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PAPER

Development of an irradiation method for superficial tumours using a hydrogel bolus in an accelerator-based BNCT

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Keywords: boron neutron capture therapy, BNCT, bolus, superficial tumour, accelerator-based BNCT

Abstract

The aim of this study is the development of an irradiation method for the treatment of superficial tumours using a hydrogel bolus to produce thermal neutrons in accelerator-based Boron Neutron Capture Therapy (BNCT).

To evaluate the neutron moderating ability of a hydrogel bolus, a water phantom with a hydrogel bolus was irradiated with an epithermal neutron beam from a cyclotron-based epithermal neutron source. Phantom simulating irradiation to the plantar position was manufactured using three-dimensional printing technology to perform an irradiation test of a hydrogel bolus. Thermal neutron fluxes on the surface of a phantom were evaluated and the results were compared with the Monte Carlo-based Simulation Environment for Radiotherapy Applications (SERA) treatment planning software. It was confirmed that a hydrogel bolus had the same neutron moderating ability as water, and the calculation results from SERA aligned with the measured values within approximately 5%. Furthermore, it was confirmed that the thermal neutron flux decreased at the edge of the irradiation field. It was possible to uniformly irradiate thermal neutrons by increasing the bolus thickness at the edge of the irradiation field, thereby successfully determining uniform dose distribution. An irradiation method for superficial tumours using a hydrogel bolus in the accelerator-based BNCT was established.

1. Introduction

Boron Neutron Capture Therapy (BNCT) is a radiation therapy that selectively destroys cancer cells using charged particles emitted by a nuclear reaction between ^{10}B atoms accumulated in cancer cells and thermal neutrons [1, 2]. The alpha particles and ^{7}Li nuclei generated by the nuclear reaction have a high linear energy transfer, with ranges that are shorter than the diameter of a cell. Cancer cells can be selectively destroyed if the ^{10}B atoms in boron drugs accumulate in cancer cells when compared with normal tissue. In recent years, neutron sources for BNCT have been shifting from reactor-based to accelerator-based treatment systems. The Institute for Integrated Radiation and Nuclear Science, Kyoto University (KURNS), has developed an accelerator-based neutron source in collaboration with Sumitomo Heavy Industries, Ltd A Cyclotron-based Epithermal Neutron Source (C-BENS) was installed at KURNS [3] in 2008. The world's first clinical trials using accelerator-based neutron sources were conducted at KURNS using C-BENS to treat recurrent brain tumours. C-BENS was also established at the Southern Tohoku BNCT Research Center [4] and the Kansai BNCT Medical Center. In addition to the cyclotron-based neutron source, other accelerator-based neutron sources using linear or electrostatic accelerators are also being developed [5–7]. The number of accelerator-based BNCT facilities is expected to increase in the future.

There are two specific challenges for the use of accelerator-based treatment systems. While accelerator-based neutron sources produce epithermal neutrons with higher energy than thermal neutrons for the successful treatment of deep-seated tumours, its energy cannot be reduced to the low thermal neutron energy range required to provide a sufficient dose for superficial tumours. Second, it is difficult to develop a uniform distribution of thermal neutrons. Therefore, it is essential to develop an irradiation method for thermal neutrons that can adapt the accelerator-based BNCT for deep-seated and superficial tumours.

A dose distribution shifter (DDS) was investigated [8]. A DDS was installed inside the collimator to moderate the neutrons and subsequently increase the surface dose. This irradiation system is an effective method to increase the thermal neutron flux at the superficial tumours for the accelerator-based BNCT. On the other hand, to form a uniform thermal neutron flux distribution, the use of a bolus is effective. A hydrogel was adapted as a bolus because it can be moulded into various shapes. Therefore, it is expected to produce a uniform distribution of thermal neutrons for complex and uneven areas by adjusting a bolus's size and thickness using three-dimensional (3D) printing technology. It is also expected that a hydrogel can efficiently moderate neutron energy in the thermal neutron energy range because of its high hydrogen content. However, the moderation ability has not been clarified.

