

Microdosimetric quantities of an accelerator-based neutron source used for boron neutron capture therapy measured using a gas-filled proportional counter

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(Received 3 March 2019; revised 5 June 2019; editorial decision 16 December 2019)

ABSTRACT

Boron neutron capture therapy (BNCT) is an emerging radiation treatment modality, exhibiting the potential to selectively destroy cancer cells. Currently, BNCT is conducted using a nuclear reactor. However, the future trend is to move toward an accelerator-based system for use in hospital environments. A typical BNCT radiation field has several different types of radiation. The beam quality should be quantified to accurately determine the dose to be delivered to the target. This study utilized a tissue equivalent proportional counter (TEPC) to measure microdosimetric and macrodosimetric quantities of an accelerator-based neutron source. The micro- and macro-dosimetric quantities measured with the TEPC were compared with those obtained via the particle and heavy ion transport code system (PHITS) Monte Carlo simulation. The absorbed dose from events >20 keV/ μm measured free in air for a 1-h irradiation was calculated as 1.31 ± 0.02 Gy. The simulated result was 1.41 ± 0.07 Gy. The measured and calculated values exhibit good agreement. The relative biological effectiveness (RBE) that was evaluated from the measured microdosimetric spectrum was calculated as 3.7 ± 0.02 , similar to the simulated value of 3.8 ± 0.1 . These results showed the PHITS Monte Carlo simulation can simulate both micro- and macro-dosimetric quantities accurately. The RBE was calculated using a single-response function, and the results were compared with those of several other institutes that used a similar method. However, care must be taken when using such a single-response function for clinical application, as it is only valid for low doses. For clinical dose ranges (i.e., high doses), multievent distribution inside the target needs to be considered.

Keywords: boron neutron capture therapy; accelerator-based neutron source; tissue equivalent proportional counter; microdosimetry

INTRODUCTION

Currently, the majority of boron neutron capture therapy (BNCT) treatments conducted worldwide use neutrons generated from a nuclear reactor. However, the emerging trend is to consider an accelerator-based neutron system as a therapeutic option as it has several proven advantages over a nuclear reactor. This shift is necessary to help BNCT move forward as a standard treatment technique in cancer therapy, as the system needs to be one that can be easily and safely installed in a hospital environment. This need has motivated

the development of accelerator-based neutron sources (ABNS) and there are already several countries that have developed or are currently developing an ABNS for BNCT [1]. An ABNS system installed at the Quantum Science Center (QSC) in Aomori prefecture, Japan, is currently utilized for BNCT research and development. This system is non-clinical, and its primary use is the irradiation of small animals for research purposes. Beam characterization is necessary to understand the quality of the beam and to determine the exact dose to be delivered to the target.

In a typical BNCT radiation field, a mixture of radiation types is present and measurements are by no means simple. Microdosimetry is a useful tool to measure several radiation qualities in a mixed radiation environment of neutrons and gamma rays, because it can measure each component separately. Microdosimetry is concerned with the measurement of ionizing energy deposited in a micrometer-sized volume, similar to that of a biological cell. The energy deposition in such a volume is called lineal energy, $y = \varepsilon/l$, where ε is the energy deposited in a volume with a mean chord length of l and $f(y)$ is the probability of an event occurring with a lineal energy value of y . From the lineal energy distribution, quantities such as absorbed dose, mean quality factor (commonly now referred to as the radiation weighting factor) and relative biological effectiveness (RBE) of a radiation field can be derived [2, 3].

The standard tool for experimental microdosimetry is the proportional gas counter. The counter is generally filled with a tissue equivalent gas of low density to simulate a micrometer-scale volume comparable to that of a living cell. Wu *et al.* [4] first applied the Rossi type proportional counter to BNCT dosimetry. This was followed by other studies by Maughan *et al.* [5] and a more recent study by Zhigang [6], which compares the measured values with the Fluktuierende Kaskade (FLUKA) Monte Carlo simulation.

