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Nanoparticle-aided Radiotherapy for Retinoblastoma and Choroidal Melanoma

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Abstract

This work investigates the dosimetric feasibility of employing gold nanoparticles (AuNPs) or carboplatin nano-particles (CNPs) to enhance radiotherapy (RT) treatment efficacy for ocular cancers: retinoblastoma (Rb) and choroidal melanoma (CM), during kV-energy internal and external beam radiotherapy. The results predict that substantial dose enhancement may be achieved by employing AuNPs or CNPs in conjunction with radiotherapy for ocular cancer using kV-energy photon beams. Brachytherapy sources yield higher dose enhancement than the external beam in kV energy range. However, the external beam has the advantage of being non-invasive

Keywords

Nanoparticles; Retinoblastoma; Choroidal Meanoma; Dose Enhancement

I. Introduction

Intraocular malignancies tend to cause loss of vision for adults and children [1][2]. These malignancies generally occur in the choroid and retina parts of the eye. In adults, choroidal melanoma (CM) is the most common eye tumor with around 2,500 new cases diagnosed each year in the United States. In children, retinoblastoma (Rb) is the primary intraocular cancer [3]. Each year, about 200 to 300 children are diagnosed with Rb in the United States, and many more worldwide [1].

For medium sized CM tumors, 2.5–10 mm in height and at most 16 mm in the diameter, plaque brachytherapy is the most commonly used treatment modality [4]. Meanwhile, the use of plaque brachytherapy to treat Rb is limited to small tumors. However, the direct irradiation from radioactive seeds of the plaque to the optic nerves and retina may lead to substantial toxicities and loss of vision some months later. This undesirable post therapy side effect is a major drawback of plaque treatment. For children, instead of plaque therapy, one of the primary treatment modalities is chemotherapy. Carboplatin is one of the chemotherapy drugs used to treat children with Rb [1]. However this drug can affect the

Conflict of Interest

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kidneys and cause hearing loss in young children [5]. To avoid these limitations, new treatment modalities or improvements to existing modalities are needed.

Recently, Ngwa *et al.* investigated the use of vasculature targeted gold nanoparticles (AuNPs) as adjuvants to improve radiotherapy treatment for neovascular age-related macular degeneration (AMD) using the non-invasive stereo-tactic radiosurgery Oraya System (Oraya Therapeutics Inc., Newark, CA) [6]. This treatment system delivers kV energy x-rays, and specifically targets the choroidal neovasculature. It was shown that, AuNPs could provide a major localized dose enhancement to the diseased endothelial cell (EC) during Oraya therapy. In another study, Monte Carlo radiation transport simulation was used to investigate the use of a small collimated external beam of low energy x-rays (BLOKX system) for the treatment of medium size CM and it was shown that this system can deliver a more conformal dose to the tumor site in comparison to standard plaque therapy [7].

In this study, we investigate the potential for using AuNPs or carboplatin nanoparticles (CNPs) to enhance the radiotherapy (RT) dose to CM and Rb in particular. Here also, both the EC and actual tumor cells are investigated, covering two recently developed kV energy external beam RT sources, as well as typical plaque brachytherapy sources. The main objective is to examine the dosimetric feasibility of achieving dose enhancement, while minimizing toxicity to normal tissue e.g., the optic nerve. To this end, analytical calculations were carried out to estimate the magnitude of the dose enhancement caused by radiation-induced photo/Auger electrons originating in AuNPs or CNPs. The results provide useful insights on the potential to develop nanoparticle-aided radiotherapy for Rb and CM.

II. Materials and Methods

The diseased EC was modeled using dimensions of 2 μm × 10 μm × 10 μm, as in previous studies, with the targeted NPs attached to the exterior of the EC (Fig. 1) [8][9]. Meanwhile, the tumor sub-volume or voxel away from the tumor vasculature was modeled using dimensions of 10μm × 10 μm × 10 μm, as in a recent study (Fig. 1) [10]. When the high-Z nanoparticles (NPs) are exposed to radiotherapy photons in the keV range, photo/Auger electrons are emitted as a result of photoelectric interaction. The emitted electrons have short range and deposit most of their energy in the tumor voxels or ECs. For the calculation of dose enhancement, the contributions from both photoelectrons and Auger electrons were taken into account. The Auger electron spectrum was obtained from the Evaluated Nuclear Data Library, ENDL97 [11]. In this work, the diameter of the NPs was chosen as 2 nm and the investigated range of concentration was between 0–31 mg nanoparticles per g tumor. The maximum NPs concentration of 31 mg/g was chosen because a previous experimental study showed minimal systemic toxicity when CNPs were used at this concentration level for treating Rb in mice [12]. The toxicity at such concentrations is not yet established for humans and needs to be further investigated. The same concentration was used for AuNPs, which was shown to be relatively non-toxic [13].

