Microdosimetric study for helium-ion beam using fully 3D silicon microdosimeters

S H Lee1, K Mizushima1, D Sakata1, R Kohno1, M Sakama1, Y Iwata1, T Shirai1, V A Pan2, L T Tran2, A B Rosenfeld2, M Suzuki3, T Inaniwa1

1Department of Accelerator and Medical Physics, National Institute of Radiological Sciences, QST, Japan
2Centre for Medical Radiation Physics, University of Wollongong, Wollongong, Australia
3Department of Basic Medical Sciences for Radiation Damages, National Institute of Radiological Sciences, QST, Japan

E-mail: lee.sung-hyun@qst.go.jp

Abstract. In this study, the survival fraction of pancreatic cancer cells exposed to a spread-out Bragg peak (SOBP) helium-ion beam are estimated using the microdosimetric method with the microdosimetric kinetic (MK) model, by measuring the specific energy with a microdosimeter. To measure the microdosimetric spectra, a 3D mushroom microdosimeter was used by mounting it on silicon-on-insulator (SOI) substrates. At different positions of the Bragg curve of a pristine helium-ion beam of 166 MeV/u, microdosimetric spectra were measured via a scanning beam port in the National Institute of Radiological Sciences. The MK parameters were determined such that the survival fraction (SF) calculated by the MK model predicts the previously reported in vitro data. For a cuboid target of 10×10×6 cm³, a treatment plan that utilised helium-ion beam was designed from the in-house treatment planning software (TPS) to achieve a 10% SF of pancreatic cancer cells throughout the target. The physical doses and microdosimetric spectra were measured for different depths by irradiating the scanning-SOBP helium-ion beam; consequently, the SF at each position of the SOBP was predicted. The predicted SFs from measured physical dose and microdosimetric spectra were in good agreement with the planned SF from TPS.

1. Introduction

Microdosimetry along with the microdosimetric kinetic (MK) model is a method for estimating the biological effects of radiation, by measuring the dose absorbed by a micrometer-sized volume (specific energy). The MK model developed by the National Institute of Radiological Sciences (NIRS) is currently the world’s standard biological model for evaluating biological effects of therapeutic carbon-ion beams [1,2]. NIRS has initiated a development project for multi-ion therapy to improve the treatment outcome by optimising the linear energy transfer (LET) in tumours. In the treatment, helium, carbon, oxygen, and neon ions will be used as treatment beams against radio-resistant tumours such as a pancreatic tumour [3-5]. However, because in vitro validation of the multi-ion therapy treatment plans consumes time and is difficult to repeat for each irradiation course, it is important to verify the biological effectiveness of the treatment plan based on physical measurements. This study estimates the survival fraction (SF) of pancreatic cancer cells exposed to a spread-out Bragg peak (SOBP)
helium-ion beam using the microdosimetric method, by measuring the specific energy with a microdosimeter.

2. Method

2.1. Biological parameters in MK model

In the MK model, the SF is calculated via the following equations [1]:

\[ SF = e^{-\alpha D - \beta D^2}, \]  

\[ \alpha = \alpha_0 + \frac{\beta}{\rho n r_d^2} y^*, \]  

\[ y_D = \int y d(y) dy, \]  

\[ y^* = \frac{y_0^2 \int [1 - e^{-y/y_0}]^2 f(y) dy}{\int y f(y) dy}, \]

where \( D \) is the physical dose; \( \rho \) and \( r_d \) are the density and radius of the domain, respectively; \( f(y) \) and \( d(y) \) are the probability densities of the lineal energy, \( y \), and of the absorbed dose in lineal energy, respectively; \( y_0 \) is the saturation parameter; \( y_D \) is the dose mean lineal energy and \( y^* \) is the saturation-corrected dose-mean lineal energy.

