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Investigating variable RBE in a 12c minibeam field with microdosimetry and geant4

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Abstract

An experimental and simulation-based study was performed on a 12C ion minibeam radiation therapy (MBRT) field produced with a clinical broad beam and a brass multi-slit collimator (MSC). Silicon-on-insulator (SOI) microdosimeters developed at the Centre for Medical Radiation Physics (CMRP) with micron sized sensitive volumes were used to measure the microdosimetric spectra at varying positions throughout the MBRT field and the corresponding dose-mean lineal energies and RBE for 10% cell survival (RBE10) were calculated using the modified Microdosimetric Kinetic Model (MKM). An increase in the average RBE10 of ∼30% and 10% was observed in the plateau region compared to broad beam for experimental and simulation values, respectively. The experimental collimator misalignment was determined to be 0.7° by comparison between measured and simulated microdosimetric spectra at varying collimator angles. The simulated dose-mean lineal energies in the valley region between minibeams were found to be higher on average than in the minibeams due to higher LET particles being produced in these regions from the MSC. This work presents the first experimental microdosimetry measurements and characterisation of the local biological effectiveness in a MBRT field.

Keywords

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Disciplines

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INVESTIGATING VARIABLE RBE IN A ^{12}C MINIBEAM FIELD WITH MICRODOSIMETRY AND GEANT4

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An experimental and simulation based study was performed on a ^{12}C ion minibeam radiation therapy (MBRT) field produced with a clinical broad beam and a brass multi-slit collimator (MSC). Silicon-on-insulator (SOI) microdosimeters developed at the Centre for Medical Radiation Physics (CMRP) with micron sized sensitive volumes were used to measure the microdosimetric spectra at varying positions throughout the MBRT field and the corresponding dose-mean lineal energies and RBE for 10% cell survival (RBE_{10}) were calculated using the modified Microdosimetric Kinetic Model (MKM). An increase in the average RBE_{10} of ~30% and 10% were observed in the plateau region compared to broad beam for experimental and simulation values, respectively. The experimental collimator misalignment was determined to be 0.7° by comparison between measured and simulated microdosimetric spectra at varying collimator angles. The simulated dose-mean lineal energies in the valley region between minibeams were found to be higher on average than in the minibeams due to higher LET particles being produced in these regions from the MSC. This work presents the first experimental microdosimetry measurements and characterisation of the local biological effectiveness in a MBRT field.

INTRODUCTION

External ion beam radiation therapy, with protons and ^{12}C ions in particular, are modalities that have experienced rapid growth in recent decades for the treatment of malignant tumours. This can be attributed to the advantageous physical and biological characteristics of using ions for therapy in comparison to conventional treatments using photons. The Bragg curve which features sharp dose gradients with the highest dose being deposited at the distal end of the ion range and the relatively small lateral scattering of the ions makes it possible to achieve a highly conformal dose delivery. This allows sparing of healthy tissues surrounding the target volume. Further, the variable LET along ion beam tracks results in an increased relative biological effectiveness (RBE) that is particularly pronounced in the Bragg peak.

Despite the high ratio of peak to entrance dose for ^{12}C ions, the dose in the entrance channel of the beam, proximal to the target volume, is one of the greatest contributors to dose in healthy tissue both in passive scattering and active scanning beam delivery systems. In order to achieve a higher therapeutic ratio for ^{12}C ion therapy the biologically effective dose to healthy tissue in the entrance channel needs to be reduced.

Microbeam studies with synchrotron produced high intensity photons have demonstrated increased healthy tissue tolerance to spatially fractionated doses compared with tumorous tissues [1]. Minibeam radiation therapy (MBRT) with ^{12}C ions is proposed to incorporate the benefits of ^{12}C therapy with the added healthy tissue sparing effects due spatial fractionation proximal to the target. ^{12}C minibeams (~0.5 mm), spread laterally with penetration depth in a medium or patient. As such, an array of ^{12}C minibeams produces a complex radiation field whereby spatial fractionation is achieved in the entrance channel of the beam and an increasingly homogeneous field is produced with penetration depth as the minibeams spread to form a solid radiation field. MBRT fields could potentially be used for spatial fractionation in the entrance channel of the beam, proximal to the target, whilst maintaining a homogeneous field in the target volume.

