Dose-enhancement from high Z elements: The importance of dosimetry in complex biological systems

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Large differences in the energy deposition by photons can be observed nearby interfaces of materials of different atomic composition. The resulting dose-enhancement produced by high Z elements in their surroundings may extend from the interface to few millimetres, depending on the energy of the photons beams. This phenomena can be utilized for radiotherapy provided that a sufficient amount of high Z elements is present inside or nearby the tumoral cells The dose enhancement is strongly dependent on the location and on the amount of high Z elements relative to the biological target. We have evaluated two different approaches for taking advantage of dose-enhancement using either contrast agents containing high Z elements, that are supposed to mainly remain extra-cellular, or high Z elements attached to the DNA.

1. Contrast agents containing high Z elements for dose-enhancement in radiotherapy has been first proposed by Santos Mello et al. (Santos Mello et al., 1983) in the early 80's and was further explored by various teams. The dose enhancement strongly depends on the contrast agent fine repartition, on the radiation energy and on the irradiation scheme (Boudou et al., 2005, Solberg et al., 1992, Verhaegen et al., 2005). *In vitro* experimental results together with theoretical and experimental dosimetry studies have provided the basis of the development of this approach (Corde et al., 2002, Corde et al., 2004, Esteve et al., 2002, Regulla et al., 2001). In the present study, we have investigated, by Monte Carlo calculations, the energy deposition in cells in various experimental configurations. Results show that the nature of the cells support and the cells geometry may influence the dose micro-distribution and could explain controversial results obtained *in vitro*.

2. The effects of ionization and relaxation effects of high Z atoms *attached to the DNA* have been investigated both theoretically using Monte Carlo calculations (Bernhardt et al., 2004, Pignol et al., 2003) and experimentally through *in vitro* and *in vivo* studies. Bernhardt and co-workers have demonstrated theoretically that the amount of energy deposition in the local area around the absorption location is quite small, when considering amount of platinum compatible with *in vivo* studies. Although the photoelectric cross section for inner-shell ionizations of Pt atoms is rather large ($2.91\ 10^3$ barns/atom at 78.39 keV), K-shell ionization events occur quite rarely because only a relatively small number of Pt atoms per base pair are tolerated by living cells. Our preclinical studies and cell survival results are in good agreement with these theoretical studies and suggest that the therapeutic gain obtained with interstitial injection of platinum compounds followed by x-

ray irradiation is *not* predominantly due to Auger electrons emitted from the Pt atoms, but involves other mechanisms.

The difficulty for achieving an accurate dosimetry in complex biological systems, both *in vitro* and *in vivo*, will be discussed in this presentation and pitfalls in the data interpretation will be underlined.

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