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Radiation therapy with presence of nanoparticles at the tumor cell level: optimizing treatment efficacy through nanoparticle design

Short Title: High-Z nanoparticle radiotherapy

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Abstract:
Today, more than half of all cancer patients receive radiotherapy as part of their treatment. However, radiotherapy efficacy is often limited by healthy tissues toxicity and needs to be optimized. One relevant solution is to increase the radiation dose deposition from within the tumor cells. The presence of high atomic number (high-Z) elements within the X-ray pathway increases the probability of interaction with ionizing radiation as compared with tissues (composed of low-Z elements). Likewise, mammalian cells can handle materials at the nanoscale. Therefore, materials made of high-Z elements designed at the nanoscale can enhance the deposit of the radiation dose at the cancer cell level.

Still, the most relevant design of these nano-objects has been scarcely explored. Here, we hypothesize that the packing of high-Z elements within the nano-object is a key parameter when considering its design. We used gold and probe how its packing at the nanoscale can achieve the best probability of interaction with ionizing radiation. 50 nm and 2 nm diameter gold nanoparticles coated with 1 nm citrate groups and the gold complex Auranofin (2,3,4,6-tetra-O-acetyl-1-thio-b-D-glucopyranosato-S-[triethyl-phosphine] gold) were considered as representative nano-objects. Many copies of each nano-object were randomly distributed within an artificial cluster to take up 10% of its volume and placed within a cell, reflecting general observation of nanoparticles bioavailability at the subcellular level. Using Monte Carlo simulation, we calculated the energy dose deposition from each cluster when activated by 6 MV energy X-ray source at a depth of 3 cm into the patient. The ratio of energy dose deposition between 50 nm and 2 nm gold nanoparticles and between 50 nm gold nanoparticles and Auranofin was approximately 8 and 70 respectively, regardless of the location of the cluster within the cell. In each case, this reflects the reduced fraction of gold atoms in the nano-object. Indeed, when compared to the 50 nm gold nanoparticle, the 2 nm gold nanoparticle is surrounded by fractionally more citrate, the atoms of which act as passive ‘spectators’ (low-Z atoms). For Auranofin, each gold atom is complexed by organic ligands (low-Z atoms), again acting as passive ‘spectators’. The reduced number of gold atoms per cluster for the 2 nm gold nanoparticles and the gold complexes respectively results in a lower average electron density per cluster. Therefore, for a given cluster filling fraction, the electron density per cluster is the highest for the 50 nm gold nanoparticles.

Nanosized objects made of high-Z elements may unlock the potential of radiation therapy by rendering the introduction of a greater energy dose, exactly within the tumor structure without passing through surrounding tissues. Here, taking a realistic approach, we show 50 nm gold nanoparticles achieve better radiation dose deposition than 2 nm gold nanoparticles and gold complexes respectively. Hence, the packing of high-Z element at the nanoscale emerges as a key parameter to achieve effective nanoparticle design and optimize the benefit/risk ratio of radiation therapy.