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

Abstract:

Purpose: To evaluate the feasibility of boron neutron capture therapy (BNCT) for breast cancer occurs during pregnancy.

Methods: Computational models of pregnant women at 3- and 6-month gestational ages were used with two various simulated tumors in their left breasts. The Monte Carlo simulation of irradiating the tumors by thermal and epithermal output beams of in-hospital neutron irradiator (IHNI), were then performed in five directions. The optimum treatment plans as a combination of the irradiation directions and output beams were then assessed using an optimization code written in this work.

Results: According to the results of this study, the total irradiation time of ≤10 minutes is needed to deliver a prescribed dose of \( R_X = 24.4 \text{ Gy-Eq} \) 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 with those from conventional radiotherapy (RT). 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) is well below the threshold for secondary cancer incidence (10 mGy) at first trimester of pregnancy, while for second trimester of pregnancy is much higher (≈35.5 mGy-Eq).
**Conclusion:** Regarding the DVH metrics for GTV, maternal OARs and the fetus, the studied treatment modality is an appropriate alternative treatment especially for breast cancer occurring at the first trimester of pregnancy.

**Keywords:** Boron neutron capture therapy; breast cancer; pregnancy; treatment plan
1. Introduction

Cancer and pregnancy coincidence is a completely challenging condition because it is crucial to save both the mother and her unborn child underwent available cancer treatments. The incidence of cancer during pregnancy is approximately from 17 to 100 in 100 000 pregnancies [1]. Breast cancer (BC) is one of the most common malignancies occurs 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 patient [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. Hence the physician may force 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 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 postoperatively, however preoperative treatments are currently considered as a possible effective option for patients with early, locally advanced or inflammatory BC [3]. The preoperative treatment strategy would be a highly cost-effective choice if targeted RT can be used instead of conventional RT in near future [4, 5]. Heretofore, the main and the only safe treatment during pregnancy is surgery. However, it does not effectively remove all microscopic cancerous cells. Therefore, this question comes to mind that if there is any safe adjuvant treatment to surgery for pregnant patients. The chemotherapy regimen is not allowed in the first trimester and confined in the second and third trimester of pregnancy. Common targeted therapy using trastuzumab is forbidden as well [1]. Both of these treatments using pharmaceuticals which are not limited to the maternal tissues and could transfer through the placenta to the fetus. RT is also not suggested due to the high fetal dose and recommended to be postponed until after delivery [6]. Carcinogenic effects of radiation are generally the incidence of childhood cancer and 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 lead to fetal doses quite higher than 10 mGy. This issue makes it prohibited to prescribe RT during pregnancy.
This brings the question to the fore that if we could propose a RT with a high dose gradient outside the target 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 the interstitial brachytherapy, proton therapy and BNCT are able to produce such a high dose gradient. More importantly, BNCT is considered as a targeted therapy which could wipe out the malignancy in one single fraction. Thus, focusing on the BNCT as a preoperative RT as well as its benefits and risks is the scope of this study. BNCT is an external RT that uses the combination of neutron irradiation and perfusion of $^{10}$B into the tumor cells to treat cancer. Using this technique, the $^{10}$B(n, α)$^7$Li reaction with its lethal effect occurs selectively in cancerous cells and kill them [7]. This selectivity leads to improved therapeutic efficiency and confines the destructive effects of radiation to boron-containing cells. Heretofore, 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, which aimed in this work. 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 simulated under the irradiation of IHNI, a new, small (30 kW) reactor specifically designed for BNCT near a hospital site in Beijing, China. The optimum treatment plans were then obtained using an optimization code. By doing this, we attempted to illustrate the great potential of BNCT to be applied even for sensitive group of pregnant patients and its superiority over conventional RT.

