Clinical trial design of Boron Neutron Capture Therapy on breast cancer using D-D coaxial compact neutron generator as neutron source and Monte Carlo N-Particle simulation method

Rosenti Pasaribu1, Kusminarto1, Yohannes Sardjono2

1Gadjah Mada University, Yogyakarta, Indonesia
2Center for Accelerator Science and Technology, National Nuclear Energy Agency

Received: 10 June 2015, Revised: 28 October 2015, Accepted: January 2016

Abstract A clinical trial simulation of Boron Neutron Capture Therapy (BNCT) for breast cancer was conducted at National Nuclear Energy Agency Yogyakarta, Indonesia. This was motivated by high rate of breast cancer in the world, especially in Indonesia. BNCT is a type of therapy by nuclear reaction 10B(n,α)7Li that produces kinetic energy totaling 2.79 MeV. High Linear Energy Transfer (LET) radiation of α-particle and recoil 7Li would locally deposit their energy in a range of 5-9 μm, which corresponds to the human cell diameter. Fast neutron coming out of Compact Neutron Generator (CNG) was moderated using Fe and MgF2 material. A collimator, along with breast cancer and the corresponding organ at risk were designed compatible to Monte Carlo N-Particle X (MCNPX). The radiation were simulated by the MCNPX software and the physical quantities were counted by tally MCNPX codes. The highest neutron thermal flux was found at a depth of 1.4 cm on fat tissue. En face and upward intersection radiation techniques were adopted for the breast cancer radiation. The average dose rate of radiation used on breast cancer was 1.72×10^-5 Gy/s for the en face method and 8.98×10^-6 Gy/s for the upward intersection method. Dose 50±3 Gy was given into cancer cell, (4.18±0.06) ×10^-2 Gy into heart and (8.16±0.06) ×10^-2 Gy into lung for 806.34 hours irradiation.

Keywords BNCT, MCNPX, CNG, breast cancer radiation, Collimator, radiation dose

INTRODUCTION

BNCT has been regarded as a potential method for cancer treatment (Anonim C, 2001; Jenkins, 2012; Andoh et al., 2014; Capoulat et al., 2014; Aihara et al., 2014). The neutron capture therapy concept was implemented for the first time after Chadwick neutron invention in 1932, followed by cross-section invention between 10B and thermal neutron by Golhaber in 1934 (Anonim C, 2001). Golhaber showed that thermal neutron reacts with 10B producing 7Li, alpha particle, and gamma radiation. This invention became the foundation for BNCT.

Boron Neutron Capture Therapy (BNCT) is a radiotherapy that utilizes 10B(n,α)7Li nuclear reaction resulting High Linear Energy Transfer (LET) of α-particle and recoil 7Li to destruct cancer cells. The reaction cross-section between Boron-10 and thermal neutron is ~3837 barn. The reaction between Boron-10 and thermal neutron is shown as:

\[
\begin{align*}
\left[\alpha\text{He}\right] + \left[7\text{Li}\right] & \rightarrow 2.79 \text{ MeV (6.1\%)} \\
\left[10\text{B}\right] + \left[\alpha\text{n}\right] & \rightarrow \left[\alpha\text{B}\right] \\
\left[\alpha\text{He}\right] + \left[7\text{Li}\right]^+ & \rightarrow 2.31 \text{ MeV (93.9\%)} \\
\left[7\text{Li}\right] + \gamma & (0.48 \text{ MeV})
\end{align*}
\]

where the α-particle LET is ~150 keV/μm and the 7Li LET is ~175 keV/μm. These heavy particles locally deposit their energy in a range of 5-10 μm, which corresponds to the human cell diameter (Shaaban et al., 2015). BNCT is a promising method for selective cancer cells destruction.
At first, BNCT was applied for high-grade brain cancer such as glioblastoma. However, along with the development of research, some researchers have investigated application of BNCT for breast cancer treatment. Some researches has been conducted to produce a breast cancer therapy protocol based on BNCT. Some of the researches related to breast cancer treatment are radiation dose evaluation (Yanagie et al., 2009; Loong et al., 2014), optimal radiation technique (Horiguchi et al., 2011) and a feasibility study evaluating BNCT for potential role (Jenkins, 2012). If the boron atoms accumulate in the cancer cells, then inflammatory breast cancer is easily invaded (Yanagie, 2012).