In order to characterise the MBRT field produced and the variable relative biological effectiveness as a function of the lateral position in the minibeam structures at varying depths, small volume, high spatial resolution microdosimeters are required in order to determine the spatial fractionation of the biological dose and potential benefits of MBRT.

In this work a monoenergetic 290 MeV/u MBRT field was produced at the Heavy Ion Medical Accelerator in Chiba (HIMAC) Japan with a passively scattered broad beam and a brass multi-slit collimator (MSC). The microdosimetric properties of the variable radiation field produced were measured using the 3D SOI Bridge microdosimeter and a single sensitive-volume microdosimeter (SSMD), both developed at CMRP, University of Wollongong.

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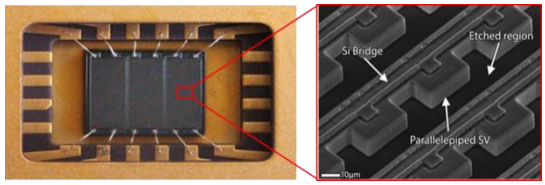

Figure 1. Bridge microdosimeter and scanning electron microscope image of sensitive volumes (right)

MATERIALS AND METHODS

Bridge and SSMD SOI microdosimeters

Two SOI microdosimeters, were used in the experimental measurements presented in this work; the 3D Bridge microdosimeter [2] and a single sensitive-volume microdosimeter (SSMD).

The Bridge microdosimeter is made up of an array of silicon sensitive volumes over a combined area of 4.1 × 3.6 mm^2 with a thickness ~10 µm. Individual sensitive volumes have an area of 30 × 30 μm^2 with connecting bridge volumes 10 × 20 μm^2. The Bridge microdosimeter is described in further detail in by Tran *et al* [2] and Rosenfeld [4] and is shown in figure 1. The Bridge microdosimeter has previously been used for RBE studies with ^{12}C ions and was shown to produce comparable results to measurements with a tissue-equivalent proportional counter (TEPC) [2].

The SSMD is operated using a single sensitive volume with an area of 10 × 250 μm^2 and thickness ~10 µm. This small single volume detector allows for microdosimetric measurements to be taken with a high spatial resolution.

While the TEPC is the gold standard detector for microdosimetry such a large detector geometry is not suited to the small, highly variable fields used in MBRT. The SOI microdosimeters used in this work are advantageous for MBRT due to their small sensitive volume size and unlike TEPC's, these detectors operate at low voltages and do not require a gas flow ensemble.

Minibeam production and experimental setup

Experimental measurements were carried out at the Heavy Ion Medical Accelerator in Chiba (HIMAC) using Biological beamline that is a passive beam using the wobbler-scatterer method. A mono-energetic 290 MeV/u ^{12}C ion broad beam and a custom brass multi-slit collimator (MSC) were used to generate a minibeam radiation field. The collimator has an area of 15×15 cm^2 and is 45 mm thick with 21 slits 0.5 mm × 25 mm at a centre-to-centre spacing of 1 mm. The collimator was positioned with the slits in a vertical orientation ~10 cm after the XY brass collimators of the beamline. The XY collimators were positioned so that a field size of 28×40 mm^2 was incident on the MSC in order to completely cover the slits whilst avoid beam loss in and activation of the MSC (as it is composed of 2.5% lead, much higher than the beamline collimators). Figure 2 shows the MSC and the experimental setup. Gafchromic film was placed before and after the MSC at various depths in a PMMA phantom in order to check the coarse alignment of the detector and observe the mini-beam structures emerging.

The Bridge and SSMD SOI microdosimeters were connected to the readout electronics µ-plus probe in a PMMA waterproof sheath attached to a 2D motion stage and water phantom (see figure 2). This allowed for the detectors to be moved throughout the MBRT field remotely with step sizes down to 100 µm both laterally and in depth within the water phantom.