In radiation therapy, boluses utilising 3D printing technology are sufficient to create a uniform dose distribution [9, 10]. It is also possible to improve the surface dose using a bolus material in the BNCT, which has been utilised in research reactors [11]. Adjustment of the bolus thickness and size for uniform irradiation has not been previously studied for BNCT.

This study aimed to establish the irradiation of superficial tumours using a bolus in an accelerator-based BNCT. The hydrogen density and molecular bonding determine the neutron moderating ability of a bolus material. However, no data exists on the thermal neutron scattering law for hydrogels. Therefore, the neutron moderating ability of the hydrogel was verified first, confirmed by the irradiation of the epithermal neutron beam. Next, irradiation tests were conducted to simulate a malignant melanoma on the foot to investigate the irradiation method for clinical application. The Monte Carlo-based neutron transportation of Simulation Environment for Radiotherapy Applications (SERA), used for the clinical studies of BNCT in the Kyoto University Research reactor (KUR), was also utilised for the irradiation simulation in this study. The simulation and experimental results were compared to verify the validity of SERA and study quality assurance (QA) methods. Finally, the bolus size was changed using SERA and the possibility of achieving a thermal neutron distribution with a target of 5% uniformity, even for irregular shapes, was investigated.

Table 1. Composition of the water-soluble polymer gel.

Element	C	H	O	S
Percentage (%)	5.82	10.88	83.28	0.02

2. Materials and methods

2.1. Evaluation of neutron moderating ability of a hydrogel bolus

The water-soluble polymer gel was manufactured by Nissan Chemical Corporation as a bolus material. The density of the gel is 1.03 g cm^{-3} at 25 °C. And the composition is shown in table 1.

Irradiation tests were carried out using a water phantom to evaluate thermal neutron moderating ability of a hydrogel bolus using an epithermal neutron beam of C-BENS.

Thermal neutron fluxes in a water phantom with a hydrogel bolus were compared to those without the bolus. A schematic layout and setup for the irradiation test is shown in figure 1.

A hydrogel bolus was placed on the surface of a 200 mm cubic water phantom. All boluses used in this study were 150 × 150 mm with three different thicknesses of 5, 10, and 20 mm.

The thermal neutron flux was measured using the gold activation method, whereby a gold wire was placed along the depth direction on the central axis. Another gold wire was also placed on the surface of the bolus and the water phantom. A gold wire covered with cadmium was also installed in a similar setting. A phantom with a bolus of each thickness was placed in front of the C-BENS irradiation port and irradiated with an epithermal neutron beam collimated in a 120 mm diameter. Thermal neutron fluxes were derived by measuring the reaction rate of activated gold wires after irradiation. The reaction rate R of the gold wire was derived from the equation below:

$$R = \frac{\lambda C}{\varepsilon\gamma e^{-\lambda t_c}(1 - e^{-\lambda t_m})\sum_{i=1}^{n}\left(\frac{Q_i}{\Delta t}(1 - e^{-\lambda\Delta t})e^{-\lambda(n-i)\Delta t}\right)} \quad (1)$$

where the constants λ, ε, γ, and C are the decay constant, detection efficiency, gamma-ray emission ratio, and total photo-peak counts measured by a high-purity germanium detector, respectively. t_c, t_m, and t are the cooling, measuring, and irradiation times, respectively. The C-BENS produces neutrons by hitting a beryllium target with protons. The variations in the proton current, expressed as $Q_i/\Delta t$, were taken into consideration to correct the irradiation time. Details of the measurement methods are presented in the reference paper [12].

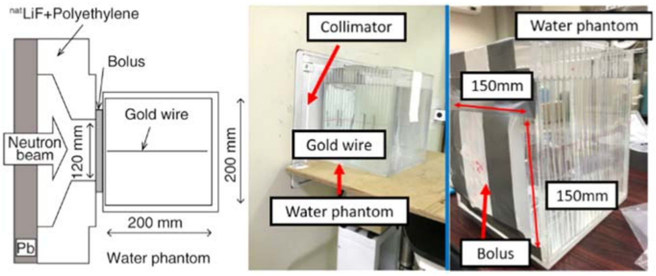

Figure 1. Schematic layout of the irradiation test.

