Feasibility study for the extra-corporal treatment of liver cancer by BNCT at the HFR Petten

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Abstract
At the BNCT irradiation facility at the HFR Petten (The Netherlands), a feasibility study has been carried out for the extra-corporal treatment of liver cancer. Based on the successful results obtained in Pavia (Italy), where rather conservative conditions were used, i.e. a thermal neutron fluence of $4 \times 10^{12} \pm 20\%\ n/cm^2$ and a tolerance dose of 15Gy, the conditions for treatment at the HFR are closely met. A rotating PMMA container with the liver inside, surrounded by more PMMA and graphite, is simulated using the Monte Carlo code MCNP. In the worst case, when healthy liver tissue contains a presumed upper limit of 15ppm $^{10}\text{B}$, a thermal neutron fluence of $3 \times 10^{12}\ n/cm^2$ can be given, with regard to the 15Gy tolerance dose, in 143 minutes for a 2.4 litre container (maximum feasible size). Under the same conditions, the tolerance dose should be 20Gy to deliver $4 \times 10^{12}\ n/cm^2$ in 190 minutes. Despite the much higher irradiation times compared with Pavia, the experiment appears feasible.

1. Introduction
Radiation oncologists have, in general, together with researchers from various fields, been trying for literally decades to prove that boron neutron capture therapy (BNCT) works for the treatment of brain tumours. Despite this tremendous effort put into BNCT worldwide, which nevertheless has given encouraging results, the overall outcome with regard to progress has been extremely slow. This is mainly due to the fact that new results give rise to new questions that should have been investigated earlier. In order to boost the whole BNCT project in Petten (The Netherlands), an investigation has been initiated to see if it is possible to repeat the successful extra-corporal treatment using BNCT of liver cancer, as done in Pavia (Italy), as reported by Pinelli \textit{et al} (2002). Regarding Petten, it would be preferable if the liver treatment is possible without the need to radically change the current set-up for treating brain tumours. It is known at the outset that the irradiation times are long, when compared to the 10-15 minutes of treatment at Pavia. The liver surgeon in Essen (Germany), where interest exists to use the Petten facility, has stated that even irradiation times of 2-3 hours could be acceptable. The overriding condition is that the extracted liver must be implanted back into the patient in less than 6 hours. Therefore, the question answered in this paper will be if it is possible to deliver the required thermal neutron fluence in the maximum time of three hours; the other three hours are reserved for transportation of the liver between Petten and Essen. The Petten beam consists mainly of epithermal neutrons; the energy spectrum is between 10eV and 10keV with two small peaks around 30keV and 70keV. The beam has

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a very small divergence (2 degrees) and by collimation, a fixed diameter. These characteristics of the neutron source are very different from the conditions in Pavia, where the irradiation was performed in a thermal column, which infers that the liver was placed in a ‘cloud’ of thermal neutrons. For the Petten beam, a different set-up is necessary in order to distribute the rather small field of directed neutrons over the total, rather large, volume of the liver. Following a series of calculations, this condition can be met only by rotating the liver as is discussed in the following sections.

2. Methods and materials
In the next sections the organ itself and the irradiation goals and limits will be discussed. Thereafter, the simulation of the rotating liver is described and finally the description of the designed irradiation facility.

2.1 The liver
The liver is the largest internal organ and is responsible to rid the blood of toxins and regulate the blood sugar. It can be characterized as a wedge-shaped spongy organ. According to literature (Gray 1918), the average weight of a male liver is around 1.5kg and for a female 1.3kg. The maximum dimensions, when in the body, measure transversally up to 22.5cm; vertically, near its lateral or right surface, up to 17.5cm; and the greatest anterior-posterior diameter is 12.5cm. The liver surgeon involved in this investigation has already confirmed these measurements, but it is common, as recently observed, for a male patient to have a liver of 2.1kg. For this study, pictures of the liver were provided by the surgeon during a liver transplant, showing the diversity of size and weight of the liver and, most importantly, how livers can be handled. As illustrated in Figure 1a, when the liver is held in a plastic bag, it can be shaped to resemble a spheroid.