D-D coaxial Compact Neutron Generator (CNG) is a safe neutron source because it does not use radioactive material, so that it is widely available in the market. D-D coaxial CNG generates neutron strength of \(~10^{12}\) n/s. D-D reaction that generates neutron is expressed as:

\[
\frac{^2}{^1}D + \frac{^2}{^1}D \rightarrow \frac{^3}{^1}n + \frac{^3}{^2}He
\]

with \(E_n = 2.45\ MeV\) and \(E_{He} = 0.82\ MeV\).

**MATERIALS AND METHODS**

This research consists of three parts: collimator design; breast cancer and organ at risk modeling; and radiation dose calculating. The simulation method used in this work is a Monte Carlo method, implemented using the MCNPX software by Los Alamos National Laboratory. Visual editor 5-4.23-12N software is used to visualize the collimator design and breast cancer model.

The collimator design is made taking into account the shape of the neutron source. Materials with high inelastic scattering cross-section are chosen as moderator. Material with high scattering cross-section and low absorption cross-section is chosen as reflector. Material with high thermal neutron absorption is chosen as thermal neutron filter. Material with high gamma absorption is chosen as gamma absorption. Then, all the chosen materials are designed into a collimator. The IAEA criteria are the standard for the collimator output. The IAEA criteria for collimator are shown in Table 1. The breast cancer and organ at risk are designed based on cross-section view from computed

<table>
<thead>
<tr>
<th>Design Source strength (n/s)</th>
<th>(\Phi_{epi} (n.cm^{-2}.s^{-1}))</th>
<th>(\Phi_{epi} / \Phi_{th} (Gy/cm^2.n^{-1}))</th>
<th>(\Phi_{epi} / \Phi_{f} (Gy/cm^2.n^{-1}))</th>
<th>(\Phi_{epi} / \Phi_{th})</th>
<th>(\Phi_{epi} / \Phi_{f})</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAEA</td>
<td>(&gt;1.0\times 10^9)</td>
<td>(&lt;2.0\times 10^{-13})</td>
<td>(&lt;2.0\times 10^{-13})</td>
<td>(&gt;100)</td>
<td>(&gt;20)</td>
</tr>
</tbody>
</table>

Figure 1. The CT cross section view imaging (Alanyah et al., 2013)

Figure 2. The ORNL phantom cross section view (Krstic et al., 2014)
tomography imaging and ORNL phantom. The tomography imaging and ORNL phantom cross-section views are shown in Fig.1 and Fig.2, respectively. Finally, physical quantities needed for radiation dose calculation are counted by MCNPX tally. Dose calculating is conducted for two techniques, en face and upward intersection radiation techniques.

The BNCT doses calculations made are as follows:

1. The neutron scattering involves thermal neutron, epithermal neutron, and fast neutron scatterings obtained from MCNPX computation. The scattering doses are obtained using the tally code “DE” and converted to Gy/s unit using the tally code “DF”.

2. Recoil proton dose is obtained from thermal neutron reaction with nitrogen-14 with reaction equation:

\[ ^{14}\text{N} + ^{1}\text{n} \rightarrow ^{14}\text{C} + ^{1}\text{P} \]

The amount of energy released in this reaction is 0.66 MeV.

3. Photon dose consists of:
   a. photon dose from the collimator (obtained from MCNPX computation)
   b. photon dose from the reaction of thermal neutron with hydrogen with reaction equation:

\[ ^{1}\text{H} + ^{1}\text{n} \rightarrow ^{2}\text{H} + \gamma \]

The amount of photon energy released from this reaction is 2.23 MeV.

   c. photon dose from the reaction of thermal neutron with boron is 0.48 MeV, with reaction probability of 93.9% (this reaction is involved in the boron dose mentioned in no. 4 below).