2. Materials and Methods

2.1. Monte Carlo simulations

2.1.1. 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 ICRP reference phantom [12, 13]. The fetal models include 20 different organs and tissues. The information about elemental composition of
fetal tissues can be found in [12, 13]. The two first trimesters of pregnancy are selected due to the following considerations. Firstly, undesired irradiation of embryo (i.e. fetal ages below 8 weeks) generally lead to spontaneous abortion [13], so 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]. Thus, 26 weeks was considered as an upper age limit in the simulations.

2.1.2. Simulated breast tumors

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

2.1.3. Boron compound uptakes

Different values of boron uptake are reported for the two common available boron delivery agents: Boronophenylalanine (BPA) and Sodium Borocaptate (BSH) [19]. The ratio of tumor to healthy tissue boron uptake (T:H) ranges from 2:1 to 8:1 for the mentioned boron agents [20, 10]. However, there are some reports of obtained 12:1 and 35:1 ratios of oligomeric phosphate diesters (OPDs) boron agent uptake for HER2+ breast cancer in animal studies [10], there is no reports on the human tissues. For the BPA-f compound in glioblastoma multiforme treatment, a boron concentration in the tumor is commonly assumed 3.5 times higher than that in blood [21]. Therefore, a uniform boron concentration of 72 ppm ¹⁰B was assumed 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 respectively in bone tissue, soft tissue and skin.
It means that a conservative T:H ratio (i.e. tumor to healthy soft tissue) of 3:1 is assumed. Unfortunately, there is no exact research or published report on boron uptake by fetus. Therefore, the boron uptake of soft tissue (i.e. 24 ppm) was also considered for the fetus. Further studies are necessary to be done in this subject to estimate the exact fetal uptake.

2.1.4. 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 thermal beam mainly consists of thermal neutrons, but contains epithermal, and fast neutron components, as well as an additional gamma ray component. The same is true for the epithermal beam. The radius of the beam aperture is 6 cm. For the neutron components, the beam radius expands to 10 cm and 15 cm to take into account the neutron leakage. Table 1 lists the source flux for different components of the IHNI beam. Details of the energy, angular and spatial distributions of the source were provided by manufacturer. According to angular distribution of the source, the maximum flux occurs at 25 degrees relative to the central beam axis.

2.1.5. Dose calculation considerations

The physical dose is assumed to be compromised of several dose components with different biological effectiveness. In order to make comparison between different techniques of RT, we should calculate the photon equivalent dose (i.e. the biologically weighted dose). In this respect, all dose components including γ-ray dose, recoil proton dose, nitrogen capture dose, and 10B capture dose were scored separately using the MCNPX 2.6.0 code. The simulation for each of the beam orientations was performed with $2 \times 10^9$ primary photon histories and $1 \times 10^9$ 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 the rectangular mesh grid was assumed to be conformed to the size of phantom’s voxel (i.e. 1.775 × 1.775 × 4.84 mm³). 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:

\[
\begin{align*}
D_w &= (\gamma\text{-ray dose}) + (\text{recoil proton dose} \cdot RBE_n) + (\text{nitrogen capture dose} \cdot RBE_N) + (^{10}\text{B capture dose} \cdot CBE) \\
&= (\gamma\text{-ray dose}) + (\text{recoil proton dose} \cdot RBE_n) + (\text{nitrogen capture dose} \cdot RBE_N) + (^{10}\text{B capture dose} \cdot CBE)
\end{align*}
\] (1)

In which relative biological effectiveness (RBE) and compound biological effectiveness (CBE) factors are used. The common unit used for the biologically-weighted dose is RBE-Gy or Gy-Eq. Based on Horiguchi et al. study, 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].

2.1.6. Irradiation configuration

Five irradiation directions were considered to cover all the spatial angles: straight to the breast (anterior-posterior) and four other directions along 45-degree rotation with respect to the straight direction (right, left, up and down). Figure 2 shows 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 6-month models, respectively.