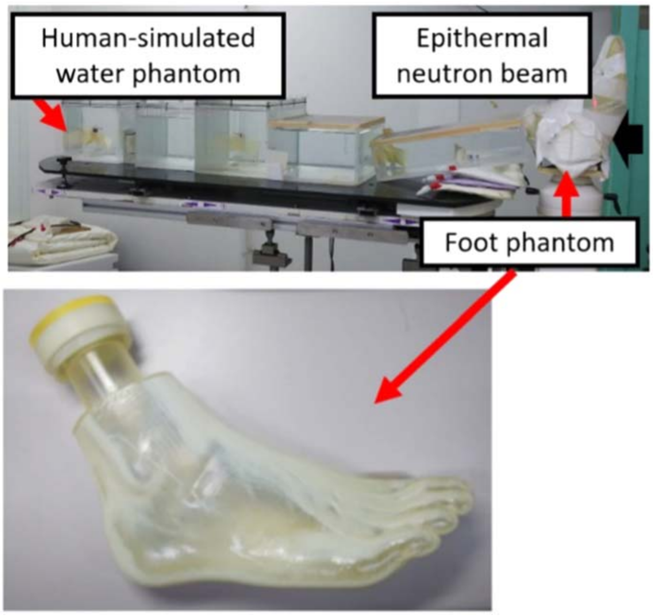

Figure 2. Photograph of the irradiation test using a phantom.

2.2. The validation test of Monte Carlo based simulation using a foot phantom

2.2.1. Fabrication of a foot phantom

To simulate irradiation of superficial tumours such as a malignant melanoma, a foot-shaped phantom was manufactured. The surface data below the ankle were created using a 3D scanner (Artec Eva Lite: Artec 3D). 3D-CAD software such as Meshmixer and Autodesk Fusion 360 (Autodesk, Inc.) were used to convert the 3D data for printing. The thickness of the phantom was set to 2 mm and had a structure that could contain water. A foot phantom was fabricated with this 3D data using an AGILISTA-31103D printer (Keyence Corporation), as shown in figure 2. The material of the modelled object of the 3D printer is a photo-curing resin.

2.2.2. Irradiation test of a foot phantom

The irradiation test was performed under the assumption of melanoma in the heel using C-BENS. A gold wire was placed on the heel of the phantom surface. A gold wire covered with Cd was also placed in the same position. Irradiation of the phantom was performed separately. Two 150 mm square and 10 mm thick sheets of hydrogel boluses were placed on the surface of the affected area. A hydrogel bolus is shaped like a pentagon because its corners are bent to adhere to the sides of a phantom. A foot phantom was placed in front of the C-BENS irradiation port and irradiated with a 12 cm diameter collimated epithermal neutron beam. The thermal neutron flux distribution on the surface of a phantom was derived by measuring the gold wire's saturated radioactivity after the irradiation. Figure 2 shows the setup of the irradiation test with a foot phantom. Figure 3 shows the irradiation setting with a bolus and setting positions of the gold wires, where nine evaluation points were set with position zero representing the irradiation centre.

2.2.3. Comparison with the simulation results

The measured results from the irradiation tests were compared with the calculated results of SERA. CT images of the foot phantom with gold wires and boluses were obtained to reproduce the foot phantom irradiation test on SERA. Thank you for your useful comments. The 3D model of foot phantom in SERA

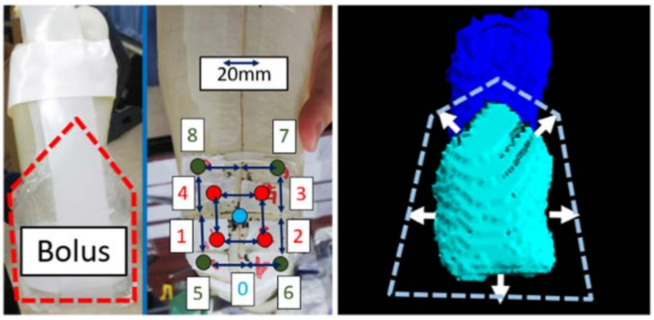

Figure 3. Setting of a bolus and the evaluation position for a foot phantom irradiation and Schematic diagram of the bolus size change.

was created using CT images. The whole 3D model of the phantom was defined as water. The calculation geometry successfully reproduced the experimental setup. The voxel size of the calculation is $1 \times 1 \times 1$ cm. In the SERA calculations, the dose at each voxel was derived using the dose conversion factor and neutron fluence. The transport particle of neutrons was 1×106, and the neutrons were transported in calculation geometry until they were absorbed or went outside of geometry. The usefulness of a bolus was also tested by comparing results with and without a bolus.