4. Boron dose is obtained from the reaction of boron with neutron with reaction equation:

\[ ^{10}\text{B} + ^{1}\text{n} \rightarrow ^{7}\text{Li} + ^{3}\text{He} \]

there are two kinds of reaction of boron-10 with neutron. First, with probability of 93.9%, it results in alpha particle (1.47 MeV), lithium (0.84 MeV), and photon (0.48 MeV). Second, with probability of 6.1%, it results in alpha particle (1.01 MeV) and lithium (1.78 MeV). So, an average energy amount of 2.33 MeV is involved in resulting alpha particle and lithium.

The BNCT total dose is formulated as:

\[ D_{\text{bw}} = Q_{\text{B}}D_{\text{B}} + Q_{\gamma}D_{\gamma} + Q_{\text{n}}D_{\text{n}} + Q_{\text{p}}D_{\text{p}} \]  \hspace{1cm} (1)

where \( D_{\text{B}} \) (boron dose), \( D_{\gamma} \) (photon dose), \( D_{\text{n}} \) (neutron scattering dose), and \( D_{\text{p}} \) (recoil proton dose) are calculated using the following formulas:

\[ D_{i} = N_{i}\phi\sigma_{i}E_{i}, D_{\gamma} = N_{\gamma}\phi\sigma E_{\gamma} + D'_{\gamma} \]  \hspace{1cm} (2)

RESULTS AND DISCUSSION

Collimator design

Reflector

The materials tested as reflector are \( ^{64}\text{Ni}, ^{209}\text{Pb}, ^{209}\text{Bi}, \text{BeO} \) and \( \text{PbF}_2 \) as IAEA recommends. The neutron current output on a fixed aperture is shown in Fig.3. Based on Fig.3, BeO and \( ^{209}\text{Bi} \) produce high amount of thermal neutron, which is not desirable. So, \( \text{PbF}_2 \) and \( ^{64}\text{Ni} \) are chosen as the best materials for the reflector. Further, the
best one is chosen by calculating neutron flux at different thicknesses of the materials. The result is given in Fig.4.

The highest neutron flux is given by PbF$_2$. Therefore, PbF$_2$ is chosen as the material of the reflector in this research.

**Moderator**

The materials tested as moderator are $^{56}$Fe, $^{27}$Al, AlF$_3$, LiF, Al$_2$O$_3$, MgF$_2$ and TiF$_3$ as IAEA recommends. Fast neutron (2.5 MeV) needs to be moderated to epithermal neutron level (0.025 eV < E < 10 keV). Most materials have inelastic scattering cross-section starting at energy ≥100 keV, but Iodine atom has inelastic scattering cross-section starting at lower neutron energy (< 50 keV). AlI$_3$ is used as part of the moderator in this research. D-D Coaxial Compact Neutron Generator produce low neutron source strength, ~10$^{12}$ n/s at radius 14 cm. So, the collimator has to be short to obtain higher neutron flux. The result obtained at the fixed aperture for some physical quantities is shown in Table 2 and the collimator design based on Table 2 is shown in Fig. 5. Thermal neutron filter and gamma filter use$^6$Li and $^{209}$Bi, respectively. Intermittent material design is used to absorb thermal neutron, so that low thermal neutron flux is obtained.

The collimator output from the proposed collimator design and other Beam

**Breast cancer and organ at risk modeling**

Breast cancer and organ at risk are modeled based on Fig.1 and Fig.2. The model is shown in Fig.6. The breast cancer and organ at risk shapes are limited by MCNPX capability. So, the made-up model was a simple model.

**Radiation techniques**

There are two radiation techniques used, en face radiation technique and upward intersection radiation technique, as shown in Fig. 7.