2.2. Optimization phase

There are several dosimetric indices which were considered to estimate a well-defined treatment plan. First of all, the tumor to normal tissue dose ratio (TNR) which is 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 tried to maximize the TNR as one of the most important dosimetric indices in the treatment plan. The tumor
dose rate is also another important feature. We should attempt to remain the average tumor dose rate high enough to prevent prolonged treatment time. The other important factor is the dose uniformity inside the tumor. In this respect, coefficient of variation (CV) introduced as a uniformity index and should be minimized in the optimization process. CV is calculated as below:

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

where the \(d_i\) is the \(i\)th point of the tumor receiving dose, \(d\) is the average receiving dose by tumor, and \(N\) is total number of points considered inside the tumor. We 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). We used the forward method to optimize the dosimetric indices following below constraints:

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

where the last constraint was substantially important to be satisfied. Considering these constraints, the ten most favorable combinations were obtained for each tumor location and gestational age. These combinations have little differences in dosimetric values. Therefore, we can choose among them the most convenient combination with respect to the following reason. It is desirable to select a combination not consisting of many different directions or irradiator outputs. The simpler the combination, the more comfortable sense for the patients and thereupon, the more accurate results.

2.3. The prescribed dose to GTV in a BNCT single fraction
According to the protocols for breast cancer patients treated with preoperative 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 OARs constraints. To evaluate the corresponding single dose, we used the biological effective dose (BED);

\[ BED = nd \left( 1 + \frac{d}{\alpha/\beta} \right) \]  \hspace{1cm} (3)

where \( n \) is the number of fractions, \( d \) is the dose per fraction, and the product \( (n \cdot d) \) is the total physical dose delivered to the target volume. The \( \alpha \) and \( \beta \) are radiobiological parameters (linear quadratic parameters) related to the irradiated tissue/organ. For any given \( \alpha/\beta \), treatment schedules which produce identical BEDs are said to be radiobiologically isoeffective. It is common to assume 10 Gy for \( \alpha/\beta \) 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 \( \alpha/\beta \) 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. We assumed the later one as an upper extreme to be confident about tumor local control.

2.4. The dose volume histogram (DVH) 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 DVH as well as a set of related parameters. The parameter \( \text{VX}\% \) is defined as the percent of volume receiving at least \( X\% \) of the prescribed dose. The \( \text{V}100\% \) is commonly used in the treatment planning systems and is often tried to be > 90\% of the target volume. The \( \text{V95}\% \) is also considered to be > 95\% of the target volume. For the OARs, the common parameters of \( \text{DMAX} \), \( \text{D}10\text{cm}^3 \), \( \text{V}10\text{Gy} \), \( \text{V}5\text{Gy} \) and \( \text{V}2\text{Gy} \) were used to illustrate the eligibility of BNCT for BC pregnant case and also make it easier to compare the results of this study with conventional RT. \( \text{DMAX/DMIN} \) was assumed to be the minimum/maximum dose to the 0.015 cm\(^3\) volume of the organ receiving the
highest/lowest doses. D10cm³ was determined as the minimum dose to the 10 cm³ of the organ that receive the highest doses. Vx Gy was also considered as the volume receiving more than x Gy.

3. Results

3.1. Optimum treatment plans

The Optimum treatment plans are determined for all four situations studied in this work. In figure 3, the contribution of each output beam and irradiation direction (%) to the optimum treatment plan is demonstrated. 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. Table 2 also lists the dosimetric indices and treatment times of the proposed treatment plans. As shown, the evaluated TNR for optimum plans are in the range of 2.98 up to 3.89, which is satisfying in therapeutic procedures. The CVs of tumor dose are also smaller 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 target volume, the total irradiation times were estimated to be from 4.8 to 10.1 minutes which seems reasonably practical. Several other dosimetric factors of suggested plans are also listed in table 3.

