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Technical Notes

Targeted radiotherapy enhancement during electronic brachytherapy of accelerated partial breast irradiation (APBI) using controlled release of gold nanoparticles

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ABSTRACT

Several studies have demonstrated low rates of local recurrence with brachytherapy-based accelerated partial breast irradiation (APBI). However, long-term outcomes on toxicity (e.g. telangiectasia) and cosmesis remain a major concern. The purpose of this study is to investigate the dosimetric feasibility of using targeted non-toxic radiosensitizing gold nanoparticles (GNPs) for localized dose enhancement to the planning target volume (PTV) during electronic brachytherapy APBI while reducing normal tissue toxicity. We propose to incorporate GNPs into a micrometer-thick polymer film on the surface of routinely used lumpectomy balloon applicators and provide subsequent treatment using a 50 kVp Xoft device. An experimentally determined diffusion coefficient was used to determine space-time customizable distribution of GNPs for feasible in-vivo concentrations of 7 mg/g and 43 mg/g. An analytical approach from previously published work was employed to estimate the dose enhancement due to GNPs as a function of distance up to 1 cm from the lumpectomy cavity surface. Clinically significant dose enhancement values of at least 1.2, due to 2 nm GNPs, were found at 1 cm away from the lumpectomy cavity wall when using electronic brachytherapy APBI. Higher customizable dose enhancement was also achieved at other distances as a function of nanoparticle size. Our preliminary results suggest that significant dose enhancement can be achieved to residual tumor cells targeted with GNPs during APBI with electronic brachytherapy.

Introduction

Breast cancer is the second leading cause of death among women in the World. According to the National Breast Cancer Foundation, one in eight women will be diagnosed with breast cancer in their lifetime. The treatment of breast cancer may include surgery, chemotherapy, radiotherapy (RT), etc. or combinations of these treatments. However, the primary treatment for early stage breast cancer is breast conserving surgery (BCS) [1]. Meanwhile studies revealed that the majority of breast cancer recurrences arise at or near the primary tumor site, around the lumpectomy cavity [2]; therefore radiotherapy is administered after BCS in order to kill any remaining cancerous cells around this cavity. This has led to the development and increasing use of Accelerated Partial Breast Irradiation (APBI) [3], with the prescribed dose delivered only to the lumpectomy cavity vicinity. Compared with whole breast irradiation (WBI), APBI is attractive because the number of treatment fractions is decreased by increasing (accelerating) the dose delivered per treatment fraction, which is relatively more convenient. While traditional external beam radiotherapy takes about 6–8 weeks, APBI delivers the whole course of radiation dose in only 5–7 days and the treatment may begin anywhere from 2 to 21 days post BCS [3].

APBI can be performed either as external beam RT (EBRT) or internal RT (brachytherapy). Currently, brachytherapy APBI is typically applied with the use of a balloon applicator [4,5]. To this day, there is very little information on normal tissue toxicity during APBI, and most information available is on multiple catheter interstitial brachytherapy [6]. Although APBI has the advantage of improving patient and staff convenience [2], recent studies showed higher long-term complications, such as normal tissue toxicity [7] and local recurrences [7], compared to WBI [8]. Therefore, there is a need to develop new approaches to address these limitations.

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Many studies [9] have shown that introducing high atomic number (Z) contrast materials during radiotherapy could substantially increase the local dose deposition in the tumor volume due to the high photoelectric interaction cross-section of high-Z materials [10,11]. In recent years, due to its biocompatibility [12] and non-toxicity [7], several authors have focused on investigating the use of gold nanoparticles to enhance cancer treatment [9,13] effectively demonstrating significant local dose enhancement in the presence of gold nanoparticles. The dose enhancement due to interactions of low energy photons with high-Z materials is expected to be much higher than those of high energy photons. This is due to higher probability of photoelectric interaction of low energy photons with high-Z materials. As a result of this, a more significant dose enhancement is predicted to be achieved with brachytherapy sources, relative to EBRT. For the first time, in this work we investigated the dosimetric feasibility of using such gold nanoparticles as localized radiosensitizers to boost the dose to the planning target volume (PTV) with residual tumor cells during APBI, while minimizing the dose to surrounding healthy tissue. Such a new approach has potential to help reduce long-term adverse outcomes on toxicity (e.g. telangiectasia) and cosmesis.

Methods

When the 50 kVp Xoft device is chosen for brachytherapy APBI following BCS, the balloon applicator is inserted into the lumpectomy cavity and the irradiation can be performed twice a day for 5–7 days [14]. Here, we propose to deliver GNPs via in-situ release from a GNP-loaded polymer film that is coated on the surface of the balloon applicator (Fig. 1a). Our hypothesis is that, once the Xoft balloon applicator is placed inside the lumpectomy cavity, the polymer film will begin to biodegrade, releasing GNPs in situ. As the GNPs release in tissue near lumpectomy cavity surface, the GNPs will begin to diffuse further away from the lumpectomy surface, while being irradiated by 50 kVp Xoft device subsequently. The spectra for the 50 kVp Xoft electronic brachytherapy device can be found in previous literature [15].

