Physica Medica 32 (2016) 944–947

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Technical note

Nanoparticle-aided external beam radiotherapy leveraging the Čerenkov effect

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ARTICLE INFO

Article history:
Received 11 April 2016
Received in Revised form 15 June 2016
Accepted 29 June 2016
Available online 5 July 2016

Keywords:
Čerenkov
Titania nanoparticles
EBRT
Tumor sensitization

ABSTRACT

This study investigates the feasibility of exploiting the Čerenkov 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 might 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 Čerenkov effect.

1. Introduction

Čerenkov 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 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/cm^2 for radionuclides, and mJ/cm^2 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 (A549) were irradiated with and without titania NPs.

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http://dx.doi.org/10.1016/j.ejmp.2016.06.015
1120-1797/

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.

2. Methods

2.1. 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:

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

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

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 Eq. (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 (10×10 cm^2) and Eldorado ^{60}Co (10×10 cm^2) [13]. The target volume was located in a cubic water phantom ($40 \times 40 \times 40$ 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.

2.2. 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,

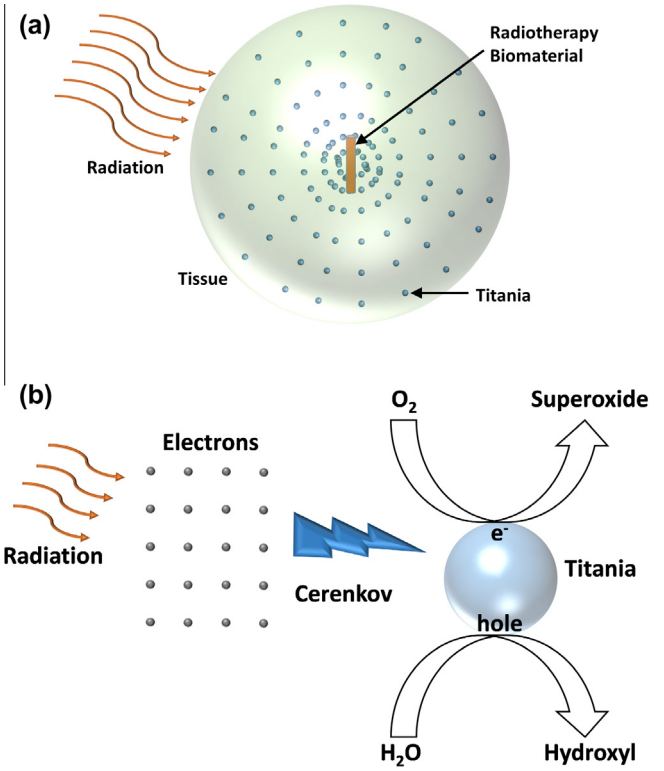

Fig. 1. (a) Titania diffuse from the radiotherapy biomaterial into tissue (not to scale). (b) Production of hydroxyl and superoxide radicals on the surface of titania excited by CR.

assuming no NP present in tissue initially, via the following experimentally validated equation [15]:

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

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, 2.2×10^{-8} cm^2/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:

$$D = \frac{K_B T}{6\pi\eta r}. \tag{4}$$

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 μg/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 μg/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].

2.3. 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 min before treating the cells. A549 were purchased from ATCC and cultured in RPMI-1640 media