2.2. Lineal energy measurement

To measure the microdosimetric lineal energy spectra, a 3D mushroom microdosimeter was used by mounting it on silicon-on-insulator (SOI) substrates with well-defined 3D-sensitive volumes (SV), developed by the Centre for Medical Radiation Physics (CMRP) at the University of Wollongong [6]. The mushroom microdosimeter is based on an array of 400 cylindrical SVs with typical cell sizes, each with a diameter of 18 \( \mu m \) and a thickness of 10 \( \mu m \); the dosimeter was developed so as to avoid pile up in the scanning beam. The readout of 3D SVs are connected to the Micro Plus probe (a low noise circuit preamplifier developed at the CMRP), and finally to a shaping amplifier with a shaping time of 1 \( \mu s \). The pulse output from the shaping amplifier was recorded with an Amptek MCA 8000D multi-channel analyser (MCA). The energy calibration was performed using a pulse generator that was calibrated with a 300-\( \mu m \)-thick planar silicon in response to 5.486 MeV alpha particles [7]. A scaling factor of 0.58 for energy absorption from silicon to tissue was used [7].

2.3. MK parameters for pancreatic cancer cells

To estimate biological effects from lineal energy, MK parameters of \( \alpha_0, \beta, r_d \) and \( y_0 \) of the cell must be determined. The microdosimetric lineal energy spectra were measured with the SOI microdosimeter along the pristine helium-ion beam of 166 MeV/u. The experiment was conducted using a horizontal beam line at NIRS-HIMAC, dedicated for the scanning beam delivery. A full description of the beam transport line and the devices at NIRS-HIMAC can be found elsewhere [8]. The helium-ion beam was scanned perpendicularly to cover the 10\times10 cm\(^2\) squared field, and it was irradiated onto the SOI microdosimeter positioned behind polymethyl methacrylate (PMMA) slabs of various thicknesses. The beam intensity of helium ions was about 1\times10\(^7\) particles per second. Figure 1(a) shows the physical dose and \( y_D \) of the pristine helium-ion beam, measured with Advanced Markus ionisation chamber (IC) (34045, PTW Freiburg, Germany) and SOI microdosimeter, respectively, at each depth level in the PMMA. The \( y_D \) value at each depth level was calculated from the microdosimetric lineal energy spectra measured at that depth, as shown in Figure 1(b). The SOI microdosimeter was capable of measuring lineal energy as low as 0.7 keV/\( \mu m \) in tissue.
The MK parameters were determined by minimising the difference between SF values of pancreatic cancer cells (MIA PaCa-2) exposed to monoenergetic helium-ion beams of several LETs reported by Inaniwa et al [5] and SF calculated by Equation (1) with the measured microdosimetric lineal energy spectra for each LET beam. Irradiation methods and SFs of MIA PaCa-2 are described in detail by Inaniwa et al [5]. The $y^*$ in Equation (2) was determined by interpolating the $y^*$ value at the depth corresponding to the LET used in the cell experiment.

2.4. SOBP beam irradiation

For a cuboid target of 10x10x6 cm$^3$, a treatment plan of helium-ion beam was made from the in-house treatment planning software (TPS) to achieve a 10% SF of pancreatic cancer cells throughout the target volume [3-5]. The SF predicted by TPS was in good agreement with that of MIA PaCa-2 cells [5]. The SOBP was formed by using the hybrid depth-scanning technique, in which three energies of helium ions (166.0, 151.9 and 136.9 MeV/μ) were provided by the synchrotron, and the beam range was fine-tuned by the placing of range-shifter plates [9]. The physical doses and microdosimetric lineal energy spectra were measured at a horizontal beam line at NIRS-HIMAC for different depth level in PMMA by irradiating the SOBP beam to the IC and SOI microdosimeter, respectively, and the SF at each position of the SOBP was predicted using Equation (1).

3. Results

Figure 2 shows the SF (marker) of the MIA PaCa-2 cells reported for each LET as well as the survival curve (solid line) calculated using Equation (1). The MK parameter best fits the cell experimental data with $\alpha_0 = 0.03$ Gy$^{-1}$, $\beta = 0.075$ Gy$^{-2}$, $r_d = 0.4 \mu m$ and $y_0 = 195$ keV/$\mu m$.