Details of the analytical approach using Cole's formula of electron energy loss to calculate the dose enhancement can be found elsewhere [10]. Briefly, emitted electrons deposit their energy locally in a "sphere of photo/Auger electron interaction" centered on the NP (Fig. 1).

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The energy loss of each electron was calculated by using Eq. (1), which represents the empirical relation between the electron energy loss dE/dR (*keV/μm*) and the residual range R (*μm*) ($R = R_{tot} - r$), where R_{tot} is the total range of the electron for a kinetic energy E and r is the distance from electron emission site (Cole):

$$\frac{dE}{dR} = 3.316(R+0.007)^{-0.435} - 0.0055R^{0.33} \quad (1)$$

The energy deposited by a single electron within the EC is calculated by integrating differential energy loss from the surface of NP (R_n) to the distal side of the EC (R_n+D_E)

$$E_{EC} = \int_{R_n}^{R_n+D_E} \frac{Shell_{hemisphere} - Shell_{spherical\ cap\ beyond\ the\ EC}}{Shell_{entire\ sphere}} \frac{dE}{dr} dr \quad (2)$$

In Eq. (2), $Shell_{hemisphere}$ is the surface area of a hemisphere, $Shell_{spherical\ cap\ beyond\ EC}$ is the area of the spherical cap beyond the EC, and $Shell_{entire\ sphere}$ is the surface area of the whole sphere. That calculation does not include energy deposited in the spherical cap beyond the EC. The total energy deposited to one EC was found by multiplying E_{EC} by total number of electrons for that energy. Eventually, absorbed dose was found by dividing total energy deposited to EC by the mass of the EC.

To calculate dose enhancement in the tumor sub-volume or voxel (Fig. 1) a slight modification of the integral in Eq. (2) is necessary. The integration was performed for a 10 μm tumor voxel containing a tumor cell, with a factor of *2* to include the contribution of the NP on the other side of the slab. The modified integral can be expressed as

$$E_{voxel} = 2\int_{R_n}^{R_n+D_E} \frac{Shell_{hemisphere}}{Shell_{entire\ sphere}} \frac{dE}{dr} dr \quad (3)$$

where E_{voxel} is the kinetic energy deposited in the voxel. The assumption of uniformly distributed NPs over a voxel and immediate neighboring voxels allows for calculations to be independent of the specific location of NP. The dose enhancement factor (*v*DEF) is defined as

$$vDEF = \frac{Dose\ with\ nanoparticles}{Dose\ without\ nanoparticles} \quad (4)$$

The investigated radiotherapy sources included:I-125 and Pd-103, chosen as typical low energy plaque brachy-therapy sources described in TG-43, the Oraya Therapy system with100 kVp energies [14], and the Beamlet Low-kVp X-ray (BLOKX)system with 90 kVp beams [7], developed specifically for treating ocular diseases. The SpekCalc program was

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used to generate the external energy spectra for the external beam sources, as in previous studies [6][15].

III. RESULTS

Figure 2(a) and 2(b) show the endothelial cell dose enhancement factor (EDEF) and the tumor voxel dose enhancement factor (*v*DEF) values versus nanoparticle concentration for Pd-103, I-125 and external beam sources. As expected there is a linear relationship between dose enhancement and NP concentration. For any given concentration and source, the dose enhancement due to the presence of NPs is higher for gold than carboplatin since only 52% of carboplatin contains high-Z platinum component, and also because gold has higher photoelectric interaction cross section than platinum. In addition, the dose enhancement to the microscopic tumor sub-volume or voxel is higher than that to EC since the calculations for the tumor sub-volume include the contribution of two NPs instead of one near the EC slab (Fig. 1). The maximum *v*DEF value was obtained with the I-125 source using AuNPs. On the other hand, the highest EDEF is achieved with Pd-103 source. This is because the electrons emitted due to photoelectric interactions of Pd-103 photons have relatively lower energies, which deposit a higher fraction of their energy in the small endothelial cell (2 microns thick). In contrast, for I-125 and external beam sources, the energy of the emitted electrons are higher, therefore a substantial amount of the energy is deposited outside the EC. For kV energies EDEF/*v*DEF values are slightly higher for 90 kVp than 100 kVp beams due to higher photoelectric interaction cross sections at lower energies.

Figure 3 shows dose enhancement factor as a function of tumor size for the maximum NP concentration. As expected, *v*DEF decreases as the size of the tumor increases since increasing the volume of the tumor decreases the NP concentration. Clinically meaningful *v*DEF> 1.2 is obtained for a tumor size of up to 553 mm^3 and 674 mm^3 when the tumor is irradiated with 100 kVp and I-125 for CNP, respectively. For AuNPs, clinically significant *v*DEF is obtained for a tumor size of up to 1124 mm^3 and 1364 mm^3 when the tumor is irradiated with 100 kVp and I-125, respectively.