**Radiation Dosimetry**

**Thermal neutron flux**

Thermal neutron flux at various depths are measured to determine maximum thermal neutron flux depth, as shown in Fig. 8. Best
Table 2. Collimator aperture outcome using different moderator, thermal neutron filter and gamma filter materials

<table>
<thead>
<tr>
<th>Design (materials arranged sequentially)</th>
<th>Source strength (n/s)</th>
<th>$\Phi_{\text{epi}}$ (n.cm$^{-2}$.s$^{-1}$)</th>
<th>$D_f/\Phi_{\text{epi}}$ (Gy.cm$^2$.n$^{-1}$)</th>
<th>$D_y/\Phi_{\text{epi}}$ (Gy.cm$^2$.n$^{-1}$)</th>
<th>$\Phi_{\text{epi}}/\Phi_{\text{th}}$</th>
<th>$\Phi_{\text{epi}}/\Phi_f$</th>
<th>$I/\Phi_{\text{epi}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAEA</td>
<td>$&gt; 1.0 \times 10^9$</td>
<td>$&lt; 2.0 \times 10^{-13}$</td>
<td>$&lt; 2.0 \times 10^{-13}$</td>
<td>$&gt; 100$</td>
<td>$&gt; 20$</td>
<td>$&gt; 0.7$</td>
<td></td>
</tr>
<tr>
<td>Al (69.8 cm)</td>
<td>$5.0 \times 10^7$</td>
<td>$3.8 \times 10^{-26}$</td>
<td>$1.4 \times 10^{-26}$</td>
<td>$64.2$</td>
<td>$2.8$</td>
<td>$71.7$</td>
<td></td>
</tr>
<tr>
<td>Fe (69.8 cm)</td>
<td>$3.2 \times 10^6$</td>
<td>$2.6 \times 10^{-25}$</td>
<td>$1.2 \times 10^{-26}$</td>
<td>$167.2$</td>
<td>$0.8$</td>
<td>$62.9$</td>
<td></td>
</tr>
<tr>
<td>AlF$_3$(69.8 cm)</td>
<td>$1.5 \times 10^7$</td>
<td>$8.4 \times 10^{-24}$</td>
<td>$2.8 \times 10^{-26}$</td>
<td>$6.1$</td>
<td>$29.4$</td>
<td>$72.1$</td>
<td></td>
</tr>
<tr>
<td>Al$_2$O$_3$(69.8 cm)</td>
<td>$9.6 \times 10^6$</td>
<td>$2.1 \times 10^{-24}$</td>
<td>$1.4 \times 10^{-24}$</td>
<td>$4.1$</td>
<td>$2.0$</td>
<td>$68.8$</td>
<td></td>
</tr>
<tr>
<td>LiF (69.8 cm)</td>
<td>$7.0 \times 10^5$</td>
<td>$7.2 \times 10^{-26}$</td>
<td>$7.9 \times 10^{-27}$</td>
<td>-</td>
<td>$9.5$</td>
<td>$69.1$</td>
<td></td>
</tr>
<tr>
<td>Fluental (69.8 cm)</td>
<td>$2.0 \times 10^7$</td>
<td>$5.0 \times 10^{-26}$</td>
<td>$1.7 \times 10^{-26}$</td>
<td>$39.7$</td>
<td>$18.1$</td>
<td>$71.5$</td>
<td></td>
</tr>
<tr>
<td>TiF$_3$(69.8 cm)</td>
<td>$2.0 \times 10^{12}$</td>
<td>$6.91 \times 10^6$</td>
<td>$2.8 \times 10^{-26}$</td>
<td>$2.6 \times 10^{-25}$</td>
<td>$30.8$</td>
<td>$72.1$</td>
<td>$72.2$</td>
</tr>
<tr>
<td>Fe (10.8 cm)+MgF$_2$(59 cm)</td>
<td>$7.1 \times 10^6$</td>
<td>$1.6 \times 10^{-26}$</td>
<td>$2.1 \times 10^{-26}$</td>
<td>$3.14$</td>
<td>$63$</td>
<td>$69.6$</td>
<td></td>
</tr>
<tr>
<td>Fe(10.8 cm)+MgF$_2$(62 cm)+Bi (1 cm)+MgF$_2$(0.1 cm)+Bi (0.9 cm)</td>
<td>$7.1 \times 10^6$</td>
<td>$1.6 \times 10^{-26}$</td>
<td>$2.1 \times 10^{-26}$</td>
<td>$3.14$</td>
<td>$63$</td>
<td>$69.6$</td>
<td></td>
</tr>
<tr>
<td>Fe(10.8 cm)+MgF$_2$(10 cm)+Li(1 cm)</td>
<td>$2.1 \times 10^6$</td>
<td>$6.7 \times 10^{-26}$</td>
<td>$3.2 \times 10^{-26}$</td>
<td>$230$</td>
<td>$21$</td>
<td>$71.4$</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Comparison between this proposed design and some published works