This study aims to measure the microdosimetric quantities of an ABNS utilized for BNCT research using a tissue equivalent proportional counter (TEPC). The experimental data obtained with the TEPC were also compared with those obtained via the Monte Carlo simulation.

MATERIALS AND METHODS

Accelerator-based BNCT neutron source

The ABNS used for this experiment was a cyclotron-based accelerator that generates a proton with an energy of 20 MeV and a maximum beam current of 150 μA when striking a beryllium target, which generates high energy neutrons. To modify the neutron spectrum for the purposes of BNCT (i.e. creating a high thermal neutron flux), moderator materials were used (a combination of lead and heavy water) to slow the high energy neutrons down. Graphite reflectors were used to increase the thermal neutron flux and a combination of lead and bismuth material was used to reduce the gamma ray dose rate. To further increase the thermal neutron flux at the measurement location, a cylindrical platform was placed inside the irradiation room. This platform was composed of polymethyl methacrylate (PMMA) material with the inside filled with water, as shown in Figs 1 and 2. The smaller cylinder (closest to the beam port) had a diameter of 10 cm with a thickness of 2.5 cm, and the larger cylinder had a diameter of 30 cm with a thickness of 2.5 cm. The thickness of the PMMA was 2 mm.

Experimental apparatus

The neutron event spectrum was measured using a TEPC (LET-1/2, 0.5" proportional counter, Far West Technology Inc.). The detector is a spherical cavity in a tissue equivalent plastic (Shonka type A-150) with a 1.27 cm internal diameter. To simulate a 1 μm diameter sphere, the TEPC was filled with methane-based tissue equivalent gas (64.4% CH_4 , 32.5% CO_2 and 3.1% N_2) at a pressure of 74.5 hPa. A bias of 500 V was applied to the detector. The signal was fed into

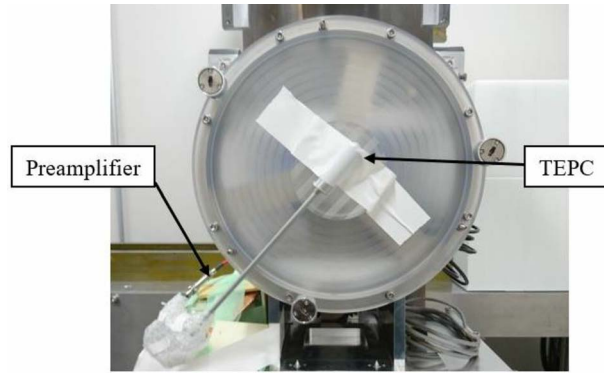


Fig. 1. Beams eye view of the experimental set up. The TEPC was placed in the middle of the irradiation field.

a low-noise preamplifier (Ortec Model 142AH), and the amplified signals were shaped with a linear amplifier (Ortec 671 amplifier), and finally, the signals were collected using a multi-channel analyzer (Fast ComTec MPA-3). Solid lithium fluoride plates were placed around the preamplifier to shield it against thermal neutrons.

The neutron beam was measured at the center of its field using the TEPC for ~ 1 h in a free-air condition. A few TEPCs have a built-in calibration alpha particle source to calibrate the energy scale. The TEPC used for this experiment did not have a built-in source; thus, the energy per channel number calibration was performed using the proton edge position. The proton edge is observed at ~ 100 keV for a 1 μm diameter tissue site [7]. A single-point calibration technique was described and applied for cylindrical TEPCs by Conte *et al.* [8] and later applied for spherical TEPCs by Moro *et al.* [9], with both results indicating an overall uncertainty of $< 5\%$. Furthermore, energy was converted to lineal energy, y , by dividing the energy by the mean chord length of the 1 μm diameter sphere, which is 0.667 μm . The final spectrum was presented in the $yd(y)$ vs $\log y$ format, which is a common format for microdosimetric spectra, as the area under the graph between two values of y will be proportional to the fractional dose in that interval.