Figure 3(a) shows the physical dose measured with IC and $y_D$ measured with SOI microdosimeter for each depth level in the PMMA of the SOBP helium-ion beam. The $y_D$ at each depth level in Figure 3(a) was calculated from the microdosimetric lineal energy spectra measured at each depth in Figure 3(b). The $y_D$ increased at the tail of the SOBP, which is thought to be a contribution of energy from recoiled particles heavier than helium ions, generated from neutrons resulting from the inelastic scattering of helium ions (see the high energy contribution of the spectrum at 220-mm depth in Figure 3b). Figure 4 shows the SF predicted by Equation (1), from physical doses measured with IC at different SOBP positions in Figure 3(a) and from the microdosimetric lineal energy spectra measured with the SOI microdosimeter, by using the MK parameters obtained in this study. The predicted SFs from measured physical dose and microdosimetric lineal energy spectra were in good agreement with the planned SF from TPS.

4. Conclusion

In this study, we measured the microdosimetric lineal energy spectra at different positions of pristine helium ions using the SOI microdosimeter developed by the CMRP to obtain MK parameters for pancreatic cancer cells. The saturation-corrected dose-mean lineal energies were calculated from the spectra measured at each position of a pristine Bragg curve of helium ions, and the MK parameters were determined such that the calculated survival curve accurately predicts the in vitro data. A treatment plan of helium-ion beam was designed to achieve a 10% SF of pancreatic cancer cells throughout the target, and the microdosimetric lineal energy spectra were measured at different positions of the SOBP. This study was able to predict the SF of pancreatic cancer cells exposed to SOBP helium-ion beam using MK parameters from measured physical doses and microdosimetric lineal energy spectra.

5. Acknowledgements

The authors appreciate the staffs at Accelerator Engineering Corporation (AEC) for their skilful operation of the HIMAC accelerator complex and their experimental assistance.
Figure 1. (a) Physical dose and its standard deviation measured with Advanced Markus ionisation chamber (IC) and at each depth in PMMA of pristine helium-ion beam, and $y_\alpha$ measured with SOI microdosimeter calculated from the spectrum in Figure 1(b); (b) The microdosimetric spectra of lineal energy at each depth in PMMA in Figure 1(a). Physical dose was measured three times at each depth.

Figure 2. Survival fraction (markers) of in vitro data of the MIA PaCa-2 cells reported for each LET of pristine helium-ion beam and the survival curves (solid lines) calculated from physical dose and lineal energy measured with SOI microdosimeter in Equation (1).
Figure 3. (a) Physical dose measured with Advanced Markus ionisation chamber (IC) at each depth level in the PMMA of SOBP helium-ion beam, and \( y_D \) measured with SOI microdosimeter calculated from the spectrum in Figure 3(b); (b) The microdosimetric spectra of lineal energy at each depth level in the PMMA in Figure 3(a). Physical doses were measured twice.

Figure 4. Survival fraction predicted by Equation (1), from physical doses measured with Advanced Markus ionisation chamber (IC) at different SOBP positions in Figure 3(a) and from the microdosimetric lineal energy spectra measured with the SOI microdosimeter, by using the MK parameters obtained in Figure (2). The solid line is the survival fraction calculated from the TPS.

6. References

[1] Kase Y et al 2006 Radiat. Res. 166 629
[2] Inaniwa T et al 2015 Phys. Med. Biol. 60 3271
[3] Inaniwa T et al 2017 Phys. Med. Biol. 62 5180
[4] Inaniwa T and Kanematsu N 2018 Phys. Med. Biol. 63 095011
[5] Inaniwa T et al 2020 Phys. Med. Biol. Accepted.
[6] Tran L T et al 2018 Radiat. Meas. 115 55
[7] Tran L T et al 2018 Med. Phys. 45 2299
[8] Furukawa T et al 2010 Med. Phys. 37 5672
[9] Inaniwa T et al 2012 Med. Phys. 39 2820