IV. DISCUSSION

This study investigated the potential use of CNPs and AuNPs to enhance radiotherapy for ocular cancers using brachytherapy sources and kilovoltage photon beams typically employed in treatment of ocular diseases. The results predict that AuNPs and CNPs can yield substantial dose enhancement to tumor cells. Such dose enhancement for CNPs could be customized to work in synergy with the chemotherapy effect, which can further improve the treatment outcome.

Intravitreal and periocular routes are the most common methods for drug delivery to the posterior segment of the eye. Intravitreal delivery involves direct injection of the drug into the vitreous humor. In periocular delivery, the drug is injected to the exterior surface of the sclera. Periocular delivery is considered less invasive to the eye compared to the intravitreal route. However, both deliveries are currently being used for both Rb and CM treatments. Direct administration of the drug into the vitreous humor has the advantage of close

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proximity and straightforward access to the Rb, however the access of the drug to the choroid is more complex due to the tissue barriers (i.e. Retinal Pigment Epithelium) on its path. The periocular route is more feasible option for drug delivery into choroid. Both delivery methods could benefit from the use of NPs functionalized to actively target molecular epitopes on the diseased cells [16]. The use of active targeting moieties during intravitreal and periocular delivery would allow NPs to attach to the tumor cells, while the very small (2 nm) NPs in normal tissues are cleared out in time to avoid substantial dose boost there. Timing, therefore, would have to be considered in such an approach. Intravenous delivery is another potential route of NP administration especially for CM as demonstrated in recent study [17].

In this work, we preferred to use small size (2 nm) NPs. Lechtman *et al.* showed that for kV-energy sources smaller NPs yield greater dose enhancement, allowing the escape of more low-energy Auger electrons into the surrounding tissue compared to large size NPs with the same mass concentration [18]. The location of NPs was assumed to be on the exterior surface of the cell or tumor sub-volume. However, to specifically achieve more damage to tumor DNA, the NPs should be adequately close to the nucleus as shown in previous studies [19]. Cellular uptake of the NPs or nuclear targeting could, thus, benefit such a nanoparticle-aided RT approach. Also, despite the small (micrometer range) tumor voxel/sub-volume considered, the local concentration of NPs may not be homogenous. Nuclear targeting of the NPs could also minimize uncertainties due to this and maximize dose enhancement to the nucleus.

At any concentration, the dose enhancement to the EC and dose enhancement to tumor sub-volume is lower for the 100 kVp Oraya therapy and the 90 kVp BLOKX system than for brachytherapy sources. This is expected because the brachytherapy sources have higher fractions of photon energies close to the L-edge of gold and platinum, leading to higher values of dose enhancement. However, the external RT approaches also yield substantial dose enhancement and are particularly attractive because these are noninvasive compared to the use of eye plaques with brachytherapy sources. The Oraya therapy device is currently being used to treat wet AMD by delivering up to 24 Gy of dose to radio-sensitive choroidal neovasculature in a 5-minute single session [20]. Our results indicate that the Oraya Therapy or BLOKX devices could be adapted/considered as an alternative to the more invasive use of eye plaques to treat ocular cancers in conjunction with the NPs. Nanoparticle-aided radiotherapy using such external beam systems may, thus, provide potential new opportunities to improve radiotherapy treatment for ocular cancers as well. Moreover, the use of high atomic number NPs, similar to those considered here, could allow for reducing the applied RT dose. As the NPs enhance the dose locally, they potentially minimize the radiation toxicity to the neighboring normal tissues e.g. the optic nerve.

V. CONCLUSION

In this work, the dosimetric feasibility of employing AuNPs or CNPs to enhance radiation therapy for ocular cancers was investigated. The results predict that substantial dose enhancement may be achieved by employing AuNPs or CNPs as adjuvants to radiotherapy treatment of Rb and CM using either eye plaque brachytherapy or external x-ray sources,

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such as the Oraya therapy or BLOKX systems. The results motivate experimental studies towards the development of such nanoparticle-aided radiotherapy approaches to enhance the therapeutic efficacy of ocular cancers.

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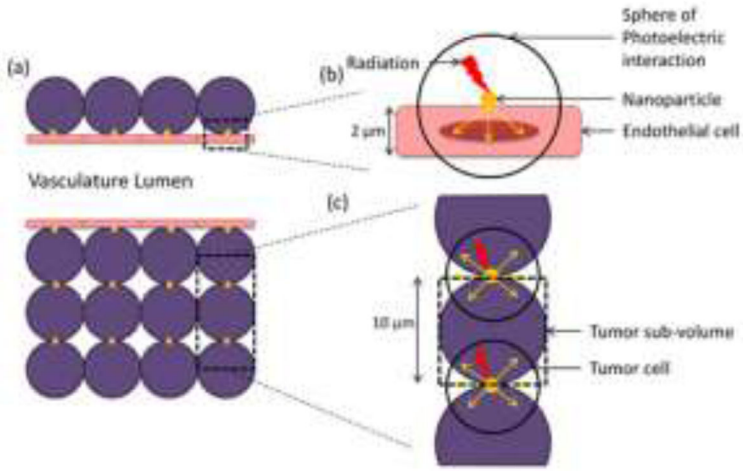

Fig. 1.

