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MINAS TIRITH: a simulation tool for assessing DNA damage in a cell population around the Bragg peak

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Introduction:
In proton therapy, in addition to better targeting of the dose delivered to the tumor, we expect greater biological effectiveness (RBE) due to the microscopic characteristics of the dose deposit. Protons are considered to be charged particles with high linear energy transfer (LET), particularly in the Bragg peak region. In this case the energy deposits are very close to each other in the track, leading to complex DNA damage that can be more difficult to repair compared to those produced by low LET irradiation such as photons and/or electrons. This effect is normally taken into account clinically by using an RBE=1.1 throughout the proton trajectory in the tissue. However, we know that the value of this relative efficiency varies with the energy of the protons, i.e. along their path, and can be very significant in the Bragg peak zone as well as in the cells at the edge of the tumor.
Materials and Methods
Existing Monte Carlo track structure codes, such as Geant4-DNA (1-4), can simulate in great detail the physical, physico-chemical and chemical processes underlying DNA damage in highly complex geometries representative of the cell cycle phase. However, the direct application of these calculations to a large cell population in order to obtain the distribution of DNA damage and its topology is unthinkable due to prohibitive computational times. Indeed, it is important to note that the stochastic nature of the energy-depositing interactions induces variation in response between different cells in the same population irradiated at the same dose, something that is often difficul to quantify. A new tool, MINAS TIRITH (5-6) has therefore been developed to calculate the distribution of double strand breaks (DSBs) produced by proton irradiations with energies corresponding to the Bragg peak irradiating a cell population at a known macroscopic dose D.
To this end, MINAS TIRITH uses two database pre-generated with Geant4-DNA. The first database corresponds to microdosimetric spectra at cell nucleus level for different charged particles. By sampling, it calculates the number, energy and nature of particles depositing their energy within the cell nucleus according to the specific energy distribution characterizing the irradiation. The second, is a database of DNA damage associated with the nature of the particles and their track length. Sampling within these two databases allows to get equivalent information as that obtained using a detailed simulation chain(7-8) with Geant4-DNA but allows to estimate, with reasonable computing time, the damage distribution (and not just its mean value) at the cell population level.
Results:
Experimental validation of this tool was carried out by comparison with the results of the γ-H2AX damage distributions obtained experimentally 30 min after irradiation with 2.5 MeV and 15.1 MeV neutrons. The results of the validation will be presented. The usefulness of this calculation method for assessing damage and biological effectiveness in the cells around the Bragg peak, particularly at the edge of the tumor, will also be discussed.

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