Microdosimetric quantities

Because lineal energy is a stochastic quantity, it is useful to express the expectation value of the lineal energy distribution, known as the frequency-mean distribution, \bar{y}_F . This is expressed in equation (1)

$$\bar{y}_F = \int_0^{\infty} yf(y)dy \quad (1)$$

The dose distribution with respect to the lineal energy distribution can also be calculated. The expectation value of the absorbed dose distribution with respect to a lineal energy, known as dose-mean lineal energy, \bar{y}_D , is expressed in equation (2)

$$\bar{y}_D = \int_0^{\infty} yd(y)dy = \frac{1}{\bar{y}_F} \int_0^{\infty} y^2f(y)dy \quad (2)$$

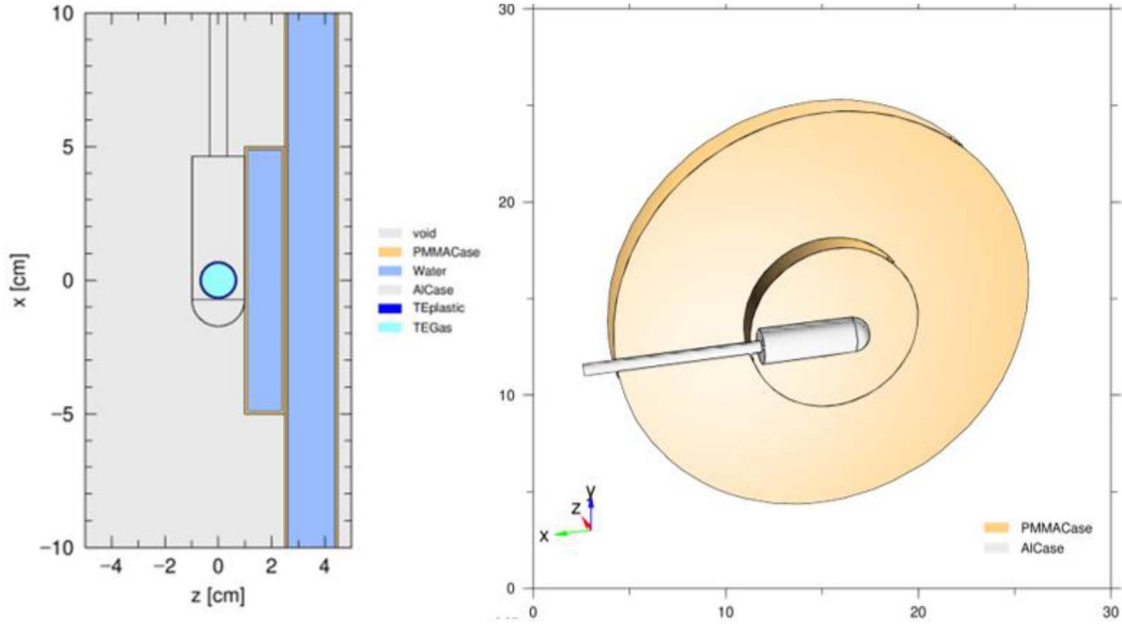


Fig. 2. 2D geometry (left) and 3D geometry (right) of the experimental set-up modelled using PHITS. TEplastic = Tissue equivalent plastic; TEgas = Tissue equivalent gas; Alcase = Aluminium case.

By considering a single event deposition from the Multi Channel Analyzer (MCA) counts per channel, the frequency-mean and dose-mean lineal energy can be rewritten as follows:

$$\bar{y}_F = \int_0^{\infty} yf(y)dy = \frac{1}{n} \sum_i n_i \bullet y_i \quad (3)$$

$$\bar{y}_D = \int_0^{\infty} yd(y)dy = \frac{\sum_i n_i \bullet y_i^2}{\sum_i n_i \bullet y_i} \quad (4)$$

where n_i is the number of counts of a single-energy deposition event per i^{th} channel and y_i is the lineal energy per i^{th} channel.

