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Radiobiology studies in proton therapy: range verification with Zn nanoparticles and studies of cell surveillance after irradiation with different LETs

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The unique properties of protons allow the treatment of specific areas avoiding surrounding tissues due to the deposition in depth of the dose and the different values of Linear Energy Transfer (LETs) along this deposition. The effect of protons is due to a high LET compared to the conventional radiotherapy and the relative biological effectiveness (RBE) as a function of LET is described to be different depending on the cell line. However, the large-scale clinical use of proton beam precision is hampered by the uncertainties of the location of the distal dose fall-off in the patient's body and the different effect of radiation depending on the cell lines. *In vivo* verification of the delivered dose and tumor irradiation effects are two variables that are highly desirable to study for reducing systematic uncertainties in delivered dose. A promising approach to study the proton range is the use of nanoparticles as proton-activable agents that produce positron emitters which could be detected by Positron Emission Tomography (PET) and/or prompt-gamma (PG) rays. For this, we developed an iron oxide nanoparticle doped with Zn (IONP@Zn-cit), studied their cytotoxicity *in vitro*, the production of PET/PG signals after proton irradiation and its biodistribution *in vivo*. In the cytotoxicity studies, we obtained the half of surveillance (IC50 values) at 64 μg Fe/ml and 100 μg Zn/ml for the U251 cell line by MTT assay. To evaluate the production of PET and PG signals, different concentrations of IONP@Zn-cit were irradiated with 10 MeV protons, obtaining negligible PET signal but PG detection at the lowest concentration measured (10 mg Zn/ml). From the biodistrubution study, IONP@Zn-cit showed a typically accumulation in liver and spleen, and an accumulation in tumor tissue of 0.95 % ID/g in a mouse model of U251 cell line.
Furthermore, to evaluate RBE with different LETs in cell cultures, a new set-up for a clinical proton irradiator was built, which allows a dose deposition with uncertainties under 9% for the less favourable cases. Moreover, cell surveillance was measured by a new method: after irradiation and growth of cells cultured in 96 well plates, cells were stained, diluted with methanol and absorbance measured as a function of seeded cells. Values were fitted to a normalized logistic function and the midpoint (number of seeded cells where the function takes 50% of its maximum signal) was used to calculate the Survival Fractions obtaining comparable results as the ones obtained with the traditional method of counting colonies in 6 well plates.
In conclusion, two different approaches are proposed to get a better knowledge on radiobiology field of proton therapy, from the range verification with nanoparticles to the *in vitro* study of LETs, opening different possibilities to the future in the research of proton therapy.

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