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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.

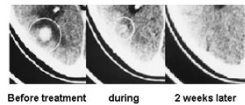
OBJECTIVES

- ❖ **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 Saclay¹ with help of C. Champion².
- ❖ **To compare** the calculations with the Geant4DNA code.
- ❖ **To validate the code with experimental measurements**, on cells or plasmids, carried out in CEA of Grenoble⁴ and in the beam line dedicated to medical studies at ESRF³.

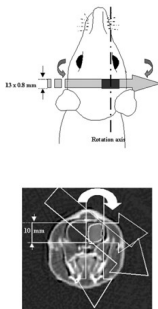
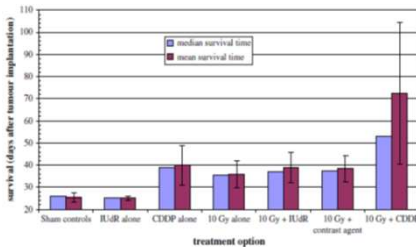
STATE OF THE ART

❖ 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.



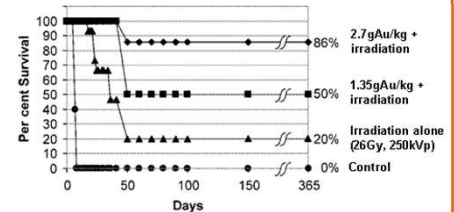
- Development of the technique at the medical beam line of ESRF using **monochromatic X-rays** in the 50-100 keV range. Several experiments were performed on **animals bearing high-grade gliomas** to optimize the treatment (3-4).
→ Human clinical trial in preparation.



❖ 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.

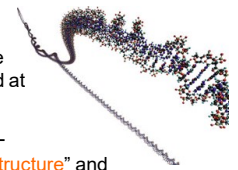


- *In vitro* studies (cells, protein or DNA) allow to optimize the vectorisation and the radiosensitivity of GNP (6-7).

- **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

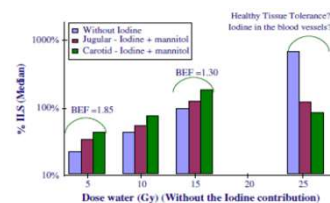
- Macroscopic dose calculation in presence of GNP were made (8). Conclusion : interactions need to be considered at the cellular level to reproduce the *in vivo* results.
- Monte Carlo codes developed to simulate the radiation-induced damages to cells and DNA following the "track-structure" and "microdosimetry" 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.

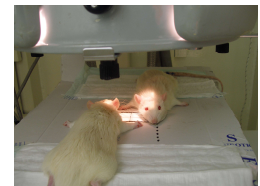


- ❖ **Groups** : 50 rats separate in 6 groups :

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