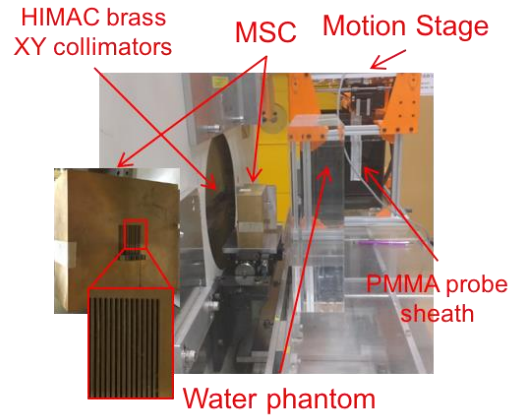

Figure 2. MSC and experimental setup

Comparison between broad beam and MBRT fields

The Bridge microdosimeter was used to measure the microdosimetric spectra at varying depths in the water phantom both with and without the MSC in place. For the MBRT case (where the MSC was used) the detector was positioned at the center of the MBRT field and as the active area of the Bridge microdosimeter covers an area of 4.1 × 3.6 mm^2, the contribution from multiple peak and valley regions of the mini-beams were acquired together in an "average" spectra. A comparison between the measured spectra for the broad beam and MBRT fields was made from the microdosimetric spectra measured and the corresponding RBE_{10} values calculated using the modified MKM (see the following section on MKM) [2][3][5][6].

Lateral profiling of MBRT field

The SSMD detector was used to measure the microdosimetric spectra in the peak and valley regions of the MBRT field at varying depths in the water

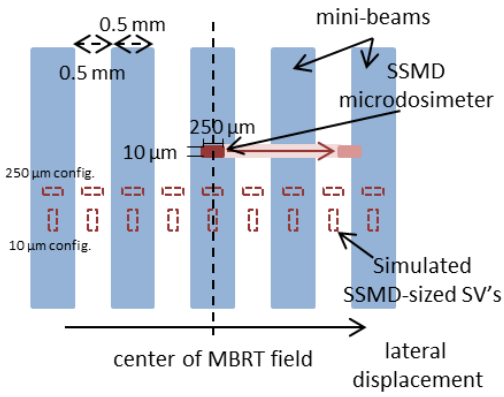

Figure 3. MSC and SSMD setup, the SSMD detector is represented by the solid box that was positioned at various lateral positions in the field. The dashed boxes represent the simulated SSMD-sized water volumes with two scoring orientations.

phantom. The detector was orientated with its 250 µm side perpendicular to the minibeams as shown in figure 3 and was moved laterally through the field in order to measure the changing dose-mean lineal energy and calculate the corresponding RBE_{10}.

This setup was also simulated with the Geant4 application where water volumes with the same dimensions as the SSMD detector were placed in the MBRT field. The 10 × 250 µm^2 area was placed in two orientations, with the 250 µm edge parallel to the scanning direction (the orientation used in the experimental measurements) and with the 10 µm side parallel to the scanning direction. This was done in order to observe the effect of minibeam "smearing" due to the long edge of the detector crossing the peak edge and valley in some positions in the experimental setup.

Monte Carlo Simulations

The HIMAC Biological beamline and experimental setup including detailed detector geometry was modelled in a Monte Carlo simulation using Geant4 version 10.2p02. The application used was adapted from that described by Bolst *et al* [5]. The electromagnetic interactions were modelled using *G4StandardOption3*, the neutron High Precision (HP) model was used to describe neutron interactions up to an energy of 20 MeV. The Binary Intranuclear Cascade (BIC) model and the *G4HadronicElasticPhysicsHP* were used for hadron fragmentation processes and elastic scattering, respectively.

The Bridge microdosimeter response was modelled for different misalignment angles of the brass MSC in order to gain insight into the experimental response and misalignment during setup. The impact of collimator misalignment on the radiation quality throughout the MBRT field was investigated and the ideal case was modelled for the two detectors and the respective measurements taken.

RBE_{10} calculation with modified MKM

The lineal energy, y, is a fundamental microdosimetric quantity and is defined as the energy deposited in a single event per average chord length in a micrometer sized sensitive volume. The dose-mean lineal energy, $\overline{y_D}$ is given in equation 1, where $f(y)$ represents the probability density function of lineal energy.

$$\overline{y_D} = \frac{\int y^2 f(y) dy}{\int y f(y) dy} \quad (1)$$

The modified Microdosimetric Kinetic Model (MKM) uses the spectra of lineal energies deposited in a sensitive volume in order to approximate the cell survival and is assumed to be independent of the radiation type. The MKM uses the linear quadratic (LQ) model of cell survival where the alpha value is calculated using equation 2. The saturation-corrected dose mean lineal energy, y^*, (see equation 3) is used here accounts for cell overkill effects resulting in a reduction in RBE at high LETs.

$$\alpha = \alpha_0 + \frac{\beta}{\rho \pi r_d^2} y^* \quad (2)$$

$$y^* = y_0^2 \frac{\int (1 - \exp(-y^2/y_0^2)) f(y) dy}{\int y f(y) dy} \quad (3)$$

For RBE calculations presented in this work the following parameters from Kase *et al*. [6] for the HSG cell line were used: α_0 = 0.13 Gy^{-1}, β = 0.05 Gy^{-2}, the domain radius r_d = 0.42 µm, the cell density ρ = 1 g/cm^3 and the saturation correction factor y_0 = 150 keV/µm.

