Extra-Corporal Treatment of Liver Metastases by BNCT at the HFR Petten

V Nievaart¹, R Moss¹, A Wittig² and W Sauerwein²

¹Joint Research Centre, Institute for Energy, P.O. Box 2, 1755ZG Petten, The Netherlands

²Dept. of Radiation Oncology, Univeritätsklinikum Essen, Hufelandstr. 55, 45122 Essen, Germany

E-mail: victor.nievaart@jrc.nl

Abstract. A computational investigation has shown that the epithermal neutron beam presently used for BNCT of the brain in the HFR in Petten The Netherlands can also be used for BNCT of extra-corporal livers. Liver BNCT has already been performed in Pavia Italy providing very promising results. By rotating the liver and surrounding it by Polymethylmethacrylate and graphite and with the appropriate dimensions of the set-up, the same homogeneity in the thermal neutron field in the liver can be obtained in Petten as in Pavia.

1. Introduction
Boron Neutron Capture Therapy (BNCT) is a cancer treatment which is investigated worldwide with ongoing clinical trials. The first step in this treatment consists of bringing the isotope boron-10 into the cancer cells by using a special agent. Secondly, non-toxic \(^{10}\)B is activated by irradiating externally the patient with neutrons at the site of the tumours. Due to the reaction:

\[^{10}\text{B} + n \rightarrow ^{7}\text{Li} + ^{4}\text{He},\]

two heavy particles arise which can destroy the cancer cell nucleus within a range of around 10\(\mu\)m due to a double strand break of the present DNA in the cell. Due to the presence of hydrogen and nitrogen in human tissue, there is always a certain dose due to neutron reactions with these elements. \(H\) generates gammas and \(N\) protons. Since there is more \(^{10}\)B in the cancer cells which are also better positioned near the cell nucleus than in the healthy cells, a large extra dose is given to the cancer. The occurrence of the neutron reactions with \(^{10}\)B, \(H\) and \(N\) increases with decreasing neutron energy; there is a 1/velocity relation. Consequently, thermal neutrons which have an energy <0.5eV are desired near the tumours.

The BNCT neutron beam of the High Flux Reactor (HFR) in Petten (The Netherlands) has a total number of neutrons per cm\(^2\) and per second (called flux) of 3.8x10\(^8\) n/cm\(^2\)s with an average energy of 10keV; so-called epithermal neutrons.

The beam is currently used in clinical trials for the treatment of certain types of brain tumors. The skin, cranium and brain tissues are used to thermalize the neutrons down to the <0.5eV regime due to the elastic scattering properties of the prevailing hydrogen. This thermalization effect is shown in Figure 1: The epithermal neutron flux decreases while the thermal neutron flux increases when the
neutrons travel into a cube or sphere of H₂O which is highly comparable with human tissue. The thermal neutron flux has a maximum around 25mm, the so-called thermal maximum.

![Figure 1](image_url)

The sphere in Figure 1, with a diameter of 250mm has a thermal neutron flux that is higher than for the cube (sides of 200mm) at deeper positions; the thermal flux is distributed over a larger area.

In 2001, BNCT researchers in Pavia (Italy) irradiated a liver, full of metastases, extra-corporally in a nuclear reactor [1,2,3]. Encouraged by the promising results, the Petten/Essen BNCT group started to study the possibility to perform the same irradiation at the HFR. In Pavia the liver was placed inside a space full of thermal neutrons; the thermal neutron fluence inside the liver deviated +/- 20% from the average as a function of position. One of its goals in Petten therefore is to obtain at least the same homogeneity in the neutron field. In addition, the challenge in Petten is to modify the epithermal neutron beam such that it is possible to irradiate the liver, a rather large organ, without changing the beam characteristics itself, thus being able to continue the current brain BNCT trials. In this work, the whole design procedure and the definition of all design parameters with their relations and restrictions together with the equations describing the necessary rotation of the liver is discussed. The final goal, to obtain the same thermal neutron fluence characteristics as in Pavia, is discussed in the results section, showing that the necessary goals can be reached.