2.3. Investigation of the irradiation method using boluses

Thermal neutron fluxes on the surface of a phantom were calculated by changing the bolus size on SERA to achieve a uniformity of thermal neutron fluxes within 5% at the evaluation points, as shown in figure 3. The change of the bolus size was performed according to the following procedure.

1. There is an air gap between the bolus and the phantom. A gap between the bolus and the phantom was filled with hydrogel materials.
2. Expanding a bolus's size in the longitudinal and transverse directions and increasing the bolus thickness at the edge of the irradiation field to increase neutrons scattered from the enlarged bolus, thereby enhancing the thermal neutron flux at evaluation points 5 to 8.
3. Until the uniformity of thermal neutron flux at evaluation points 0–8 was within 5%, 2. was carried out. The uniformity index u is defined as follows when the thermal neutron flux is defined as $\phi_{\rm i}$ and the mean value of the thermal neutron flux is defined as $\phi_{\rm av}$:

$$u = \sum_{i=0}^{8} \left| 100 \times \left(1 - \frac{\phi_i}{\phi_{av}}\right) \right| /9 \qquad (2)$$

A schematic diagram of the bolus size changing is shown in figure 3.

2.4. Evaluation of the dosimetric characteristics

To evaluate the total dose delivered to a patient by neutron irradiation, the equivalent dose was derived by multiplying the relative biological effectiveness (RBE) or compound biological effectiveness (CBE) with the physical dose in the SERA simulation. The equivalent doses for tumour ($\rm ED_{tumour}$) or skin ($\rm ED_{skin}$) were respectively derived from the equations below,:

$$ED_{tumour} = C_B \times D_{B,ppm} \times CBE_{tumour} + D_H \times RBE_H + D_N \times RBE_N + D_\gamma \times RBE_\gamma \qquad (3)$$

$$ED_{skin} = C_B \times D_{B,ppm} \times CBE_{skin} + D_H \times RBE_H + D_N \times RBE_N + D_\gamma \times RBE_\gamma \qquad (4)$$

where C_B is the concentration of boron-10 and $\rm D_{B,ppm}$ is the physical dose caused by the reaction of $^{10}\rm B(n,\alpha)^7Li$ with a boron concentration of 1 ppm. $\rm D_H$ and $\rm D_N$ are the physical doses for the components of hydrogen and nitrogen, respectively. In this research, the $\rm RBE_H$ and $\rm RBE_N$ values of nitrogen and hydrogen doses were set to 3. The $\rm CBE_{tumour}$ and $\rm CBE_{skin}$ values, assuming the use of borono-phenylalanine for tumour and skin, were set to 3.8 and 2.5, respectively. These RBE and CBE values are referred to in reference papers [3, 13].

The skin boron concentration, which is assumed to be the same as blood, was set to 24 ppm [14]. The tumour to blood ratio of the boron-10 concentration was set to 3.5. The derived equivalent doses of the tumour for each evaluation point were evaluated under a skin dose of 15 Gy-eq.

3. Results

3.1. Evaluation of neutron moderating ability of a hydrogel bolus

Figure 4 shows the thermal neutron flux distribution of a water phantom on the surface and in the centre axis of the beam obtained from the experiment. The use of a bolus showed a shift in the thermal neutron flux peak in a water phantom. When a 20 mm thick bolus was used, the thermal neutron flux peak was