The relative biological effectiveness for 10% cell survival, RBE_{10}, values were calculate according to equation 4 where 200kVp x-ray radiation was used as the reference with D_{10} = 5 Gy[6].

$$RBE_{10} = \frac{2\beta D_{10,ref}}{\sqrt{\alpha^2 - 4\beta \ln(0.1)} - \alpha} \quad (4)$$

The SOI microdosimeters used in this work are not tissue-equivalent and thus a correction factor was applied in order to relate the average chord length through the silicon sensitive volumes to that in water. A correction factor of 0.57 was applied to the chord length when computing the lineal energy in accordance with the findings of Bolst *et al* [7].

RESULTS AND DISCUSSION

Comparison between broad beam and MBRT fields

The microdosimetric spectra measured with the Bridge microdosimeter placed at the center of the ^{12}C broad beam and MBRT fields are shown in figure 4. This plot clearly shows a shift to higher lineal energies with increasing depth in the water phantom leading up to the Bragg peak. The microdosimetric spectra for the MBRT field with the MSC in place shows a decrease in the height of the peak as well as a greater contribution of high energy deposition events. This is attributed to degradation of the primary beam energy and thus increasing primary ion LET in the MSC. The production of secondary fragments in the MSC also contributes to the high energy tail beyond the peak in the microdosimetric spectra.

The RBE_{10} values calculated using the spectra measured with the Bridge microdosimeter and equation 4 at varying depths in water are plotted in figure 5 for both experimental measurements and from the Geant4 simulation. The shift in the microdosimetric spectra to higher lineal energies with the introduction of the MSC is reflected here in higher RBE_{10} values; an average increase in the RBE_{10} of around 30% in the plateau region of the Bragg curve was observed when the MSC was used.

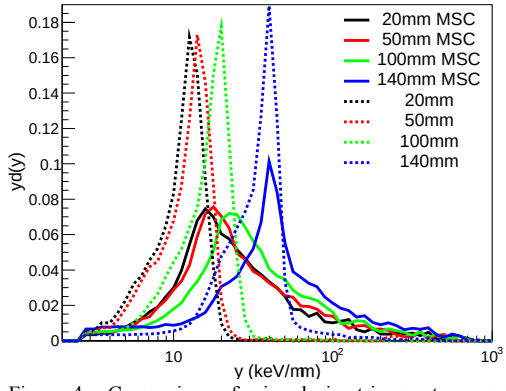

Figure 4. Comparison of microdosimetric spectra measured with the Bridge in a ^{12}C ion broad beam (dashed lines) and MBRT field (solid lines) at varying depths in a water phantom.

The simulated spectra for perfect MSC alignment (with 0° rotation relative to the beam axis) results in RBE_{10} values approximately 10% greater than for the broad beam case. The disagreement between the spectra obtained for experiment and simulation for the MBRT field was suspected to be due to misalignment of the MSC in the experimental measurements. As such, the Geant4 application was used to further investigate the impact of collimator misalignment on the radiation field and the resulting spectra. These findings are presented in the following section.

Effect of collimator misalignment

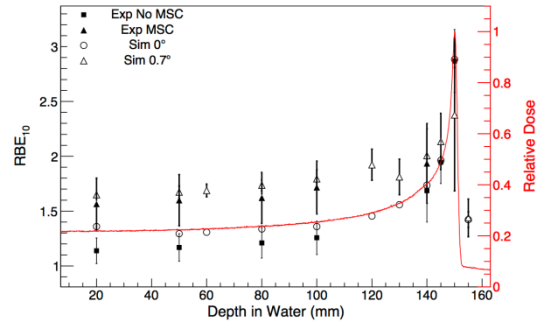

Figure 5. RBE_{10} values calculated from microdosimetric spectra measured with the Bridge microdosimeter detector from experiment and Geant4 simulation.