In order to calculate the dose enhancement to the target volume, the diffusion profiles of 2 and 10 nm GNPs as a function of time and position were first determined. To this end, a previous experimentally determined diffusion coefficient, $D = 2.2 \times 10^{-8}$ cm^2 s^{-1} for 10 nm nanoparticles [16] was employed to calculate the value of the same coefficient but for 2 nm size nanoparticles by using the Stokes–Einstein equation (Eq. 1):

$$D = \frac{K_B T}{6\pi\eta r} \tag{1}$$

where, k_B is Boltzmann's constant, T is the absolute temperature, η is the dynamic viscosity of the medium and *r* is the radius of the nanoparticles. Stokes–Einstein equation is used to calculate the diffusion coefficient of a spherical particle moving in liquid based on the forces acting on it. We assumed that the Stokes–Einstein relation for the diffusion coefficient of nanoparticles is valid in tissue media, and that the mean viscosity is constant in the particle size and concentration ranges considered in this paper. Based on this, the concentration of GNPs at any time and at any point inside the target volume was calculated by using one dimensional solution of Fick's second law diffusion:

$$\frac{C(x,t)-C_0}{C_s-C_0} = 1 - erf\left(\frac{x}{2\sqrt{Dt}}\right) \tag{2}$$

Here, C_0 is the initial concentration at anywhere in the tissue prior the burst release (considered zero), C_S is the concentration on the lumpectomy cavity surface (considered $C_s = 7$ mg/g for case I and 43 mg/g for case II). C(x, t) is the concentration as a function of distance (x) from the surface of the lumpectomy cavity over time (t), and *erf* is the error function, which describes the probability of the magnitude by which the measured results deviated from the mean. The diffusion of GNPs from the lumpectomy cavity surface to the target volume is illustrated in Fig. 1b. The number of gold nanoparticles interacting with photons in the target area depends on the initial concentration as well as the diffusion rate of the nanoparticles. In this work, we considered two initial GNP concentrations (C_0): 7 mg/g and 43 mg/g for a lumpectomy cavity size of 2 cm in diameter. An in-vivo animal study showed that there are no toxic side effects of GNPs when used with a 7 mg/g concentration [17]. In addition, we used 43 mg/g GNP concentration since it is the FDA approved concentration of cisplatin, which is relatively more toxic than gold [18].

We hypothesize that localized dose boost to tumor cells will result from micrometer ranged photo-/Auger electrons emitted from the high-Z GNPs due to the interactions with low energy photons during APBI. The calculated dose enhancement factor (DEF) is defined as the ratio of dose to each tumor voxel with and without GNPs. Physically, for example, if the DEF is 2, it means the delivered dose in the presence of GNPs is doubled (or 100% higher) compared to dose without GNPs. In order to calculate the DEF in the presence of GNPs, we employed an analytical calculation method, which was used in a previously published work [19,20]. Briefly, in this approach a tumor voxel is modeled as a slab of 10 μm × 10 μm × 10 μm, representing a sub-volume containing a tumor cell of diameter 10 μm. The energy deposited by an emitted electron, *E*, is calculated by Cole's electron energy loss formula [21] (Eq. 3):

$$\frac{dE}{dR} = 3.316(R+0.007)^{-0.435} + 0.0055R^{0.33} \tag{3}$$

Here $R = R_{tot} - r$, where *r* is the distance from the photoelectron emission site and R_{tot} is the total range of the photoelectron (Eq. 4).

$$R_{tot} = 0.431(E+0.367)^{1.77} - 0.007 \tag{4}$$

By integrating Eq. 4 over the range of emitted electron energies, the total energy deposited in a tumor sub-volume was calculated.

In DEF calculations, the GNPs at equal distances away from the surface of the balloon applicator are assumed to be uniformly

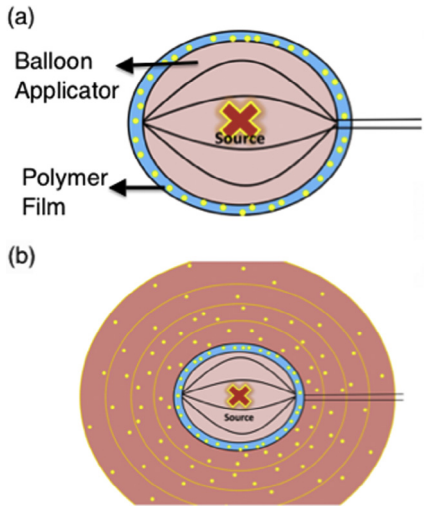

Figure 1. (a) A schematic diagram of the distribution of GNPs in lumpectomy cavity surface from Xoft balloon applicator. (b) The distribution of GNPs in tissue toward residual tumor cells.

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