Published in final edited form as:

Phys Med. 2016 July ; 32(7): 944–947. doi:10.1016/j.ejmp.2016.06.015.

Nanoparticle-aided external beam radiotherapy leveraging the bremsstrahlung effect

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Abstract

This study investigates the feasibility of exploiting the bremsstrahlung radiation (CR) present during external beam radiotherapy (EBRT) for significant therapeutic gain, using titanium dioxide (titania) nanoparticles (NPs) delivered via newly designed radiotherapy biomaterials. Using Monte Carlo radiation transport simulations, we calculated the total CR yield inside a tumor volume during EBRT compared to that of the radionuclides. We also considered a novel approach for intratumoral titania delivery using radiotherapy biomaterials (e.g. fiducials) loaded with NPs. The intratumoral distribution/diffusion of titania released from the fiducials was calculated. To confirm the CR induced enhancement in EBRT experimentally, we used 6 MV radiation to irradiate human lung cancer cells with or without titania NPs and performed clonogenic assays. For a radiotherapy biomaterial loaded with 20 µg/g of 2-nm titania NPs, at least 1 µg/g could be delivered throughout a tumor sub-volume of 2-cm diameter after 14 days. This concentration level could inflict substantial damage to cancer cells during EBRT. The Monte Carlo results showed the CR yield by 6 MV radiation was higher than by the radionuclides of interest and hence greater damage may be obtained during EBRT. In vitro study showed significant enhancement with 6 MV radiation and titania NPs. These preliminary findings demonstrate a potential new approach that can be used to take advantage of the CR present during megavoltage EBRT to boost damage to cancer cells. The results provide significant impetus for further experimental studies towards the development of nanoparticle-aided EBRT powered by the bremsstrahlung effect.

Keywords

bremsstrahlung; Titania nanoparticles; EBRT; Tumor sensitization

Introduction

bremsstrahlung radiation (CR) is light emission when charged particles travel faster than the phase velocity of light in a dielectric medium [1]. It has a broad-band spectrum with a large percentage falling in the ultraviolet region [2]. Radiotherapy beams produce CR within

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tissue, which has been widely studied recently for imaging purposes [3, 4]. Much less research has been done on utilizing CR for therapy partially due to its lack of penetration. Previous studies [2] have indicated that the use of CR for therapy is highly unlikely without the use of appropriate photosensitizers successfully delivered to the tumor.

Titanium dioxide (titania) is a photosensitizer, considered as an inert and safe material used in a wide range of applications—from paint to sunscreen to food coloring. Titania is a semiconductor with a band gap of about 3 eV [5]. After being excited by CR, titania forms electron-hole pairs and induces the production of reactive oxygen species (ROS) [6]. ROS have the potential to damage the DNA and are significantly responsible for cell killing during radiotherapy [7]. Kotagiri et al. have recently reported radiotherapy experiments with remarkable results—more than three times in cancer cell killing *in-vitro*, and complete tumor shrinkage *in-vivo*—due to the interaction of titania and CR generated by radionuclides used in imaging [8]. A much larger population of patients would benefit from this approach if it could be applied in external beam radiotherapy (EBRT). Monte Carlo simulations show that the CR energy fluence is in the order of nJ/cm² for radionuclides, and mJ/cm² for radiotherapy beams [2]. We therefore propose that the greater CR present in EBRT could be leveraged to substantially amplify damage to cancer cells using titania nanoparticles (NPs) targeted to the tumor. To confirm the hypothesis that titania can be used for tumor sensitization in EBRT, we performed *in-vitro* experiments using 6 MV radiation—human lung cancer cells were irradiated with and without titania NPs.

In order to deliver sufficient titania to achieve potent tumor sensitization, we consider the approach of using newly designed radiotherapy biomaterials loaded with titania NPs, similar to that recently proposed for gold nanoparticle-aided radiotherapy [9]. The use of such radiotherapy biomaterials (fiducial markers, beacons, etc.) loaded with titania NPs that can be released *in-situ* would come at no additional inconvenience to cancer patients, and with minimal systemic toxicity, given the direct delivery into the tumor sub-volume. The feasibility of this innovative approach is considered in this study.

Methods

Monte Carlo simulation of CR production

Monte Carlo simulation was done using Geant4 [10] for both external beam radiation and radionuclides in a water phantom. To facilitate this study, the Geant4 standard electromagnetic physics option 3 was used. Dose deposition by radiation sources and CR production spectra in the excitation range of titania (200–400 nm) were calculated.

Based on Eqs (1) and (2) [11], the CR production depends on charged particle energy and on the water refractive index:

$$\frac{dN}{dx} = 2\pi\alpha \left(1 - \frac{1}{\beta^2 n^2}\right) \left(\frac{1}{\lambda_1} - \frac{1}{\lambda_2}\right), \quad (1)$$

$$\beta = \sqrt{1 - \left(\frac{mc^2}{E + mc^2} \right)^2}. \quad (2)$$

Here, dN/dx is the production of CR per unit length of the electron track and α is the fine structure constant, $1/137$. β is the relativistic phase velocity, which is given by equation (2). n is the water refractive index, and λ_1 and λ_2 are the CR wavelengths between which the calculations are performed. The energy-dependent refractive index of water was used as reported by Daimon and Masumura [12].