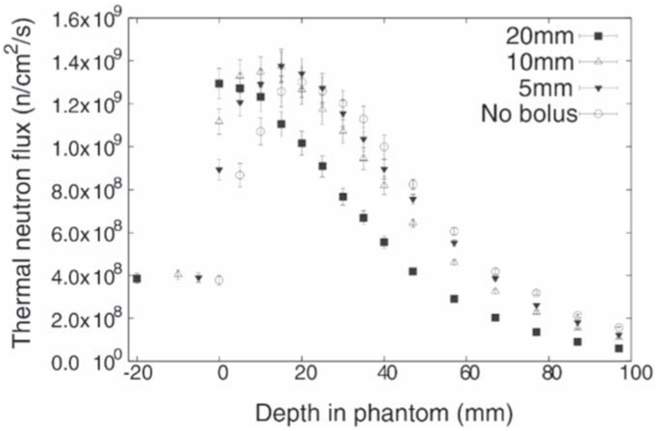

Figure 4. Measured thermal neutron fluxes on the surface and inside of a water phantom. The horizontal axis 0–100 mm indicates the depth in the phantom, and −20–0 mm indicates the bolus thickness.

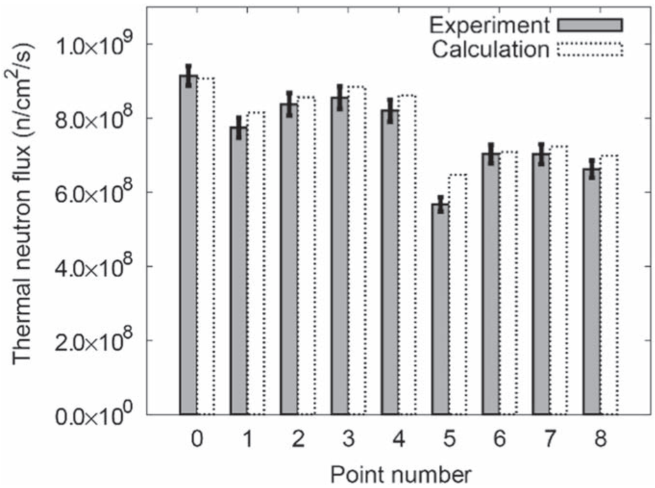

Figure 5. Thermal neutron flux distribution on the surface of a phantom by foot phantom with bolus irradiation tests. Comparison of experimental and SERA calculations for the foot phantom irradiation test.

located on the phantom surface. It was also confirmed that the maximum intensity of thermal neutron fluxes was almost equal to the value without the bolus for each bolus thickness.

The thermal neutron flux on the phantom surface with the 20 mm thick bolus was approximately three times higher than without the bolus. The thermal neutron fluxes without the bolus at a 20 mm depth were almost the same as the thermal neutron fluxes on the phantom surface with the 20 mm thick bolus. It was confirmed that the hydrogel bolus had the same thermal neutron moderating ability as water. In consideration of this result, the material of the bolus was set as water in the simulation with SERA.

3.2. Comparison between measurement and calculation results in the irradiation of a foot phantom

Figure 5 shows the experimental results of the thermal neutron flux distribution at each position of a foot phantom. It is expected that the irradiation test using a 3D printed phantom can confirm the actual thermal neutron fluxes in complex geometries with uneven surface regions.

Figure 5 shows the comparison between the measurements and calculation results of the thermal neutron flux distribution at each evaluation position. Figure 6 shows the rate of deviation of the calculated value from the experimental value. The calculated values obtained from the SERA simulation and the measured values obtained from the irradiation tests were similar except for point 5.

One of the possible causes of this discrepancy is the difference in the shape of the air gap between a bolus and phantom. In particular, the difference between the measured and calculated values may be caused by the difference in air shape between the bolus's setting position at the time of the irradiation test and CT image acquisition. The calculated value tends to be slightly higher overall, which is also considered to be due to the difference in the air gap. Another potential cause could be a setup error of the gold wires.