Figure 6 compares the microdosimetric spectra measured in experiment (with and without the MSC) at a depth of 20 mm in water and the simulated spectra from the Geant4 application at the same depth for varying MSC misalignment angles. The peak height and sharpness decreases with increasing misalignment angle and a greater proportion of high energy deposition events is seen to occur. This is expected as the thickness of brass traversed by the primary beam increases with the angle of misalignment resulting in more energy loss and fragmentation of primary ions. A simulated MSC angle of 0.7° was found to give the best agreement to the microdosimetric spectra measured with the Bridge microdosimeter in experiment.

Figure 5 also depicts the calculated RBE_{10} values for the simulated MSC at a 0.7° misalignment and has good agreement with the experimental MSC values. The lateral physical dose profile for perfect alignment of the collimator and for 0.7° misalignment are shown in figure 7.

The valley dose is seen to increase with misalignment angle of the collimator. This is expected as the proportion of the primary beam travelling through brass before emerging from the collimator is higher with greater angles. The overall beam profile also becomes less symmetric and a shift in the peak maxima is observed. Figure 8 shows a 2D plot of the physical dose deposited in the water phantom for perfect MSC alignment and for the 0.7° offset. The minibeam structures cannot be clearly resolved for the experimental MSC misalignment that was used. Further with this 0.7° MSC misalignment the physical dose delivered in the entrance region is a factor of ~10 higher than at the expected depth of the Bragg peak.

The collimator alignment therefore is crucial to the MBRT to being a beneficial modality if implemented clinically.

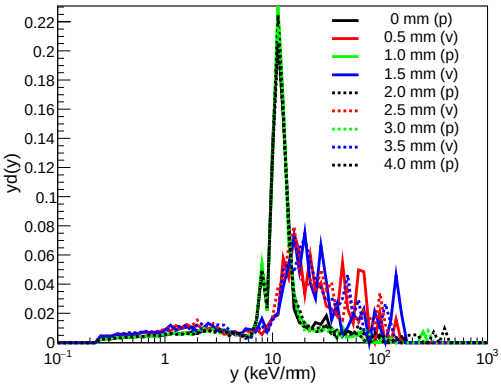

Figure 9. Simulated microdosimetric spectra in SSMD-sized water volumes in 10 µm orientation for different lateral positions in the MBRT field at a depth of 20 mm in water.

collimator angles relative to the incident beam direction.

Local RBE_{10} across lateral profile in MBRT field

The $\overline{y_D}$ values calculated from experimental measurements with the SSMD showed little variation with lateral displacement in the MBRT field due to the collimator misalignment causing the minibeams to be misformed (see figures 7 and 8).

Figure 9 shows the simulated microdosimetric spectra at various lateral displacements from the centre of the MBRT field (center minibeam) with perfect collimator alignment. Events were scored in the water volumes orientated with their 10 µm side parallel to the lateral axis. Measurements at positions 0, 1, 2 mm etc correspond to the centre of the minibeam and those at 0.5, 1.5, 2.5 mm etc. correspond to the valley region. The spectra measured at the center of the minibeams have a lower lineal energy peak than for the valley positions as the valley dose is primarily from ^{12}C ions that have traversed some of the brass material and therefore have lower kinetic energy and higher LETs. Figure 10 depicts the calculated $\overline{y_D}$ from the simulated

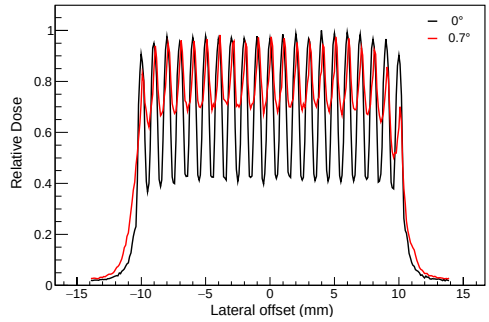

Figure 7. Simulated lateral dose profile of MBRT field at a depth of 20 mm in water for 0° and 0.7° MSC alignment relative to the beam axis.

water volumes in both the 10 µm and 250 µm orientations and the corresponding RBE_{10} values calculated. This figure clearly depicts an elevated dose-mean lineal energy and RBE_{10} in the valley regions between minibeams resulting in a reduction of the peak-to-dose valley ratio in the biologically effective dose compared to that of the physical dose. Despite this the biologically effective dose deposited in these valley regions is still less than that for a broad-beam case in the entrance channel of the beam. The RBE_{10} values calculated in the peak positions agree with those for the broad beam case at the same depth, while the biological effectiveness in the valley was found to slightly higher than the "average" RBE_{10} values simulated with the Bridge microdosimeter.