<table>
<thead>
<tr>
<th>Design</th>
<th>Source strength (n/s)</th>
<th>$\Phi_{\text{epi}}$ (n.cm$^{-2}$.s$^{-1}$)</th>
<th>$D_f/\Phi_{\text{epi}}$ (Gy.cm$^2$.n$^{-1}$)</th>
<th>$D_y/\Phi_{\text{epi}}$ (Gy.cm$^2$.n$^{-1}$)</th>
<th>$\Phi_{\text{epi}}/\Phi_{\text{th}}$</th>
<th>$\Phi_{\text{epi}}/\Phi_f$</th>
<th>$I/\Phi_{\text{epi}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fantidis et al., 2013</td>
<td>$10^{11}$</td>
<td>$1.17 \times 10^6$</td>
<td>$1.11 \times 10^{-17}$</td>
<td>$2.32 \times 10^{-17}$</td>
<td>$128.81$</td>
<td>$20.81$</td>
<td>-</td>
</tr>
<tr>
<td>Durisi et al.,</td>
<td>$10^{11}$</td>
<td>$1.83 \times 10^6$</td>
<td>$1.82 \times 10^{-12}$</td>
<td>$2.98 \times 10^{-13}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>This proposed collimator design</td>
<td>$10^{12}$</td>
<td>$2.1 \times 10^6$</td>
<td>$6.7 \times 10^{-26}$</td>
<td>$3.2 \times 10^{-26}$</td>
<td>$230$</td>
<td>$21$</td>
<td>$71.4$</td>
</tr>
</tbody>
</table>
Clinical trial design of Boron Neutron Capture Therapy on breast cancer using D-D coaxial compact neutron generator as neutron source and Monte Carlo N-Particle simulation method

**Figure 6.a.** Breast cancer and organ at risk 3D Vised visualization, cross-section view

**Figure 6.b.** Breast cancer and organ at risk 3D Vised visualization, en face view

**Figure 7.a.** En face radiation technique

**Figure 7.b.** Upward intersection radiation technique

**Figure 8.** Thermal neutron flux versus depth

**Figure 9.** Radiation dose at cancer cell and organ at risk
radiation technique will be determined by maximum thermal neutron depth. Neutron flux is calculated by MCNPX tally for en face and upward intersection radiation techniques, then dose radiation is calculated. The dose radiation comparison between the two techniques is given in Fig.9.

**Exposure time**

Exposure time is calculated based on maximum dose at healthy tissue 12.5 Gy/s, maximum dose at skin 8 Gy/s and minimum dose to destruct breast cancer~50 Gy/s. Exposure time calculation based on the three criteria is shown in Fig. 10.

Based on exposure time calculated on diagram, 806.34 hours is the acceptable exposure time. This result is chosen for skin and healthy tissues exposure safety. But, 806.34 hours irradiated produce 50 ± 3 Gy on breast cancer cell, (4.18±0.06) ×10⁻² Gy on heart and (8.16±0.06) ×10⁻² Gy on lung.

**CONCLUSION AND REMARKS**

The low radiation dose on cancer cells shows that the result obtained in this research is still inadequate. The main factor resulting in the low dose is a low amount of neutron source strength. To obtain high neutron flux, neutron source with high source strength is needed. Other efforts to optimize the result are trying varying radiation techniques and optimizing the collimator design.

**ACKNOWLEDGMENT**

This work was supported by National Nuclear Energy Agency (BATAN), Yogyakarta, Indonesia.

**REFERENCE**


Anonim H., 2013, Latest world cancer statistic, Global burden rises to 14.1 million new cases in 2012: Marked increase in breast cancer must be addressed, World Health Organization.


Wu, Ying, 2009, *Development Neutron Generator to be Used for Associated Particle Imaging Utilizing RF-Driven Ion Source*, A Dissertation, Nuclear Engineering, University of California, Berkeley.