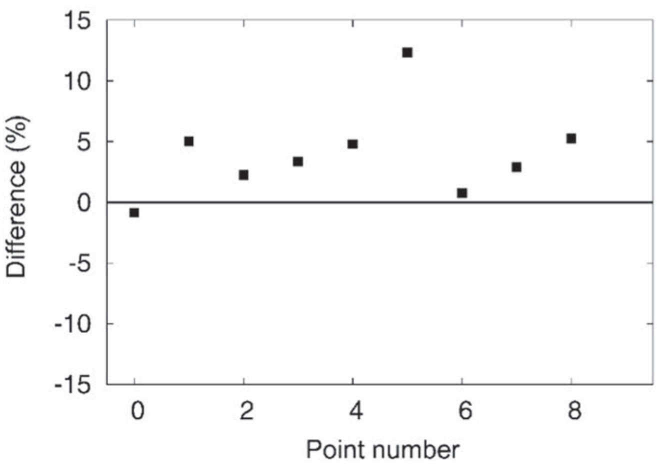

Figure 6. The rate of deviation of the experimental value from the calculated value.

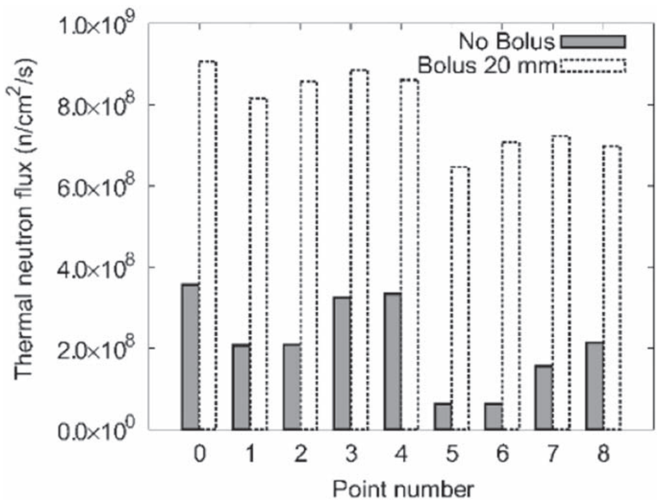

Figure 7. Comparison of calculated thermal neutron fluxes on the foot phantom surface with and without the bolus.

The average deviation of the experimental value from the calculated value was within 4.1%. The SERA simulation was able to reproduce the measured data within an error of 5%. It is useful to validate the treatment plan and the irradiation test using the 3D printed phantom as a QA method.

To confirm the bolus' usefulness, the thermal neutron fluxes calculated by SERA on the foot phantom surface, with and without the bolus, are shown in figure 7. The thermal neutron flux using a bolus at each evaluation point is approximately three times higher when compared to the flux without a bolus. Therefore, the hydrogel bolus can be expected to enhance the boron dose on the skin surface and improve the treatment effect.

3.3. Change of the bolus size to achieve uniform thermal neutron distribution

Figure 5 shows that each thermal neutron flux at evaluation points 5 to 8 is lower than at evaluation points 0 to 4. This suggests that the thermal neutron flux was not uniform on the surface of the phantom. If the tumour area is not uniformly irradiated with thermal neutrons, a sufficient dose might not be given. Therefore, it is important to create a uniform distribution of thermal neutron fluxes. Figure 8 shows the change in the thermal neutron flux at each evaluation point due to the bolus shape change.

The thermal neutron flux at points 5 to 8 increased with the expansion of the bolus size. Conversely, the change in the thermal neutron flux at evaluation points 1 to 4, closer to the irradiation centre, was small. The thermal neutron flux did not change at evaluation point 0, which corresponds to the centre of the irradiation. The thermal neutron flux did not increase at evaluation points 5 to 8 for widths exceeding 10 cm. This was due to the saturation of the incident neutron flux in the lateral direction. Therefore, further expansion of the bolus in the horizontal direction did not contribute to uniformity improvement.

Figure 9 shows the change in uniformity due to changes in the bolus size. When the bolus was

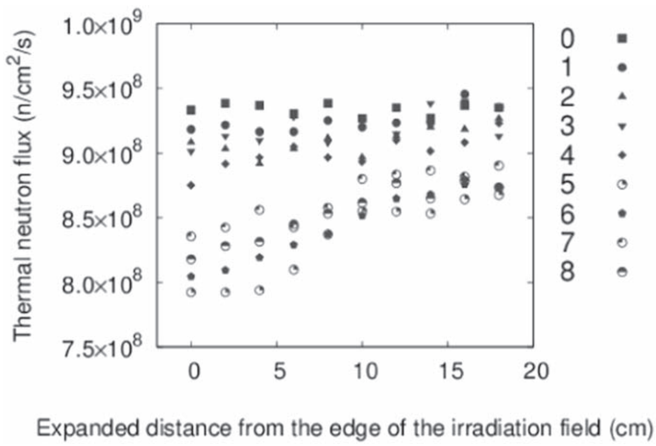

Figure 8. Change in calculated thermal neutron flux with the change of the bolus size.