The dose equivalent (denoted by the symbol H) for a single secondary charged particle that deposits its kinetic energy in a microscopic tissue volume is calculated using equation (5) [10]

$$H = \bar{Q} \times D \quad (5)$$

where \bar{Q} is the mean quality factor and D is the absorbed dose (Gy), calculated from equations (6) and (7)

$$\bar{Q} = \frac{\sum_{i=1}^n Q(y_i) yf(y_i)}{\sum_{i=1}^n yf(y_i)} \quad (6)$$

where $Q(y_i)$ is the radiation quality factor expressed as a function of the lineal energy [3], and

$$D = \frac{1.6 \times 10^{-13} \sum_{i=1}^n y_i n_i \bar{l}}{\rho_g V_g} \quad (7)$$

where ρ_g and V_g are the density ($\text{J}\cdot\text{m}^{-3}$) and volume (m^3) of the gas cavity, respectively, and 1.6×10^{-13} is a conversion constant ($\text{Gy}\cdot\text{g}\cdot\text{keV}^{-1}$).

RBE calculation

RBE is an important parameter to evaluate the radiation quality. Tilikidis *et al.* used measured microdosimetric distributions and associated experimental biological data to estimate the RBE for different therapeutic beams [11]. This study utilized RBE values for jejunum crypt cell survival obtained in therapeutic neutron beams, and low-energy neutron beams as well as RBE values for Ne ions. The RBE for this study was estimated using a 2 Gy biological response of fractional cell survival $r(y)$, (see Fig. 2 of [11] for $r(y)$ versus y plot)

$$RBE = \int_0^{\infty} r(y)d(y)dy \quad (8)$$

To compare the measured RBE with other studies, the mean energy of the neutron spectrum was calculated using the following expression from the International Commission on Radiation Units and Measurements (ICRU) report [12].

$$\bar{E}_\phi = \int_0^{\infty} E\psi_E dE / \psi = \int_0^{\infty} E^2 \phi_E dE / \int_0^{\infty} E\phi_E dE \quad (9)$$

where ϕ_E is the neutron fluence at energy E .

Monte Carlo simulation

The particle and heavy ion transport code system (PHITS) version 2.88 was employed in this study. PHITS can transport most of the species of the particle with energies up to 1 TeV by using several nuclear reaction models and data libraries. Low energy neutron (10^{-5} eV to 20 MeV) induced nuclear reactions were simulated using JENDL 4.0 (Japanese Evaluated Nuclear Data Library). The energy loss of charged particles was calculated using the Atomic Interaction with

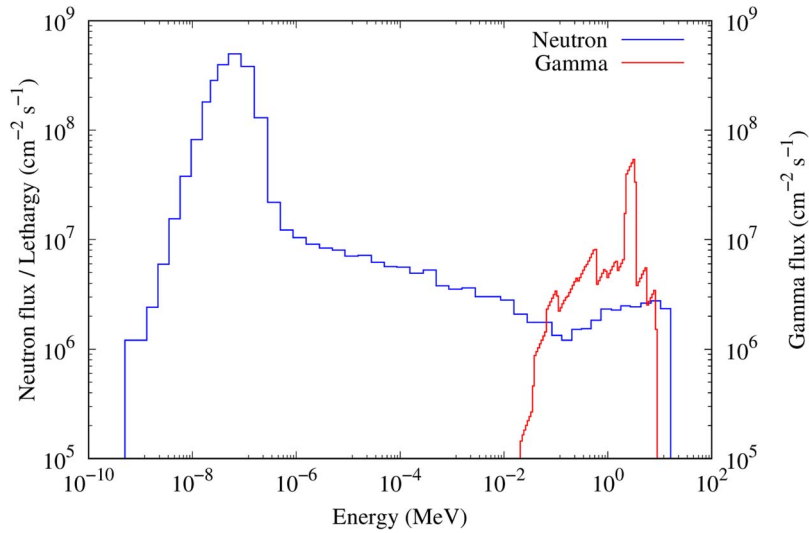


Fig. 3. Neutron and gamma ray energy spectra calculated inside the cavity of the proportional counter.