![Figure 1a (left): In a plastic bag, the liver can be formed as a spheroid. Figure 1b (right): Testing of custom-manufactured spheroid-shaped mould, to see if a typical liver can fit.](image)

Such manipulating and forming of the liver into a spheroidal shape, was requested based on the evolving calculations, which suggested that a more even dose distribution would be possible with such a shape. As such, spheroid-shaped moulds were made to fit some real livers. As can be seen in Figure 1b, a female liver of 1.3kg fits perfectly in the spheroid mould.
2.2 Irradiation goals and limits
The irradiation goals are defined as a certain number of thermal neutrons, which need to be attained, which would cause enough $^{10}$B -reactions to kill the cancer cells, and which must be given within about three hours while not exceeding the tolerance dose in healthy tissue. From the Pavia study it is stated in referenced work (Pinelli et al 1996 and 2001) that in healthy tissue a very conservative (photon-equivalent) tolerance dose of 15Gy, defined at a point, may not be exceeded. This is a conservative value as values from 25 to 30Gy are reported (Hassan 1993, Martinenghi 1984 and Cromheecke et al 1999) for the case of a single photon dose, averaged over the whole liver. In this study, to calculate the weighted dose, the weighting numbers for the $^{10}$B -carrier BPA (Coderre et al 1996), for brain BNCT, will be used as described in the Pavia papers; in healthy tissue this factor is 1.4 for the $^{10}$B dose, 3.2 for the thermal and fast neutron dose and 1.0 for the photon dose. Furthermore, from discussions, it is known that the two irradiated livers in Pavia received a thermal fluence of $4\cdot10^{12}$ n/cm$^2$ ($\pm20\%$).

As the tumours are spread throughout the liver, the thermal neutron flux distribution, which is directly related to the number of $^{10}$B reactions, should be as homogenous as possible.

2.3 Rotating liver
When dealing with a thermal column, like in Pavia, it is best to position the liver in its natural form on a flat surface, as the thermal neutron flux, around 3cm from the surface, will be half the surface value. From the same series of pictures taken by the surgeon in this study, it appears that most livers would fit into an imaginary cylindrical container with a diameter of 25cm and a height of 8cm. The thermal neutrons, coming from both sides, will in this way deliver a homogeneously distributed dose in the liver.

On the other hand, in Petten, the liver should be as compact as possible in order to use optimally the more penetrating epithermal neutrons. The thermal neutron flux caused by moderation of the epithermal beam has a maximum at 3cm from the surface and is half this maximum value at 0.5cm and 6.5cm. As already described, the liver can fit into a spheroid-shaped container with, to get an idea about the dimensions, equatorial radius of 8.5cm and polar radius of 7cm.

For BNCT, in order to distribute the most effective part of the neutron fluence, between 0.5cm and 6.5cm, it became apparent that this is best achieved if the liver is rotated around the polar axis. In this way, when the thermal maximum is slightly moved nearer the surface by the scattering properties of the container material, the highest thermal fluence will be smeared out over the largest volume, because an imaginary volume at the equator of the spheroid will describe the largest trajectory when rotating. Closer to the centre of the spheroid, the thermal fluence of course, is lower but at the same time distributed over a smaller volume when rotating. To simulate rotating bodies and to calculate the overall thermal neutron fluence distribution is not possible when using one of the currently available treatment planning programs available in BNCT, such as BNCT_rpte (Wessol et al 1997), SERA (Wessol et al 1999) or NCTPlan (Zamenhof et al 1996). Therefore, this study was carried out using the Monte Carlo code MCNP (Briesmeister 2000). A MCNP model of the Petten BNCT facility, containing the geometry and material definitions facility is already available, which is normally used, for example, to simulate experiments and to verify the source description. This geometry
will be further discussed in the next section. By programming torus-shaped volumes to keep track of the particles (called tallies in MCNP), rotation is simulated (see Figure 2a). There is therefore only one calculation needed in which the beam irradiates the liver from one direction. MCNP adds all the track lengths of the particles inside the torus volume and gives, when dividing by the volume of the torus, the flux. This averaging of the calculated flux over the whole torus is an excellent simulation of the flux distribution since the liver is rotating, by which the flux will be evenly distributed. As a consequence, purely aesthetically, the flux becomes a time-averaged flux inside the rotating liver.

![Figure 2a (left): Isometric view of the spheroidal liver model, which contains a torus-shaped tally to simulate rotation. Figure 2b (right): Cross-section of the liver with several tori; the flux in the whole liver can be determined.](image)

As illustrated in Figure 2a, the torus is positioned symmetrical around the vertical axis through the centre of the spheroidal liver. With several tori, all centred on the vertical axis but with different sizes, the flux in the whole liver can be determined. Figure 2b shows such a configuration with several tori in the liver and some near the surface inside the container. Note that the tori at the vertical axis become spheres. Due to symmetry, only half the liver has to be filled with tallies.

2.4 Liver irradiation set-up
The design concept for the set-up to irradiate the extra-corporal liver does not require significant changes to the existing patient treatment environment, which is currently installed to treat brain cancer. Also due to this reason, the neutron source spectrum and source strength need not be adapted. The liver set-up must also be portable in such a way that it can be easily installed and removed. Furthermore, the design must be economical with regard to use of standard materials and components, such as readily available in Petten. The design has evaluated from surrounding the liver container by water (good scatterer, moderater and coolant), as was the initial set-up, towards a solid surrounding bearing the same characteristics. It seems that the solid surrounding gives no significant difference in yield, it is though easier to manufacture in comparison with something that has to be watertight and the cooling of the liver can be taken over by injecting cold air. After testing many configurations, the final set-up for irradiating a volume (liver) of 2.4 litre is shown in Figure 3.
Figure 3. The final set-up as designed to irradiate extra-corporal livers in Petten.