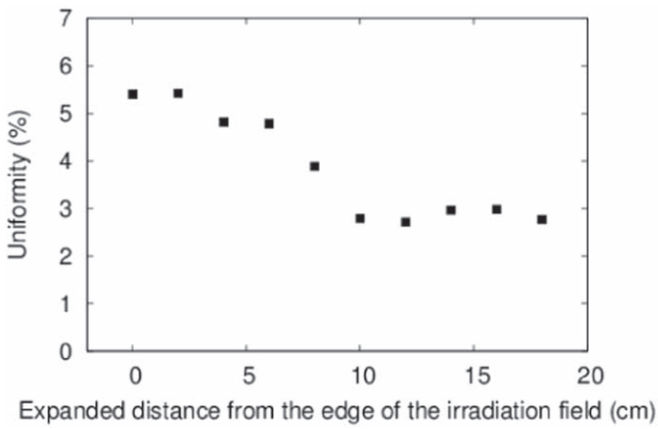

Figure 9. Change in uniformity with the change of the bolus size by calculation.

extended, the thermal neutron fluxes at evaluation points 5 to 8 increased because neutrons are scattered by an expanded bolus. The size of the extended distance from the edge of the irradiation field was called 'width'. As a result, the uniformity was improved. The uniformity change was small for width exceeds 10 cm because the thermal neutron flux at evaluation points 5 to 8 did not increase. It was confirmed that uniformity could be achieved at 5% or less by setting the bolus width to 4 cm or more. Furthermore, the uniformity was reduced to approximately 3% by changing the bolus size.

Figure 10 shows the comparison with the thermal neutron fluxes at each evaluation point when the bolus was extended by 10 cm with no gap between the bolus and phantom. The extended bolus thickness was also set to 20 mm. The thermal neutron fluxes with the 20 mm thick bolus calculated by SERA are also shown in figure 10. The bolus size change resulted in a uniform thermal neutron flux at each evaluation point compared with the 20 mm-thick boluses. Therefore, it is expected that a uniform thermal neutron flux on the skin surface can be formed by adjusting the size and thickness of the hydrogel bolus. The hydrogel bolus can be moulded into various shapes. Thus, shape-adjusted hydrogel boluses can be made using 3D printing technology. An adjustable shape can be created by creating a bolus shell and pouring hydrogel bolus inside it.

3.4. Evaluation of the dosimetric characteristics

A comparison of the equivalent doses at each evaluation point under the above conditions using changed and 20 mm-thick boluses is shown in figure 11.

An equivalent dose was uniformly delivered to the tumour compared to the 20 mm-thick bolus. Sufficient doses could be administered even in areas far from the irradiation centre, such as points 5 to 8. Using the changed bolus, a uniform dose distribution with an equivalent dose of 60 Gy-eq could be achieved in an area of 16 cm^2. This suggests that it is possible to achieve a uniform dose distribution over a wider area by further adjusting the bolus shape.

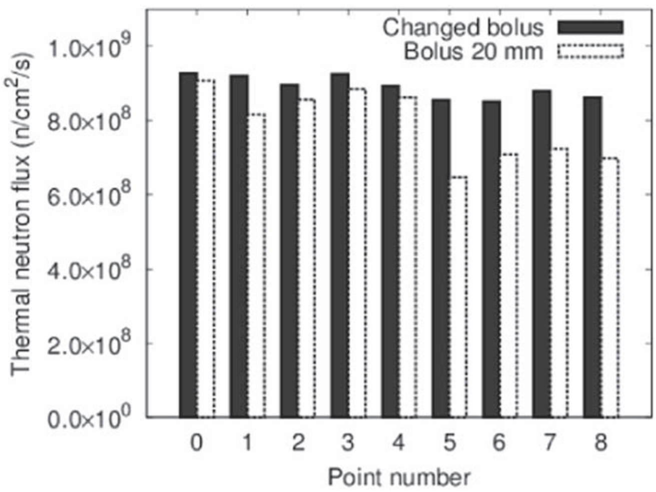

Figure 10. Comparison of calculated thermal neutron fluxes at each evaluation point between the changed bolus and the 20 mm thick bolus.

