

# Latest Trends in Nanoparticle Aided X-Ray Radiation Therapy

## Abstract

Radiation therapy is one of the most commonly used treatments for cancer. In radiation therapy, cancer cells or tumors are exposed to ionizing radiations (X-rays, gamma rays) either from an external source or internally using radioactive sources (as in brachytherapy). The biggest challenge faced by radiation therapy treatments is to selectively expose cancer cells while sparing surrounding healthy tissues from radiation. Over the past few decades, advances in radiation modalities and nanotechnology have made significant progress in radiation therapy, especially with the use of targeted nanoparticles that selectively tag cancer cells and enhance radiation dosage by acting as radiosensitizers due to their high atomic numbers. In this review, I present a brief summary and current status of nanoparticle aided radiation therapy. Newer approaches involving internationalization of nanoparticles within the nuclei of the tumor cells are discussed in addition to the prospects for materials such as bismuth and platinum as in alternative to more conventional gold nanoparticle standards. Photodynamic therapy (PDT) with scintillating nanoparticles and hyperthermia using magnetic nanoparticles are also highlighted briefly in this review.

## Introduction

Radiation therapy has been one of the most popular techniques to treat cancer, where ionizing radiations (X-rays, gamma rays or charged particles) are targeted at cancer cells to directly kill them or generate free radicals that can damage the DNA and eventually lead to the death of the cancer cells. However, conventional radiation therapy using radiation from external sources (X-rays, proton beam etc.) or from internalized radioactive sources (brachytherapy) can barely differentiate cancer cells from normal healthy tissues. One of the major challenges in radiation therapy is, therefore, to specifically target cancer cells with the radiation and minimize damage to the surrounding healthy cells. Intensity-modulated radiation therapy (IMRT), image-guided RT (IGRT), stereotactic ablative body radiation therapy (RT), proton therapy, electron beam therapy are some of the commonly used radiation therapy modalities. Despite significant advances in these techniques, a majority of cancer patients treated with radiation therapy suffer from recurrence, metastasis and toxic effects to healthy tissues [1]. The advent of biocompatible high Z, metallic nanoparticles has opened up new avenues for targeted radiation therapy [2-5]. In targeted radiation therapy, nanoparticles undergo extensive surface modifications that allow them to bind specifically to cancer cells. For example, folate receptors are overexpressed in most cancer cells. Metallic nanoparticles, modified with folic acid ligands, preferentially bind to these receptors, enabling radiation dosage to be localized within the tumor [6]. Nanoparticles with high Z metals are chosen because they offer larger photoelectric cross sections where the probability of interaction between the X-ray photons and the metal increase approximately as  $Z^3$  [3]. Interaction of metallic nanoparticles with X-rays generates photoelectrons and Auger electrons which hydrolyzes water molecules inside cells to generate free radicals that can damage the DNA of the cells. The DNA damage is irreparable, preventing the cells to further grow and divide, eventually leading to their death. Therefore, once incorporated

inside the body to target cancer cells and irradiated with external X-rays, these nanoparticles can act as radiosensitizers to boost the localized dose. Here, we discuss the latest trends, advances and future prospect of nanoparticle aided radiation therapy.

## Nanoparticle design for radiation therapy

Gold nanoparticles have been the prime choice of interest for nanoparticle aided radiation therapy particularly because of their high atomic number, biocompatibility and inherently low toxicities. The success of nanoparticle aided radiation therapy heavily relies on the selective targeting and internalization of these particles inside the cancer cells. Earlier studies were done using micro-sized gold particles. However, micron-sized particles had low cellular intakes and so the focus soon shifted towards using gold nanoclusters or nanoparticles, which were injected intravenously into the body of the cancer patient. Smaller size of the particles facilitated their intake into the cancer tissue. Preclinical studies with mouse models showed 2.7g Au/kg body weight resulted in 7mg Au/g accumulation inside the tissues. 60s exposure to 250kVp X-rays resulted in a 1-year survival rate of 86% (compared to 20% with X-rays alone and 0% with gold alone). Size of the nanoparticles therefore play an important role in radiation therapy. Studies reported that 100-nm gold particles injected intravenously into the patient has 4.3 times greater accumulation than that achieved by 60- and 80-nm particles; nine-times greater than the 40-nm particles; and 38-times greater than the 20-nm particles. Other investigations show that, for gold particles ranging between 2-100nm, the 50nm particles have the highest uptake in cells [7].