The spheroid container holding the liver is made from PMMA and consists of two equal parts that are connected after inserting the liver. The modelled liver composition and density is taken from ICRU46 (1992). The liver is together with a conservation solution (at this stage modelled as water) already packed in a plastic bag. The container will be filled as much as possible, with liquid (water or more conservation solution) in order to fill empty spaces as any air gaps would influence the prescribed dose. The advantages of PMMA are that it can be shaped easily, it is non-toxic, behaves well at 4°C, which will be the liver conservation temperature, will not be activated by the irradiation and is transparent, which allows observation of the liver. The container is placed in a PMMA square cube with sides of 20cm. The axis needed for the rotation will be from PMMA as well. The PMMA cube is also easy to manufacture and behaves as a good scatterer especially for the top and bottom of the spheroid. For back scattering, the cube is surrounded by pure, 1.6 g/cm³, graphite blocks with at the entrance a graphite cone. Normally, inside the beam shutter, there is a beam collimator. The maximum available collimator diameter is 15cm. However, by removing the collimator, the beam diameter will be 16cm, thereby giving significantly higher fluxes at the edges of the beam.

3. Results
After selecting the materials and geometry according to the criteria explained in section 2.4 and the design evolution, the iteration process analysed the results of the thermal neutron flux density, the gamma production and their distribution in the liver. In this feasibility study, two optimal set-ups will be discussed representing the lower and the upper limits. The lower limit is an irradiation volume capacity of 1.5 litre; it is not expected that there will be livers, together with the necessary amount of conservation
liquid (in the order of 100ml), that are smaller than this volume. The upper limit, an irradiation volume capacity of 2.4 litre is constrained by the existing beam characteristics. Figure 4a and 4b show the thermal neutron flux distribution for the case of the 2.4 litre volume: equatorial radius of 8.5cm and a polar radius of 8cm. Thermal neutrons are defined as neutrons with an energy below 0.414eV. A proportionally sized image of the PMMA container is given as background to this contour plot. Note that the statistical uncertainties in the MCNP results, presented in this study, are always below 1%. They will not be further mentioned.

Figure 4a (left): Thermal neutron flux inside the 2.4 litre container when irradiated from one side. Figure 4b (right): Like the left figure but now with the container, with the liver inside, rotating.

Figure 4a gives the thermal neutron flux, at the vertical cross section along the beam line, when the liver is not rotating. As the neutron beam is coming from the left, it is not surprising to see the highest flux values, at the thermal peak, positioned at the left side of the liver. In Figure 4b, when the liver-container rotates, the effect of this rotation on the flux distribution is obvious.

In order to distribute the neutron flux as homogeneously as possible, the wall of the PMMA container is the thickest at the equator and decreases towards the top and bottom of the spheroid. This thickness represents a compromise of slowing down enough epithermal neutrons to have a satisfactory number of thermal neutrons at the surface and to allow enough neutrons to reach the centre of the liver. At the top and bottom, the PMMA is thinner which allows a better passage of neutrons scattering into the liver from the PMMA surrounding cube. Clearly from Figure 4, the thermal maximum is $4.2 \cdot 10^8$ n/cm$^2$s, which is 2.5cm away from the surface. Similar results can be seen in Figure 5 where the thermal neutron flux contours are plotted for the 1.5 litre liver container (equatorial radius of 7.5cm and polar radius of 6.5cm).
Figure 5. Thermal neutron flux contours inside the 1.5 litre container.

For this model, a modification is made to the PMMA surrounding cube in order to decrease an initial ‘second’ thermal neutron flux maximum positioned near the top and bottom. A piece of PMMA at the entrance is taken out of the cube causing less scattering from the top and bottom towards the non-rotating spots on the axis. Without this modification the thermal neutron flux was 20% higher than the ‘normal’ thermal maximum, which is disturbing the homogeneity demand on the thermal neutron flux distribution. For this same reason of distribution, extra lump-shaped pieces of PMMA are attached to the container.

A summary of the results for both containers is given in Table 1. As well as the statistical characteristic thermal neutron flux values, the irradiation time to deliver $4 \cdot 10^{12} \text{ n/cm}^2$ and the irradiation time to reach the tolerance dose of 15Gy in the liver are also given. To calculate the weighted dose, the weighting factors as described in section 2.2 are used together with 15ppm of $^{10}$B in the healthy liver tissue. For the gammas present in the beam, a value of 1Gy/h is added, as used in the brain BNCT trials in Petten.