2. Design parameters

Before discussing the parameters of the design process, the fixed parameters will be given first together with the derivation of the final design of a spherical liver irradiation holder. The fixed parameters are all source related: neutron energy spectrum, intensity and a maximum radius R_{source disk} of the irradiation beam, i.e. 80mm. Note that at the edge of this disk shaped beam, the neutron intensity drops steeply. An average liver has a weight of around 1.7kg [4] and would fit in an imaginary cube with sides of 1200mm. From Figure 1 it can be seen that the liver has to be irradiated from more than one side in order to get an homogeneous thermal neutron field. By extrapolating the idea of irradiating a body from more sides, the step to irradiate a rotating body which is rotational-symmetric seems straightforward. The rotation is discussed in section 4. A spheroid shaped liver holder (see Figure 2) with a polar axis R_{polar} and a azimuthal axis R_{azimuthal} is chosen of which the volume V_{spheroid} can be calculated with:

\[
V_{\text{spheroid}} = \frac{4}{3} \pi R_{\text{polar}}^2 R_{\text{azimuthal}}
\]

The advantage of a spherical design is that the intensity fall off near the edges of the beam is compensated by the presence of less liver material to irradiate near the bottom and top: R_{polar} can be chosen the same as R_{source disk}. The R_{azimuthal} should be a compromise of being large enough to create space
for the liver and still provide enough thermal neutrons at the centre of the liver. In fact the thermal neutron profile, as shown in Figure 1, is distributed over a volume resembling a torus due to rotation of the spheroidal liver holder. The volume of a torus is given by

\[ V_{\text{torus}} = 2\pi R_{\text{torus}} \cdot A_{\text{torus}} \]  

(2)

with \( A_{\text{torus}} \) defined as the area of the vertical cross section of the torus. At the edges of the liver holder the tori-volumes are large which will decrease even more the already low thermal neutron density. This has to be compensated by surrounding the holder by neutron-moderating and reflecting materials in order to increase the number of thermal neutrons at the edges. In addition to selecting appropriate materials (discussed in the next section), the dimensions of the materials are also variable. Typical dimensions that can be varied in order to optimize are \( a, b, c, d \) and \( e \) which are given in Figure 2.

![Figure 2. Schematic overview of the liver irradiation set-up with all the design parameters and 3D drawn tori for tallying neutrons simulating rotation.](image)

3. Materials

For moderation of the epithermal source neutrons, a scattering medium containing a lot of hydrogen should be selected. This requirement is met by the plastic Polymethylmethacrylate (PMMA) which is solid and stiff. PMMA has a mass fraction for hydrogen which is around 20% less compared with liver tissue. This difference is reduced to 10% due to the higher density of the plastic. PMMA is non-toxic and transparent and therefore suitable for holding the liver. The difference in elastic scattering properties in PMMA and liver tissue is shown in Figure 3.
Figure 3. Microscopic elastic scattering and radiative capture cross sections of liver, PMMA and graphite for neutrons.

Figure 3 contains 2 sets of 3 curves: For 3 materials (liver tissue, PMMA and graphite) the probabilities that a neutron will scatter elastically and the probabilities that a gamma will be produced, are given per unit area. These are so-called microscopic cross sections which can be translated into macroscopic ones by multiplying with the atomic densities. These are 0.107, 0.102 and 0.080 for liver, PMMA and graphite respectively with unit atoms/barn cm. A disadvantage of hydrogen is the production of 2.2MeV gammas (so-called radiative capture). For this reason the rotating liver holder is surrounded by just enough PMMA to create the necessary thermal neutron build-up and is supplemented by graphite for more scattering of the neutrons with less production of gammas. In Figure 2 these two materials are defined as build-up and reflector. In Figure 3 it can be seen that graphite has a probability to scatter which is 10 times less than PMMA. On the other hand the probability that graphite produces a gamma is 100 times less. These numbers should be multiplied by 1.33 to take into account the atomic density.

After selecting these materials, the computer code MCNP [5] is used to simulate the neutrons and gammas through the geometry. By varying the parameters \(a\) to \(e\), one at a time and tracking changes, the optimal set-up can be chosen. During this phase the thermal neutron flux \(\phi_{th}\) is monitored at certain characteristic positions, at which it is checked if

\[
\phi_{th}(centre) = \phi_{th}(thermal \ max) = \phi_{th}(equator) = \phi_{th}(top) \approx \phi_{th}(bottom)
\]

as much as possible. At the same time, as low as possible gamma production is checked. When these criteria are closely met, the thermal neutron flux is checked everywhere in the liver by simply programming many tori inside the liver.