In addition to size, the shape and morphology of nanoparticles also affect cellular uptake. In vitro experiments have demonstrated that spherical particles have higher cellular uptake than rod-shaped cylindrical particles. Size, shape and design are modulated to allow longer circulation, higher uptake and renal excretion.

## Mini Review

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The material and composition of the nanoparticles is important for radiotherapy [8]. The primary requirement is to have high atomic number elements since higher Z metals offer larger photoelectric cross-section and therefore higher probability of interaction between the particles and the radiation. In addition biocompatibility and inherent toxicities of the particles need to be taken into account while synthesizing these particles. Although, gold (Z=79) has been the main focus for decades, new materials such as bismuth (Z=83) and platinum (Z=78), gadolinium (Z=64) are currently being investigated. Theoretical studies have shown that, under similar conditions of size, shape and morphology platinum has similar dose enhancement factors as gold while bismuth has the maximum dose enhancements [9].

### Nanoparticle targeting

Advances have been made in modifying the surface chemistry of nanoparticles for specifically targeting cancer cells. In most cases, surfaces of cancer cells have overexpressed receptors compared to normally healthy cells. Nanoparticles are tagged with appropriate ligands that can specifically bind to these receptors, thereby facilitating their intake. Recent experiments are focusing on targeting the cancer cell nuclei, instead of the cell itself, as theoretical studies based on numerical models show that nanoparticles located closest to the center have the highest dose enhancements. This is attributed to the short-range of the Auger electrons, generated from the X-ray and nanoparticle interactions. These short range Auger electrons deposit more energy closer to the nanoparticles; therefore, the highest nDEFs are achieved for nanoparticles that are located closest to the nucleus.

### Alternative Strategies

In a recent hybrid approach, combining photodynamic therapy (PDT) with radiation therapy, scintillating nanoparticles are combined with photosensitizing molecules taking advantage of the deep penetration depth of ionizing radiations such as X-rays as well as the benign side effects of PDT. Ionizing radiation is used to excite scintillating nanoparticles, which may be located deep within tissue. The nanoparticles transfer energy to attached photosensitizer molecules, generating reactive oxygen species and killing cells by the same mechanism as photodynamic therapy. Gd is a common contrast agent in MRI. Gd<sub>2</sub>O<sub>3</sub> core nanoparticles encapsulated in a polysiloxane shell have shown potential as an image guided radiotherapeutic tool in a gliosarcoma rat model. Moreover, magnetic nanoparticles in addition to gold nanoparticles are also being considered as a possible candidate for combined hyperthermia and radiation therapy in cancer patients [10].

### Conclusion

Although, significant progress has been made in nanoparticle aided radiation therapy for cancer treatment, much need to be

done before this can be implemented in clinical practice. Research efforts are underway to minimize toxicity of nanoparticles, improve targeting and combine radiation therapy with other therapeutic modalities in order to improve the efficacy of the method for in vivo applications and potential clinical trials [11]. Theoretical studies involving Monte Carlo simulations are extensively being used to understand the interaction between X-rays and metallic nanoparticles. This also includes study of the properties and geometry of the radiation beam and associated hardware (filters, collimators etc.) that can be designed for precise targeting of the beam within cancer tissues, without affecting nearby healthy tissues. Such studies are essential before the full benefits of nanoparticle aided radiation therapy can be realized.

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