3.2. The target volume (GTV)

Table 3 shows the biological-weighted dose to the target and maternal OARs. Dose volume histograms (DVH) are also provided from the proposed treatment plans (figure 4). As shown in the table 3 and figure 4, the GTV dose was ranged from 17.3 Gy-Eq to 45.5 Gy-Eq in a BNCT single fraction. The target coverage factors are also indicated in table 3. The V100% is greater than 90% for all four studied situations. It means that more than 90% of target volume received 100% of the prescribed dose (Rx = 24.4 Gy-Eq). Furthermore, V95% shows that the delivered dose to 95% of the target volume is greater than 95% of Rx. It should be
noted that the results are based on the assumption that $\alpha/\beta = 10$ Gy. It means that if $\alpha/\beta$ was less than this value as previously estimated by several investigators [25], even the minimum dose to the tumor (17.3 Gy-Eq) is larger than the dose required to completely ablate the tumor. Figure 5 also indicates a 2D view of isodose contours in unit (Gy-Eq). As can be seen, the target coverage is quite adequate in this slice.

3.3. The OARs

Our determined treatment plans show satisfying low OARs doses. It was shown that the OARs did not exceed than 10 Gy-Eq in all selected plans (table 3), even in the normal tissues of ipsilateral breast (<9.8 Gy-Eq). The skin received the maximum biological weighted dose (up to 10 Gy) among the OARs, however it is well below than the skin tolerance (radiation dose of ~21 Gy in one fraction). In addition, in order to illustrate the eligibility of BNCT, we made a comparison between this study and what routinely used in external RT. For example, one of common OAR dose constraints for the skin is the D10cm which should be less than 20 Gy in a single fraction treatment. Table 3 indicates that the skin D10cm is below 5.9 Gy-Eq in all four studied situations here.

To estimate the risk of OARs late complications, the OARs doses are compared to the report of Emami on the tolerance of normal tissue to the therapeutic radiation. According to Emami’s study, if the lung tissue receives a mean dose of 20 Gy, there will be 20% risk of radiation pneumonitis. For heart tissue, Emami stated that if 25% of heart tissue received > 6 Gy, there is a risk of <1% of cardiac mortality at 15 years after the treatment. He also reported <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; does not exceed 5 Gy-Eq (Table 3). Thus, the OARs doses are well below these values and there is no risk of the late effects.

4. Discussions
According to the results of this study, a single fraction of BNCT with treatment duration of few minutes and prescribed dose of 24.4 G\text{y} to the GTV, is able to kill the tumor cancerous cells as well as spare the OARs. However, the essential limitation of the treatment during pregnancy is the presence of the fetus. In order to investigate the fetal dose constraint in the optimization process, we performed additional optimization programs with the last constraint omitted (the constraint on fetal dose). The selected combinations were approximately the same as the reported ones (in table 2 and figure 3).

It means that the fetal dose constraint is independent of treatment plan specification and that could only be determined by observing the first three constraints. Notwithstanding this, in order to examine the feasibility of BNCT for breast cancer during pregnancy, the treatment plan should be justified considering the risks and benefits of the mother and her fetus. Delivering 24.4 G\text{y-Eq} to the tumor, will lead the fetal physical dose of $\leq 4.7$ and $\leq 30.9$ m\text{Gy} for 3- and 6-month pregnant patients, respectively (table 4). These values of physical doses are much lower than the case of RT, reported to be between 0.1\% and 0.3\% of the prescribed dose in the first trimester [27]. It means that the fetal dose would be about 60 to 180 m\text{Gy} in RT, whereas it is well less than the threshold of 10 m\text{Gy} in the suggested treatment plans.

In the late second trimester, the fetal physical dose is considerable ($\leq 30.9$ m\text{Gy}) and the secondary cancer chance will be more than 1.4\%, so 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 G\text{y} as the fetus grows up and advances toward the radiation field [28].