(a). Schematic representation of tumor cells with vasculature and nanoparticles. (b) Endothelial cell model for calculating EDEF for tumor endothelial cells. (c) Model for calculating *v*DEF to tumor sub-volume. Details of the calculational approach using these models are described in previous studies [10][9][8].

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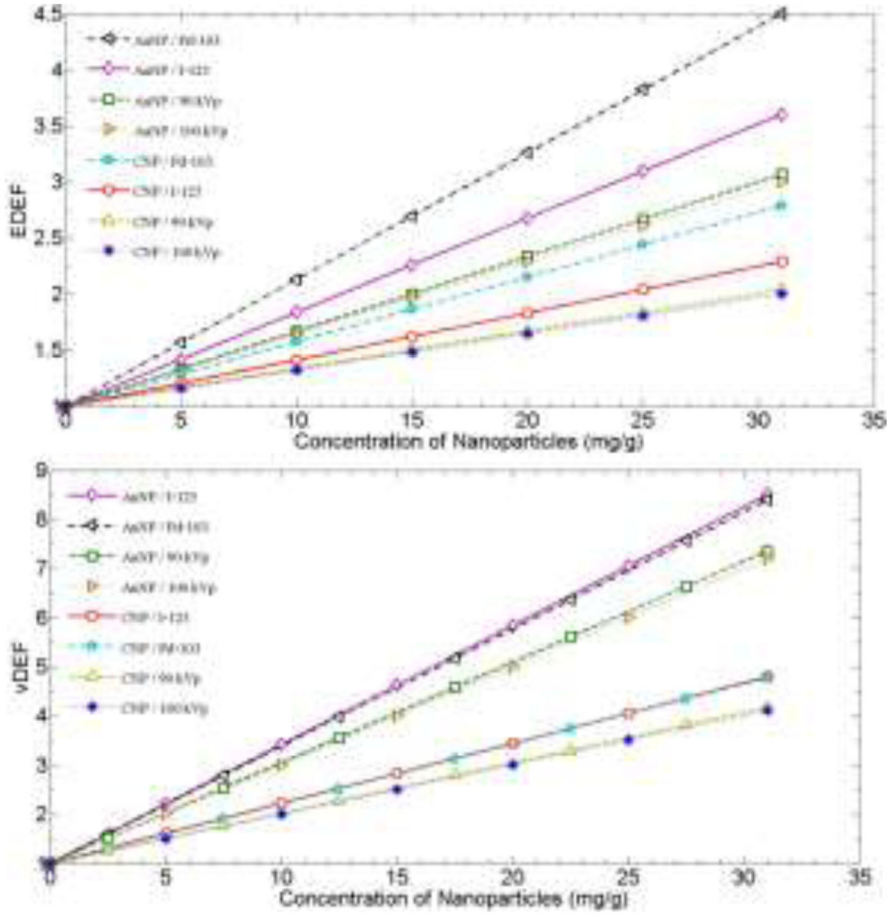

Fig. 2.

(a). The EDEF and (b) the *v*DEF values as a function of NP concentration up to 31 mg/g in conjunction with plaque therapy sources and recently developed kV-energy external beam sources.

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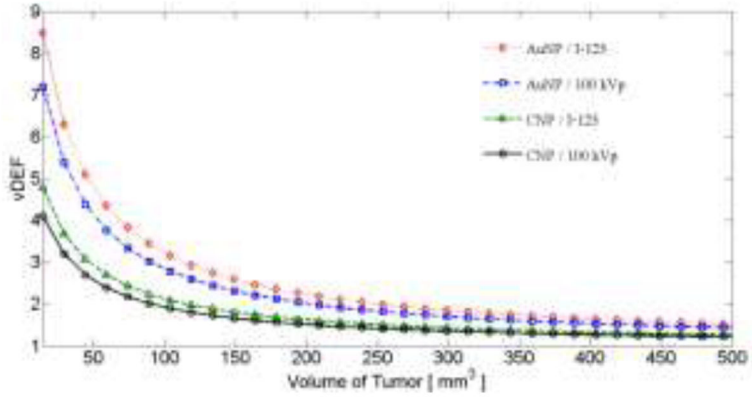

Fig. 3.

*v*DEF as a function of Rb tumor volume for AuNPs and CNPs for 31 mg/g NP concentration.