Modélisation et validation expérimentale de l'interaction rayonnement-milieu cellulaire en radiothérapie par photo-activation d'éléments lourds

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Modeling and experimental validation of the radiation – DNA interaction in radiotherapy by photon activation of heavy elements

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CONTEXT

❖ Malignant brain tumors represent a few percents of adult cancers and the most frequent of children cancers. Because of the delicate location and the radio sensitivity of healthy brain, the current treatments are not efficient for resistant tumors as high-grade gliomas.

❖ Promising treatment : An innovative approach using X-rays in addition with heavy elements, as iodine or gold nanoparticles.

❖ Principle : heavy elements introduced in the target volume allow to increase the photoelectric cross section what has for consequence to enhance the dose effect into the tumor.

❖ Limitation : physical processes and biological impact of this technique are not well understood. The experimental results can not be explained from macroscopic dose calculations.

❖ Proposition : to consider the radio-induced damages at the cell level.

OBJECTIVES

❖ To model and simulate, with a Monte Carlo code, the photon interactions in an inhomogeneous media as cells or DNA, in presence of heavy elements. This will be done at CEA Saclay[1] with help of C. Champion[2].

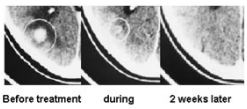
❖ To compare the calculations with the Geant4DNA code.

❖ To validate the code with experimental measurements, on cells or plasmids, carried out in CEA of Grenoble[4] and in the beam line dedicated to medical studies at ESRF[3].

STATE OF THE ART

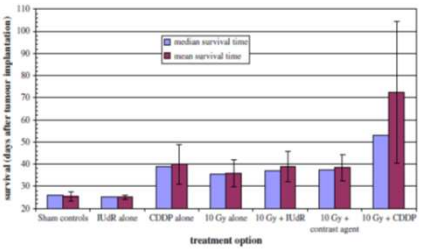
❖ Photon activation therapy with injection of iodinated contrast agent (ICA)

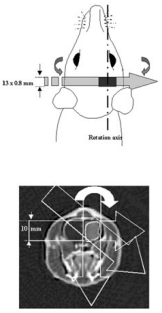
- First proposition of this technique by Norman and co-workers (1-2), using a modified CT scanner. Performed the first and lonely human clinical trial on 8 patients bearing brain metastasis and Showed that the method was sure and potentially beneficial.



- Development of the technique at the medical beam line of ESRF using monochromatic X-rays in the 50-100 keV range. Several experiments were performed on animals bearing high-grade gliomas to optimize the treatment (3-4).

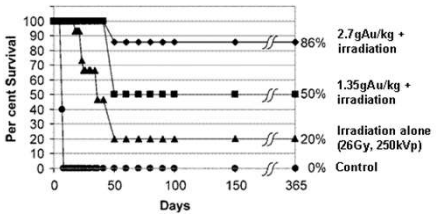
→ Human clinical trial in preparation.





❖ Photon activation therapy in presence of gold nanoparticles (GNP)

- Hainfeld 2004 (5) : first *in vivo* experiment which proves the advantage of gold nanoparticles in radiotherapy for cancer treatment.
Study : mice bearing a carcinoma on leg.
Survival at 1 year : increase until a factor 4.3 for GNP compared to irradiation alone.



- *In vitro* studies (cells, protein or DNA) allow to optimize the vectorisation and the radiosensitivity of GNP (6-7).
- Current limitation of the use of GNP in therapy : the cost, the lack of *in vivo* toxicity studies of GNP and the lack of clinical trials.

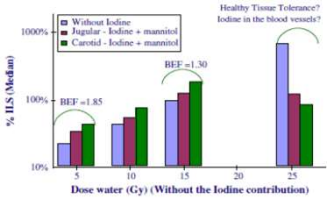
❖ Monte Carlo Simulations

- Macroscopic dose calculation in presence of GNP were made (8). Conclusion : interactions need to be considered at the cellular level to reproduce the *in vivo* results.
- Monte Carlo codes developed to simulate the radiation-induced damages to cells and DNA following the "track-structure" and "microdosimetry" formalisms (9 -11).
- Geant4DNA : implementation of a new package into the code Geant4 which aims to simulated the physical interactions for low energies (12), the chemical process, the DNA damages and the molecular geometries.

FIRST EXPERIMENT

❖ Aim of the study : to show an enhancement of the relative dose-effect in presence of heavy elements with a *fractionated dose* according to previous results which showed a such effect for small doses (4).

❖ Study : Mars 2010 at ESRF. 50 fisher rats bearing F98 gliomas.

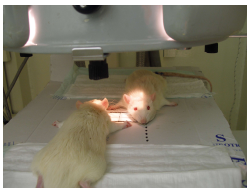


❖ Groups : 50 rats separate in 6 groups :

- Control
- ICA only
- GNP only
- irradiation only
- irradiation + ICA
- irradiation + GNP.

❖ Irradiation : 10 fractions of 4Gy on the right cerebrum from an X-Ray tube (150 kVp, 20 mA).

❖ Results under way.



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