The biological-weighted dose to the fetus was also reported in table 4. The results show a fetal biological-weighted dose of $\leq 4.8$ and $\leq 35.5$ m\text{Gy} for 3- and 6-month pregnant patients, respectively. The biological-weighted dose to the fetus is up to 15\% larger than the physical dose. But the good news is that the photons are the major contributor to the fetal dose. The results also indicate that these photons are not the primary photons emitted from the source beams, which we could stop them by covering the mother’s belly with a photon shield. The photons are induced by neutrons inside the body and so the resulting dose is inevitable.
5. Conclusion

In this study, BNCT was virtually examined for a pregnant patient diagnosed with stage II breast cancer. Monte Carlo simulations of irradiating breast tumors at 3- and 6-month gestational ages were performed and optimum treatment plans for each case were produced. The results showed that the total treatment time to deliver a prescribed dose of 24.4 Gy-Eq to the GTV is less than ~10 minutes and so reasonably practical. It has been also shown that the fetal dose did not exceed than 10 mGy for first trimester of pregnancy and thus has no stochastic risk of secondary cancer, whereas higher values of fetal dose (~35.5 mGy) obtained for second trimester. Therefore, clinical application of BNCT in the second trimester of pregnancy should be considered with caution. Moreover, OARs dose constraints for RT are well satisfied with a single fraction BNCT. To sum up, pregnant patient at first trimester of pregnancy could be well treated by BNCT with minimal effect to the fetus and maternal OARs.

Acknowledgements

We hereby acknowledge that a part of this computation was performed on the HPC center of Ferdowsi University of Mashhad. This work was supported by grant no. 33151, 3/10/2015 from Vice President for Research and Technology of Ferdowsi University of Mashhad.

References


Table 1 Particle flux (cm$^2$ s$^{-1}$) for different IHNI outputs.

<table>
<thead>
<tr>
<th>IHNI output</th>
<th>Source particle</th>
<th>Flux (cm$^2$ s$^{-1}$)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Beam aperture</td>
<td>Beam leakage</td>
<td>Beam leakage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(radius 0-6 cm)</td>
<td>(radius 6-10 cm)</td>
<td>(radius 10-15 cm)</td>
</tr>
<tr>
<td>Thermal Beam</td>
<td>Neutron</td>
<td>1.75E9</td>
<td>8.95E7</td>
<td>1.33E7</td>
</tr>
<tr>
<td></td>
<td>Photon</td>
<td>2.10E7</td>
<td>1.49E7</td>
<td>2.36E7</td>
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<tr>
<td>Epithermal Beam</td>
<td>Neutron</td>
<td>5.30E8</td>
<td>7.05E7</td>
<td>5.10E6</td>
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<tr>
<td></td>
<td>Photon</td>
<td>3.08E7</td>
<td>2.35E7</td>
<td>6.76E6</td>
</tr>
</tbody>
</table>
Table 2 The TNR, CV and irradiation time of proposed treatment plans.

<table>
<thead>
<tr>
<th>Fetal age</th>
<th>Tumor location</th>
<th>Abbreviated name</th>
<th>TNR</th>
<th>CV(%)</th>
<th>Irradiation time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month</td>
<td>Nipple neighborhood</td>
<td>6m-Nipp</td>
<td>3.64</td>
<td>17.77</td>
<td>10.1 1.7 8.4</td>
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<td>6-month</td>
<td>Upper outer quadrant</td>
<td>6m-Quad</td>
<td>3.84</td>
<td>9.20</td>
<td>5.9 0.0 5.9</td>
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<td>3-month</td>
<td>Nipple neighborhood</td>
<td>3m-Nipp</td>
<td>2.98</td>
<td>4.95</td>
<td>4.8 2.2 2.5</td>
</tr>
<tr>
<td>3-month</td>
<td>Upper outer quadrant</td>
<td>3m-Quad</td>
<td>3.77</td>
<td>11.38</td>
<td>6.3 1.3 5.1</td>
</tr>
</tbody>
</table>
Table 3  The estimated DVH metrics of tumor and maternal OARs for the four simulated situations.