CONCLUSIONS

A ^{12}C ion MBRT field was produced at the HIMAC biological beam line using a broad beam and a multi-slit collimator. The introduction of the MSC greatly affected the radiation quality of the field and the calculated RBE_{10} values with ~30% increase in the plateau region measured in experiments and ~10%

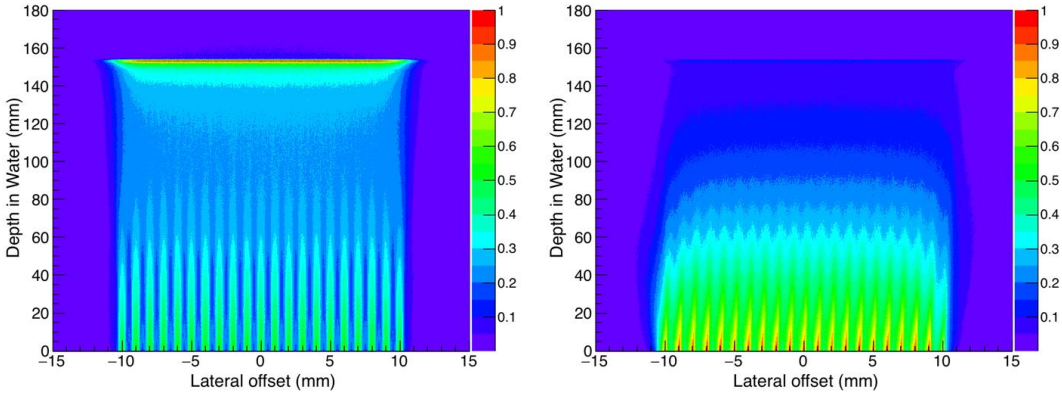

Figure 8. Simulated relative physical dose scored in a water phantom for perfect MSC alignment (left) and for a 0.7° misalignment (right) relative to the central beam axis.

increase in the simulation with the ideal setup both measured using the Bridge microdosimeter. The simulation component was used to determine that the experimental collimator misalignment was 0.7° from the incident beam direction resulting in the higher RBE_{10} values observed. The simulated microdosimetric spectra with SSMD-sized sensitive volumes showed elevated $\overline{y_D}$ and thus RBE_{10} values observed in the valley regions between the minibeams. Despite this the low physical dose in the valley region still allows for a lower biological dose delivered in the valley regions compared with broad beam ^{12}C ion therapy. The benefits of MBRT however are shown to be heavily reliant on the alignment of the MSC.

Experimental validation of the simulation findings will be possible with the SOI microdosimeters and precise MSC collimator alignment with a goniometer and moving stage setup to ensure accurate alignment. The small sensitive volumes of these detectors make them very well suited for micrometer resolution measurements in highly variable fields with sharp dose gradients such as those in MBRT.

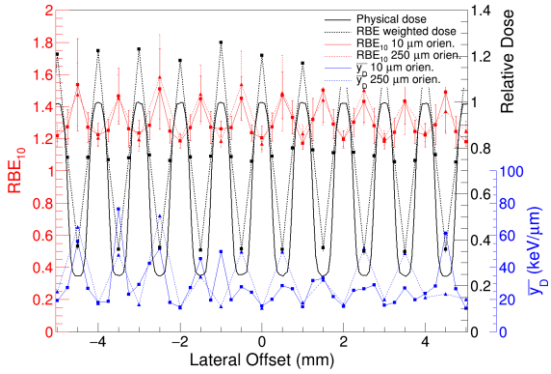

Figure 10. RBE_{10} and $\overline{y_D}$ calculated for events scored in simulated water volumes as a function of lateral displacement in MBRT field at a depth of 20 mm in water for 10 and 250 µm orientations. Physical dose at this depth is depicted by the solid black line and the RBE_{10} weighted dose calculated from the 10 µm orientation RBE_{10} values is shown in the broken black line.

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