Matter (ATIMA) package, which is based on the model proposed by Lindhard and Sorensen [13]. The charged particles simulated in this study were a proton, an alpha particle, a carbon ion, an oxygen ion and electrons. PHITS can calculate microscopic probability densities using a mathematical function that can instantaneously calculate quantities around trajectories of charged particles. This special tally is named T-SED, which stands for specific energy distribution. The details of this tally and how the specific energy distribution is calculated can be found in existing studies [14, 15]. The TEPC experimental set-up was modelled in PHITS. The material of the wall was set to A150 tissue equivalent plastic and the gas inside the cavity was set to a methane-based tissue equivalent gas, obtained from ICRU report 44 [16]. The diameter of the cavity was set to 1.27 cm and the thickness of the A150 wall was set to ~ 0.35 cm. The neutron and gamma ray energy spectra inside the cavity of the proportional counter calculated by PHITS are shown in Fig. 3.

The microdosimetric spectrum was calculated using the T-SED tally and compared with the experimental result. The macrodosimetric quantity (i.e. absorbed dose) was calculated using the T-deposit tally, which scores the energy loss of charged particles. The energy deposited inside the spherical cavity from each charged particle was simulated and compared with the experimental result. The geometry of the experimental set up generated using PHITS is shown in Fig. 2.

RESULTS

The microdosimetric frequency distribution and dose distribution spectra of the QSC ABNS measured with the TEPC are shown in Figs 4 and 5, respectively. The events ranging between 25 and 150 keV/ μm are primarily protons from the $^{14}\text{N}(n,p)^{14}\text{C}$ and $^1\text{H}(n,n')p$ reaction. Events above 150 keV/ μm are from heavier particles such as alpha particles and carbon ions; events below 25 keV/ μm were predominantly from electrons. However, these events could not be distinguished from the background electronic noise of the system. As a result, the secondary

Table 1. Quantities derived from the microdosimetric lineal energy distribution measured with the TEPC

Source	\bar{y}_F	\bar{y}_D	\bar{Q}	D (Gy)	H (Sv)
QSC ABNS	38.07	53.49	11.65	1.31 ± 0.02	15.26

electrons produced from the gamma rays with a lineal energy of < 25 keV/ μm could not be accurately measured with this experiment. The events below 25 keV/ μm could only be determined using the PHITS Monte Carlo simulation. The PHITS simulated results were compared with the measured data by normalizing the area under both curves to unity.

The microdosimetric quantities derived from the measured frequency and dose distribution spectrum are summarized in Table 1. The dose mean lineal energy of the QSC ABNS was calculated to be 53.49 keV/ μm and the absorbed dose was calculated to be 1.31 ± 0.02 Gy using equation (7). The absorbed dose deposited from each charged particle traversing the gas cavity of the proportional counter was simulated using PHITS and is summarized in Table 2. The PHITS simulated absorbed dose from events above 25 keV/ μm was calculated to be 1.41 ± 0.07 Gy, which was in good agreement with

Table 2. Absorbed dose inside the gas cavity of the proportional counter simulated using the T-deposit tally of PHITS

Partical	Absorbed dose (Gy)
Proton	0.76 ± 0.06
Electron	0.55 ± 0.02
Carbon	0.07 ± 0.03
Alpha	0.01 ± 0.01
All ^a	1.41 ± 0.07

^aIncludes contribution from other particles not tailed in the calculation.