Note that there is an energy threshold for CR production, i.e., $\frac{1}{\beta^2 n^2}$ must be smaller than 1, which sets a lower limit (about 210 keV in water) for the incident radiation energy. During the simulation, to make sure that the cut-off energy of charged particles was lower than the CR production threshold, the gamma photon, electron and positron production cutoffs were set to 0.2 mm in water.

Geant4.10.1 was used to simulate ionizing radiation induced CR production in a 1 cm diameter spherical volume using two external radiotherapy phase-space sources: Varian Clinac IX 6 MV ($10 \times 10 \text{ cm}^2$) and Eldorado ^{60}Co ($10 \times 10 \text{ cm}^2$) [13]. The target volume was located in a cubic water phantom ($40 \times 40 \times 40 \text{ cm}^3$). The volume was placed at maximum dose depth for both cases—1.5 cm for 6 MV source and 0.5 cm for ^{60}Co .

^{18}F , ^{192}Ir and ^{60}Co were simulated using Geant4 radioactive decay models as internal sources. For ^{60}Co and ^{192}Ir , the sources were located in the center of scoring volume, whereas ^{18}F was uniformly distributed in the volume to model clinical scenarios. Target volume was the same as that of external beam radiation.

NP delivery modeling

A schematic of the radiotherapy biomaterials loaded with titania NPs for sustained *in-situ* release is shown in Fig. 1. While the intratumoral biodistribution of the NPs is relatively more complex, we adopt a diffusion model with a steady state isotropic release as was done in previous studies for gold NPs [14]. NPs diffuse directly into the tumor over time from the radiotherapy biomaterial, assuming no NP present in tissue initially, via the following experimentally validated equation [15]:

$$C(x, t) = C_s \left[1 - \operatorname{erf} \left(\frac{x}{2\sqrt{Dt}} \right) \right]. \quad (3)$$

Here, C_s is the initial NP concentration, defined at the surface of the new design radiotherapy biomaterial. $C(x, t)$ is the final concentration at distance x and after diffusion time t . D is the diffusion coefficient with units cm^2/s .

An *in-vivo* determined value, $2.2 \times 10^{-8} \text{ cm}^2/\text{s}$, was published as the diffusion coefficient for 10 nm NPs [15]. The Stokes–Einstein diffusion formula was used to estimate the D values for other sized NPs:

$$D = \frac{K_B T}{6\pi\eta r}. \quad (4)$$

In this equation, K_B is the Boltzmann constant, T is the absolute temperature, η is the viscosity of medium, which was assumed constant, and r is the radius of spherical NPs [16].

The minimum concentration desired in each tumor voxel was 0.625 $\mu\text{g/g}$ in order to achieve significant therapeutic gain based on the *in-vivo* study by Kotagiri et al. [8]. Initial concentration, C_s , was taken to be 20 $\mu\text{g/g}$, which has been shown to be relatively safe [17, 18]. A clinically relevant wait time, 14 days, was used for the evaluation [19, 20].

In-vitro experiment

5 nm anatase titania NPs (99.5% wt/wt) were purchased from US Research Materials, Inc. (Stock #: US3838). NP stock solution was made at 1 μg in 10 μL of sterile distilled water, and sonicated using an ultrasonic water bath for 20 minutes before treating the cells. A549 were purchased from ATCC and cultured in RPMI-1640 media supplemented with 10% FBS. Cells were incubated at 37 °C in a humidified atmosphere (5% CO_2 , 95% air).

6 MV radiation was delivered using a Clinac TX machine at 100 cm SAD with 10 cm buildup and 5 cm backscatter (using solid water). The beam was delivered at gantry zero with a field size 15×15 cm^2 . Dose rate was set to be 400 MU/min with 121.5 MU/Gy.

500 A549 cells per well were seeded in 6-well plates on day one. 0.5 $\mu\text{g/g}$ (NP per cell culture media) of NPs were treated to the cells on day three by replacing the regular cell media with NP-added media. Radiation was delivered on day four. Cell culture media were changed once 24 hours after irradiation and then biweekly. One week after irradiation, colonies were stained with crystal violet (1% by weight) and counted. Experiments were run in triplicates. Student's t-tests were performed using Mathematica.

Results

Monte Carlo simulation of CR production

Fig. 2 shows the number of CR photons produced by different radiation sources. The simulation results were normalized by CR wavelength, tumor volume, and dose deposition. The results showed that 6 MV radiation produced the most CR per unit dose deposition—about 10 times higher than ^{18}F . Overall, CR yield decreased as its wavelength increased. Note that ^{60}Co was able to produce relatively high CR whether it was used as an external or an internal source.