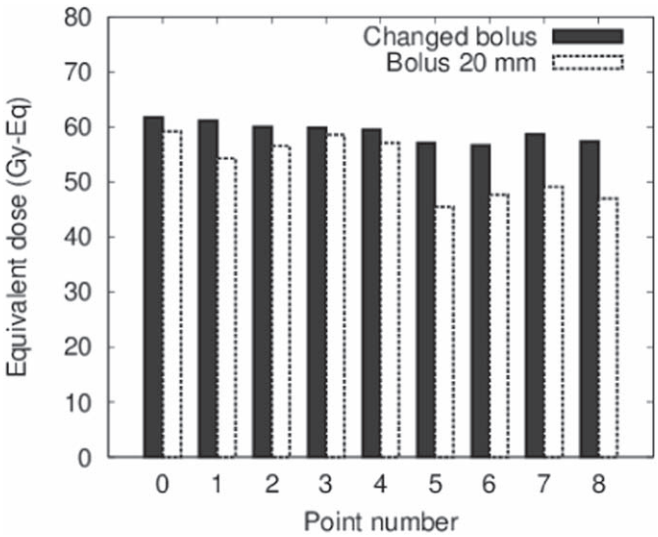

Figure 11. Calculated equivalent dose comparison between the changed and 20 mm thick bolus at each endpoint.

4. Discussion

The neutron moderation ability of a hydrogel bolus was evaluated by comparing the simulation and irradiation tests using a foot phantom. The irradiation method was investigated by changing the size of the bolus. To confirm the usefulness of this method in clinical settings, equivalent doses at each evaluation point were discussed in the case of the accelerator-based BNCT for the assumption of melanoma treatment.

By using a bolus, it was shown that thermal neutrons could be uniformly irradiated in an irradiation field of about 50 mm in diameter. The optimization of the bolus shape could be effective for further uniformity. On the other hand, for tumours that spread more widely, it is difficult to obtain a uniform thermal neutron distribution with a single irradiation, even by using a bolus. Therefore, we need to consider methods other than the bolus. It is effective to use different methods depending on the size of the tumours.

It has been proven that the use of a bolus reduces the dose to deep normal tissue. By adjusting the bolus shape, we could achieve improved uniformity for deep-seated tumours.

The 3D-printed phantom and its irradiation tests are useful as a QA method for measuring the distribution of thermal neutron flux in complex geometries and for validating treatment planning. A 3D model was created based on surface data obtained from 3D scanners, CT, and MRI medical imaging. A phantom of the affected area was created using 3D printing technology. By using this phantom, the treatment plan could be verified by comparing the measurement results. This will subsequently improve the quality of individual patient QA. When targeting superficial tumours, a more accurate treatment plan can be validated by actually fabricating an adjusted bolus and conducting irradiation tests.

The irradiation test using the 3D printed phantom made it possible to simulate the patient's actual treatment setting. This enabled verification of the issues that occur during treatment and improved the efficiency of the position setting during the actual treatment.

5. Conclusion

To establish the irradiation method for superficial tumours in the accelerator-based BNCT, the neutron moderation ability of a hydrogel was confirmed. The applicability of a bolus was demonstrated for actual treatments and simulated treatments. By adjusting the size and thickness of a hydrogel bolus, it was possible to develop a uniform thermal neutron flux on the skin surface and to ensure sufficient thermal neutron flux for the treatment.

The formation of the adjusted bolus can be achieved using a freely deformable hydrogel and 3D printing technology. In the future, irradiation tests will be conducted using an adjusted hydrogel bolus and the potential for the clinical application of a hydrogel bolus will be further investigated. In addition, an automated method to adjust the shape of the bolus will be investigated.

Acknowledgments

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Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

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