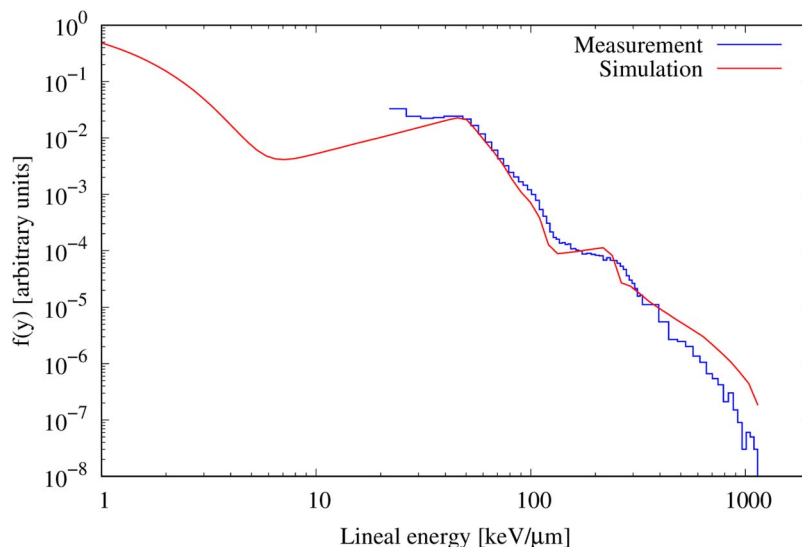


Fig. 4. Experimental and simulated microdosimetry $f(y)$ spectra of QSC ABNS.

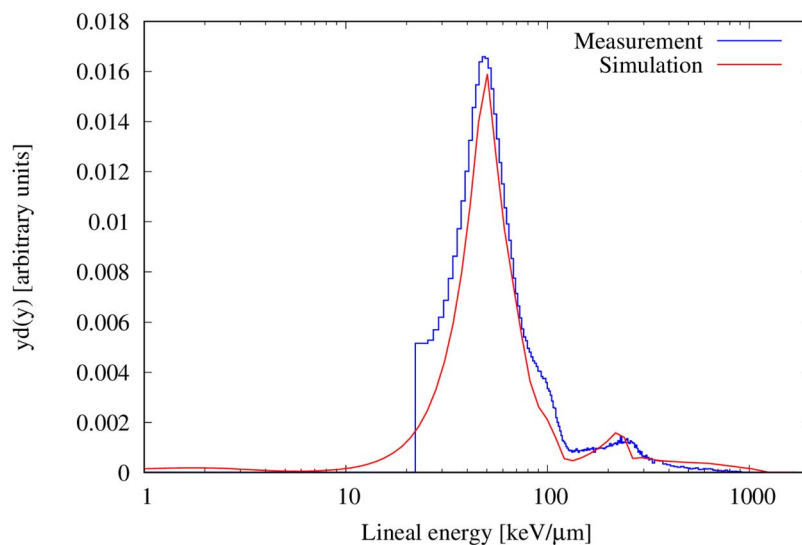


Fig. 5. Experimental and simulated microdosimetry $yd(y)$ spectra of QSC ABNS.

Table 3. Measured and simulated RBE of QSC ABNS

Source	Measured	PHITS ^a	PHITS ^b
QSC ABNS	3.70 ± 0.02	3.80 ± 0.10	3.00 ± 0.10

^a $yd(y)$ was integrated from 20–1000 keV/ μm .

^b $yd(y)$ was integrated from 0.01–1000 keV/ μm .

the experimentally measured result. Furthermore, the absorbed dose rate from gamma rays (i.e. events < 25 keV/ μm) was calculated from the PHITS simulation to be 1.75 ± 0.05 Gy.

Table 3 lists the measured and simulated RBE values calculated by using equation (8). The PHITS-simulated RBE value of 3.8 ± 0.1 was close to the value calculated from the measured data of 3.70 ± 0.02 .