NP delivery modeling

With a fixed diffusion time of 14 days, the needed/minimum titania concentration of 0.625 $\mu\text{g/g}$ could be achieved at a distance of 1 cm for 2 nm titania. The diffusion distance corresponded to the tumor radius. The distance decreased with increase in nanoparticle size, as would be expected (Fig. 3). For a tumor sub-volume size of 1 cm diameter, the minimum

concentration could be achieved for a range of titania sizes up to 20 nm. We were also interested in a particular tumor size (radius = 1 cm), and obtained the concentration profile over a range of time (7–21 days), since the actual treatment schedule could vary among different clinics (Fig. 4). Altogether, these results showed the possibility of treatment optimization based on clinical schedule and tumor size.

In-vitro experiment

As shown in Fig. 5, adding titania NPs alone did not increase cancer cell killing significantly. When A549 cells were irradiated by 2 Gy of 6 MV radiation, cell survival remained almost the same as that of the control group. Synergistic effect for the combination of ionizing radiation and titania NPs was observed in the 6 MV experiments, where 20% more cancer cells were killed in the group with both radiation and 0.5 $\mu\text{g/g}$ NPs—compared to that with radiation alone.

Discussion

The Monte Carlo simulations show that much more CR is produced by MV radiation than by radionuclides. Therefore, more titania NPs can be excited and used for cancer cell killing. Together with published experiments [8], we demonstrate there is a great potential in advancing EBRT by leveraging the bremsstrahlung effect. To improve the simulation, in the future we shall consider optical properties of tissue instead of using water phantom data. Furthermore, CR transport in tissue is not trivial. For more realistic modeling, CR transport and CR-NP interaction should be integrated in the simulation. However, further refinement requires experimentally determined absorption and scattering data for different tissue components and titania NPs.

The NP delivery model shows the feasibility of providing sufficiently potent concentrations of titania released from new design radiotherapy biomaterials to tumor volumes/sub-volumes during EBRT. As discussed in previous publications [14, 21, 22], this *in-silico* diffusion study assumed a single NP source and isotropic steady release. However, NP diffusion would be affected by tumor inhomogeneity, particle interactions, and other *in-vivo* activities. Clinically, more than one radiotherapy biomaterial loaded with titania can be used, which would result in enhanced tumor coverage. The typical number of radiotherapy biomaterials ranges from 2 to 5. Besides, a higher initial concentration may be used, which can accelerate the diffusion process.

By using the diffusion method, the highest NP concentration is at the center of the tumor. Only a small amount of titania—at most 1 $\mu\text{g/g}$ with the initial conditions used in our model—can possibly reach the surrounding normal tissue. Besides, more research should be done in order to customize the radiotherapy biomaterials and achieve precisely controlled NP release. In any case, normal tissue toxicity is minimized and should not be a concern when applying this new method to improve EBRT results. Previous studies [2] have indicated that the use of CR for therapy is highly unlikely without the use of appropriate photosensitizers delivered to tumor. This study proposes an innovative approach with potential benefits of enhancing therapeutic efficacy during radiotherapy, which could improve survival and quality of life for cancer patients.

The *in-vitro* experiment, although very simple, provided supporting evidence that titania NPs significantly increased cell killing during MV radiotherapy. In a single layer cell culture, due to its very small liquid depth, charged particle equilibrium is hard to achieve. Although we added solid water for buildup and backscatter, airgaps might still exist. More systematic and controlled studies are ongoing comparing different energies and doses for different titania concentrations to better synergize and optimize this approach towards enhancing radiotherapy using titania, sustainably delivered *in-situ* using radiotherapy biomaterials.

Conclusions

Overall, our findings demonstrate a potential new approach that can be used to take advantage of the CR present during megavoltage EBRT to significantly boost damage to tumor cells. The results provide impetus for further experimental studies towards development of nanoparticle-aided EBRT leveraging the Cherenkov effect.

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Figure 1 (a)

Figure 1 (b)

Figure 1.
(a) Titania diffuse from the radiotherapy biomaterial into tissue (not to scale). **(b)** Production of hydroxyl and superoxide radicals on the surface of titania excited by CR.

Figure 2 (a)

Figure 2 (b)

Figure 2.

CR production per unit dose deposition inside a target volume (a) by external radiation sources: 6 MV and ^{60}Co ; (b) by internal radiation sources: ^{18}F , ^{192}Ir and ^{60}Co . Note: different source-target geometries were used in order to be close to clinical scenarios.

Figure 3.

Titania concentration in tumor (radius = 2 cm) after 14-day diffusion with 20 $\mu\text{g/g}$ initial concentration. Different sized NPs can be used for different size tumor.

Figure 4. Minimum concentration of titania in tumor (radius = 1 cm) with up to 30-day diffusion and $20 \mu\text{g/g}$ initial concentration.

Figure 5.

A549 cell survival fraction with 2 Gy radiation and 0.5 µg/g of titania NPs. 6 MV radiation was delivered using a Clinac TX (*p<0.05). Note: groups with no radiation showed no significant difference, which meant titania NPs by themselves had no or little effect on cell survival fraction.