<table>
<thead>
<tr>
<th>DVH metrics</th>
<th>Gestational age-Tumor location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6m-Nipp</td>
</tr>
<tr>
<td><strong>Tumor</strong></td>
<td></td>
</tr>
<tr>
<td>$D_{\text{MAX}}$ (Gy-Eq) (^1)</td>
<td>45.5</td>
</tr>
<tr>
<td>$D_{\text{MIN}}$ (Gy-Eq) (^2)</td>
<td>19.7</td>
</tr>
<tr>
<td>$V_{100%}$</td>
<td>94.0%</td>
</tr>
<tr>
<td>$V_{95%}$</td>
<td>95.7%</td>
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<tr>
<td><strong>Skin</strong></td>
<td></td>
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<tr>
<td>$D_{\text{MAX}}$ (Gy-Eq)</td>
<td>10.0</td>
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<tr>
<td>$D_{10\text{cm}^3}$ (Gy-Eq) (^3)</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Left Breast</strong></td>
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</tr>
<tr>
<td>$D_{\text{MAX}}$ (Gy-Eq)</td>
<td>9.8</td>
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<tr>
<td>$V_{5\text{Gy}}$</td>
<td>47%</td>
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<tr>
<td>$V_{10\text{Gy}}$</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Left Lung</strong></td>
<td></td>
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<tr>
<td>$D_{\text{MAX}}$ (Gy-Eq)</td>
<td>4.3</td>
</tr>
<tr>
<td>$V_{5\text{Gy}}$</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td></td>
</tr>
<tr>
<td>$D_{\text{MAX}}$ (Gy-Eq)</td>
<td>3.3</td>
</tr>
<tr>
<td>$V_{5\text{Gy}}$</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
</tr>
<tr>
<td>$D_{\text{MAX}}$ (Gy-Eq)</td>
<td>4.5</td>
</tr>
<tr>
<td>$V_{5\text{Gy}}$</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Spleen</strong></td>
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<tr>
<td>$D_{\text{MAX}}$ (Gy-Eq)</td>
<td>0.8</td>
</tr>
<tr>
<td>$V_{2\text{Gy}}$</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(^1\) $D_{\text{MAX}}$ is the minimum dose to the 0.015 cm\(^3\) volume of the organ receiving the highest doses

\(^2\) $D_{\text{MIN}}$ is the maximum dose to the 0.015 cm\(^3\) volume of the organ receiving the lowest doses

\(^3\) $D_{10\text{cm}^3}$ is the minimum dose to the 10 cm\(^3\) of the organ that receive the highest doses
Table 4 The physical and biological-weighted dose to the fetus and contribution of neutron-induced photons and source photons to fetal dose.

<table>
<thead>
<tr>
<th>Gestation age</th>
<th>Tumor location</th>
<th>Physical dose (mGy)</th>
<th>Biological-weighted dose (mGy-Eq)*</th>
<th>Contribution of neutron-induced photons</th>
<th>Contribution of source photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month</td>
<td>Nipp</td>
<td>30.90</td>
<td>35.48</td>
<td>88.6%</td>
<td>10.7%</td>
</tr>
<tr>
<td>6-month</td>
<td>Quad</td>
<td>14.01</td>
<td>14.88</td>
<td>93.3%</td>
<td>6.1%</td>
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<tr>
<td>3-month</td>
<td>Nipp</td>
<td>3.52</td>
<td>3.53</td>
<td>73.8%</td>
<td>14.6%</td>
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<tr>
<td>3-month</td>
<td>Quad</td>
<td>4.74</td>
<td>4.76</td>
<td>63.4%</td>
<td>12.2%</td>
</tr>
</tbody>
</table>

*The RBE or CBE factors for the fetal tissues were assumed to be the same as the maternal soft tissues since the factors for the fetus are not reported in the literature.
Figure 1 a) 3D view of 3- and 6-month fetal models. b) MCNP plot of pregnant phantoms
Figure. 2 3D 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.
Figure. 3 Irradiation combination composed of various output beams and irradiation directions for the proposed treatment plans.
Figure. 4 Dose volume histograms for tumor and OARs, for different gestations and tumor locations.
Figure 5 A 2D plot of isodose (Gy-Eq) contours for 6 month pregnant phantom with breast tumor at nipple neighborhood.