Several authors have utilized the microdosimetric spectrum that was measured using a TEPC along with a lineal energy dependent biological weighting function to determine the RBE of a neutron field [17–19]. Using equation (9), the mean neutron energy of the accelerator-based neutron source at QSC was calculated to be ~ 35 keV. When compared with existing studies, the RBE of the ABNS was similar. Furthermore, the dose-mean lineal energy as a function of mean neutron energy also showed a similar trend to the results published by Endo *et al.* and Coyne [2].

DISCUSSION AND CONCLUSION

The microdosimetric $f(y)$ spectrum of the ABNS located at QSC was measured using a TEPC simulating a $1 \mu\text{m}$ diameter site. The measured

data showed good agreement with the PHITS-simulated results. At the high lineal energy region (>300 keV/ μm), the PHITS simulation showed a slight overestimation. A similar trend was found with a study performed by Baba *et al.* [20]. However, when converted to the $yd(y)$ spectrum, the effect was found to be minimal.

The absorbed dose delivered to a tissue-equivalent 1 μm diameter site when irradiated by the accelerator-based BNCT source at QSC for 1 h was measured to be 1.31 ± 0.02 Gy (not including the secondary electrons produced by gamma rays). The absorbed dose measured with the TEPC was in good agreement with the PHITS-simulated result. The PHITS simulation showed the contribution of each component to the total dose delivered to the tissue. The absorbed dose component delivered from the gamma rays was simulated to be 1.75 ± 0.05 Gy using PHITS. A study performed by Tanaka *et al.* [21] compared the characteristics between an accelerator-based and reactor-based neutron source for clinical BNCT. This study showed the free-air gamma ray dose rate to be ~ 0.5 – 0.6 Gy/h. The gamma ray dose rate for this study was found to be significantly higher. This was because the ABNS at QSC has been modified to produce a high flux of thermal neutrons for biological experiments and basic research purposes. To produce a high flux of thermal neutrons, the high-energy neutrons produced from the target must be slowed down using moderators. A large amount of moderator material produced a large amount of gamma rays.

The RBE was calculated using equation (8), and the results were found to be higher than the currently reported clinically utilized RBE value of 3.2 [22, 23]. This can be explained by the fact that the events below 25 keV/ μm were not included in the RBE calculation, as events below this threshold could not be distinguished from the detector noise, resulting in a higher RBE. To verify this, the $yd(y)$ spectrum simulated using PHITS was integrated from 0.01 to 1000 keV/ μm (i.e. to include events from low-energy particles), and the RBE was calculated to be 3.0 ± 0.1 , similar to the reported value of 3.2. The RBE of the ABNS at QSC was compared with several other studies that employed a similar method [18, 19]. The measured mean-dose lineal energy using a TEPC simulating a 1 μm diameter site showed a similar energy dependence to the values calculated by Coyne [2].

Using a single-response function to determine RBE is a suitable method to conduct intercomparison between different centers, as described by Gueulette *et al.* [24]. However, RBE not only depends on the lineal energy, but also depends on many other factors such as dose, dose rate, α/β ratio of the cell and endpoint. Hence, these calculated RBE values using a weighted response function may be used to characterize the radiation quality of a neutron beam; however, they cannot be used for clinical purposes. At low doses, this single-response function can be used to estimate the RBE, because single tracks are the dominant events. However, at clinically relevant doses, multiple-event energy deposition increases and calculating multi-event spectra from the single-event spectra is necessary [25]. One method to calculate high-dose RBE from low-dose RBE is to use the standard linear quadratic model. A more realistic approach using information from survival experiments to calculate the photon-isoeffective dose may also be clinically suitable [26, 27].

The measurement system used for this experiment could not accurately evaluate the gamma ray events. From the PHITS simulation, the gamma ray component is significant and should not be ignored when quantifying the radiation quality and characteristics of the beam. The high electronic noise could not be reduced during the experiment, owing to time restrictions and the limited access to, and supply of, equipment at QSC. In the future, the electronic noise in the system will need to be reduced to accurately measure and evaluate the gamma ray events.

CONFLICT OF INTEREST

None declared.

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