4. Rotation

By programming tori, only one MCNP calculation is needed in which the beam irradiates the liver from one direction. MCNP adds all the track lengths of the neutrons or gammas inside the torus volume and gives, when dividing by the volume of the torus, the neutron and/or gamma flux. From another point of view, the flux can be seen as a time-averaged flux inside the rotating liver. Mathematically, the above explanation of the calculation of a flux in a rotating torus is as follows: Imagine the torus to be fixed and that the beam is rotating around it with a revolution time \(T\). This
means that the angular flux $\Phi(\tilde{r}, \Omega, E, t)$, as defined in Bell and Glasstone [6] at $\tilde{r}$ within the torus becomes a function of time $t$. The angular flux is also depending on the direction $\Omega$ and energy $E$ of the neutrons. Integrating over time $T$ and dividing by $T$ gives a time averaged angular flux. This part is shown in equation (3) between the brackets. In fact,

$$\bar{\Phi}_{\text{rev}}^{\text{V}_{\text{torus}}} = \frac{1}{V_{\text{torus}}} \int dV \int d\Omega \int dE \left\{ \frac{1}{T} \int_0^T d\Phi(\tilde{r}, \Omega, E, t) \right\}$$

(3)

gives the total flux averaged over $V_{\text{torus}}$ per revolution (rev). On this ‘per revolution’ basis, the total flux averaged over $V_{\text{torus}}$ can also be obtained by

$$\bar{\Phi}_{\text{rev}}^{\text{V}_{\text{torus}}} = \bar{\Phi}_{\text{rev}} = \frac{1}{V_{\text{torus}}} \int dV \int d\Omega \int dE \Phi(\tilde{r}, \Omega, E)$$

(4)

which is exactly what MCNP calculates with the so called F4 tally [5]. Note that the total averaged flux in equation (4) is equal in the whole torus after each revolution.

5. Results

After several MCNP calculations, the following parameter settings give the optimal configuration that is actually the ‘best compromise’; it takes into account the contradicting demand to have a high thermal neutron flux, homogeneous neutron field, low production of gammas and as large as possible volume to irradiate for the liver.

| Parameter | $R_{\text{polar}}$ | $R_{\text{azimuthal}}$ | $a$ | $b$ | $c$ | $d$ | $e$ |
|-----------|------------------|------------------|-----|-----|-----|-----|-----|
| Value [mm]| 80              | 85              | 5   | 30  | 35  | 150 | 10  |

With equation (1) it can be calculated that the volume is 2.4 liters, thus amply sufficient to hold livers of 2.1kg, which has been seen during the research done for this project. Although parameter $c$ is 35mm to obtain the optimum, for engineering reasons parameter $c$ is set to 45mm. Parameter $d$ has no more influence on the result for a graphite thickness $>150$mm. The graphite contributes up to 15% of the thermal neutron flux at the edge of the liver. Parameter $e$ has no significant influence on the thermal neutron flux and gamma production. Figure 4 shows a cross section of the thermal neutron field in the liver.

**Figure 4.** The thermal neutron flux in the 2.4 litres liver holder.
The average $\phi_{th}$ is $3.8 \times 10^8$ n/cm$^2$ s with a deviation of -20% and +17%. This minimum is at the edge and centre of the liver (dark blue color in Figure 4) and the maximum (red color in Figure 4) is at the thermal maximum. The thermal maximum is still present and recognizable but the ratio of maximum over minimum within 85mm becomes 1.5 instead of almost 4 as seen in Figure 1. Although there seems to be no improvement in homogeneity over the Pavia thermal neutron field, it has to be recalled that the Petten beam is rather small for such a large organ. In Pavia, the liver received a thermal neutron fluence of $4.0 \times 10^{12}$ n/cm$^2$, which translates in Petten to an irradiation time of 175 minutes ($=4.0 \times 10^{12}/3.8 \times 10^8$).

6. Conclusion
A computational study has shown that it is possible to irradiate satisfactorily a liver extra-corporally with the existing epithermal neutron beam in Petten. The following steps in this project will be to perform dosimetry measurements and thereafter, start the animal studies.

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