{MAX} (Gy-Eq)	3.3	3.0	2.9	2.8					
Heart	V5Gy	0%	0%	0%	0%					
T :	D _{MAX} (Gy-Eq)	4.5	2.2	2.6	1.7					
Liver	V5Gy	0%	0%	0%	0%					
0.1	D _{MAX} (Gy-Eq)	0.8	1.0	0.4	0.8					
Spieen	V2Gy	0%	0%	0%	0%					

 ${}^{1}D_{MAX}$ is the minimum dose to the 0.015 cm³ volume of the organ receiving the highest doses

²D_{MIN} is the maximum dose to the 0.015 cm³ volume of the organ receiving the lowest doses

³D10cm³ is the minimum dose to the 10 cm³ of the organ that receive the highest doses

DVH: Dose-volume histogram, OARs: organs at risk

To estimate the risk of OARs late complications, the OARs doses were compared to the results of a study carried out by Emami on the tolerance of normal tissue to the therapeutic radiation. According to the aforementioned study, if the lung tissue receives a mean dose of 20 Gy, there will be a 20% risk of radiation pneumonitis. For heart tissue, Emami stated that if 25% of the heart tissue received > 6 Gy, there will be a risk of < 1% of cardiac mortality at 15 years after the treatment. In addition, he reported a < 5% rate of radiation-induced liver disease with the mean liver dose of ~30 Gy in patients without preexisting liver disease

or primary liver cancer [26]. The maximum biological weighted dose of lung, heart, and liver in the suggested BNCT therapy did not exceed 5 Gy-Eq (Table 3). Therefore, the OARs doses were well below these values and there was no risk of the late effects.





Figure 4. Dose-volume histograms for tumor and organs at risk, for different gestations and tumor locations



Figure 5. A two-dimensional plot of isodose (Gy-Eq) contours for the 6-month pregnant phantom with breast tumor at nipple neighborhood

Discussion

According to the results of the present study, a single fraction of BNCT with a treatment duration of a few mins and a prescribed dose of 24.4 Gy to the GTV was able to kill the tumor cancerous cells, as well as spare the OARs. However, the presence of the fetus was the limitation of the treatment during pregnancy. In order to investigate the fetal dose constraint in the optimization process, additional optimization programs with the last omitted constraint (the constraint on fetal dose) were performed. The selected combinations were approximately the same as the reported ones (in Table 2 and Figure 3).

Through observation of the first three constraints, it was determined that the fetal dose constraint was independent of the treatment plan specification. Notwithstanding the evidence, in order to examine the feasibility of BNCT for BC during pregnancy, the treatment plan should be justified considering the risks and benefits to the mother and her fetus. Delivering 24.4 Gy-Eq to the tumor will lead the fetal physical dose of \leq 4.7 and \leq 30.9 mGy for 3- and 6-month pregnant patients, respectively (Table 4). Being between 0.1% and 0.3% of the prescribed dose in the first trimester, these values of physical doses were much lower than the case of RT, [27]. As a result, the fetal dose would be about 60 to 180 mGy in RT, whereas it is much lower than the threshold of 10 mGy in the suggested treatment plans.

In the late second trimester, the fetal physical dose is considerable (\leq 30.9 mGy) and the secondary cancer chance will be more than 1.4%; as a result, certain considerations should be taken into account. However, the amount of fetal dose is very lower than the case of external RT which is reported to exceed 2 Gy as the fetus grows and advances toward the radiation field [28].

The biological-weighted dose to the fetus was also reported in Table 4. The results showed a fetal biological-weighted dose of ≤ 4.8 and ≤ 35.5 mGy for 3and 6-month pregnant patients, respectively. The biological-weighted dose to the fetus is up to 15% higher than the physical dose. However, the positive point is that the photons are the major contributor to the fetal dose. Furthermore, the results indicated that since these photons were not primary photons emitted from the source beams, they could be stopped by covering the mother's stomach with a photon shield. The photons were induced by neutrons inside the body; consequently, the resultant dose was inevitable.

Conclusion

Based on the findings of the present study, BNCT was virtually examined for pregnant patients diagnosed with stage II BC. Monte Carlo simulations of irradiated breast tumors at 3- and 6-month gestational ages were performed and optimum treatment for each case was planned. The results showed that the total treatment time to deliver a prescribed dose of 24.4 Gy-Eq to the GTV was less than ~10 min, which was reasonably practical. In addition, it has been shown that the fetal dose did not exceed 10 mGy for the first trimester of pregnancy and had no stochastic risk of secondary cancer, whereas higher values of fetal dose (~35.5 mGy) were obtained for the second trimester. Therefore, the clinical application of BNCT in the second trimester of pregnancy should be considered with caution. Moreover, the OARs dose constraints for RT were well satisfied with a single-fraction BNCT. In conclusion, pregnant patients in the first trimester of pregnancy could be well treated by BNCT with minimal effects on the fetus and maternal OARs.

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