<table>
<thead>
<tr>
<th>Description</th>
<th>1.5 litre container</th>
<th>2.4 litre container</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average thermal neutron flux:</td>
<td>$4.1 \cdot 10^8 \text{ (n/cm}^2\text{s)}$</td>
<td>$3.5 \cdot 10^8 \text{ (n/cm}^2\text{s)}$</td>
</tr>
<tr>
<td>Minimum thermal neutron flux:</td>
<td>$3.7 \cdot 10^8 \text{ (n/cm}^2\text{s)}$ (-10% from average)</td>
<td>$2.7 \cdot 10^8 \text{ (n/cm}^2\text{s)}$ (-23% from average)</td>
</tr>
<tr>
<td>Maximum thermal neutron flux:</td>
<td>$4.5 \cdot 10^8 \text{ (n/cm}^2\text{s)}$ (+10% from average)</td>
<td>$4.2 \cdot 10^8 \text{ (n/cm}^2\text{s)}$ (+20% from average)</td>
</tr>
<tr>
<td>Time to deliver thermal fluence of $4 \cdot 10^{12} \text{ n/cm}^2$:</td>
<td>163 min</td>
<td>190 min</td>
</tr>
<tr>
<td>Maximum weighted dose rate (time to reach tolerance dose of 15Gy):</td>
<td>6.9Gy/h (=130min)</td>
<td>6.3Gy/h (=143 min)</td>
</tr>
<tr>
<td>Average weighted dose rate in the liver</td>
<td>6.2Gy/h</td>
<td>5.6Gy/h</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of the thermal neutron flux together with the irradiation times for the two liver containers.

4. Conclusions
A single MCNP-calculation with torus-shaped volumes to keep track of the particles enables the simulation of a rotating liver. A set-up with inexpensive and easy to use materials has been designed and presented here for the case of two extremes regarding the liver volume: 1.5 litre and a 2.4 litre containers.

Focussing on the maximum time given by the surgeon to irradiate, which is 180 minutes, together with the thermal neutron fluence given in Pavia (\(4 \times 10^{12} \text{ n/cm}^2 \pm 20\%\)); the 1.5 litre container meets the requirement and the 2.4 litre exceeds the time with 10 minutes. The range of the thermal neutron flux varies between -23% and +20%. The 2.4 litre container can be regarded as the very upper limit of what is possible in Petten. Nevertheless, the 2.4 litre container can hold the largest 2.1kg liver, which will be rarely the case. Therefore, this container can be used as an emergency solution whenever the liver is bigger than expected which could be the case due to the enlargement of the sick liver by the tumours. The thermal neutron flux range in the smaller container shows, with values of –10% and +10%, the most possible homogeneous dose distribution.

For a tolerance dose of 15Gy in a point in healthy tissue, respective times of only 130min and 143min for the two containers is possible. This means that, compared with the average Pavia thermal fluence, only \(3 \times 10^{12} \text{ n/cm}^2\) would be given in both cases. Possible means to increase the thermal fluence includes a further reduction of the beam gammas and/or decreasing the highest occurring thermal flux value in the liver. Regarding the beam gammas (1Gy/h), it would need a new beam design although it is doubtful if it is possible to decrease the existing gamma component even further without affecting the epithermal neutron spectrum and flux. Decreasing the maximum thermal neutron flux at the thermal peak is impossible since this thermal peak is inherent to the use of an epithermal beam. Although it is feasible to shift slightly the position of the hot spot, this procedure is limited by its significant influence on the fluxes at the surface and near the centre of the organ.

Nevertheless, this calculation is done with 15ppm of \(^{10}\text{B}\) in healthy tissue that may be decreased; in Pavia, for example, one of the treated livers had only 10ppm in healthy liver tissue. This specific amount of \(^{10}\text{B}\) would mean a 10% increase of the neutron fluence. Another possibility is to reconsider the tolerance dose; a tolerance dose of at most 20Gy in a point enables a fluence of \(4 \times 10^{12} \text{ n/cm}^2\). Regarding the average weighted dose in the two liver-models (see Table 1), with respect to deliver a thermal neutron fluence of \(4 \times 10^{12} \text{ n/cm}^2\), the average weighted dose will be 18Gy; tolerance doses of 25Gy to 30Gy for the whole liver have been reported.

In conclusion, therefore, the given requirements to irradiate an extra-corporal liver with BNCT at the HFR in Petten can be closely met. With the therapeutic approval that the tolerance dose and \(^{10}\text{B}\) concentrations allow a safe and effective treatment, then from the technical point of view, liver irradiations in the existing BNCT facility in Petten are feasible.

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