

## Microdosimetry for proton radiotherapy

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Ion radiotherapy as a treatment for cancer is increasingly used worldwide, particularly with protons. Heavy ions have high linear energy transfer (LET) compared to x-ray, which means that ionizations tend to be locally concentrated around the particle track. This, in turn, corresponds to a greater capability of producing lethal damage to the DNA, eventually leading to chromosome aberrations and cell death. Current clinical indications for proton therapy assume a constant relative biological effectiveness (RBE) of 1.1 with respect to x-ray radiotherapy, meaning that protons are considered to produce a 10% higher effect delivering the same dose as with low-LET radiations (e.g. x-rays). However, there is growing evidence of variable RBE depending on the point of the proton track within the patient. RBE also depends on the considered endpoint and the biological properties of different cells and tissues as well as on the dose fractionation scheme. Microdosimetry is a theory that studies the patterns of energy deposition in microscopic sized volumes. By determining the local concentration of the energy imparted at such dimensions, it is possible to characterize the quality of the beam from this theory, which is strongly related with the production of lethal damage to the DNA.

We have established a connection between elementary description of proton-matter interaction in microdosimetric terms and its clinical application. First, the basics of microdosimetric quantities and their dependencies and focuses on how to produce correct microdosimetric results from Monte Carlo (MC) simulations were studied. Simulations of monoenergetic protons traversing sites made of liquid water were performed, gathering distributions of energy imparted to those sites. These distributions were used to create analytical models to derive microdosimetric quantities in polyenergetic beams instead performing dedicated MC simulations for each individual case. Results were compared to actual measurements with silicon-based microdosimeters exposed to monoenergetic proton beams. Independently, a formalism to calculate spectral fluences in clinical proton beams as a function of depth and lateral position in water was developed. The combination of both formalisms allowed to produce calculations of dose distributions in a treatment planning system (TPS). Finally, these results were compared to independent MC simulations with the code MCsquare and analytical calculations clinically validated from a commercial TPS, showing consistent results. Microdosimetric calculations of dose-mean lineal energy ( $yD$ ), and both unrestricted and restricted dose-averaged LET can also be obtained from the combination of these formalisms.

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