Physics Contribution

Brachytherapy Application With In Situ Dose Painting Administered by Gold Nanoparticle Eluters

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Summary

This in silico study investigated the intratumor biodistribution and corresponding dose enhancement over time due to gold nanoparticles (GNP) released from GNP-loaded brachytherapy spacers. Results showed that dose enhancement to tumor voxels or subvolumes can be customized by varying the sizes of the released GNP and brachytherapy source type. These findings provide a useful basis for further work toward development of a potential new

Purpose: Recent studies show promise that administering gold nanoparticles (GNP) to tumor cells during brachytherapy could significantly enhance radiation damage to the tumor. A new strategy proposed for sustained administration of the GNP in prostate tumors is to load them into routinely used brachytherapy spacers for customizable in situ release after implantation. This in silico study investigated the intratumor biodistribution and corresponding dose enhancement over time due to GNP released from such GNP-loaded brachytherapy spacers (GBS).

Method and Materials: An experimentally determined intratumoral diffusion coefficient (D) for 10-nm nanoparticles was used to estimate D for other sizes by using the Stokes-Einstein equation. GNP concentration profiles, obtained using D, were then used to calculate the corresponding dose enhancement factor (DEF) for each tumor voxel, using dose painting-by-numbers approach, for times relevant to the considered brachytherapy sources’ lifetimes. The investigation was carried out as a function of GNP size for the clinically applicable low-dose-rate brachytherapy sources iodine-125 (I-125), palladium-103 (Pd-103), and cesium-131 (Cs-131).

Results: Results showed that dose enhancement to tumor voxels and subvolumes during brachytherapy can be customized by varying the size of GNP released or eluted from the GBS. For example, using a concentration of 7 mg/g GNP, significant DEF (>20%) could be achieved 5 mm from a GBS after 5, 12, 25, 46, 72, 120, and 195 days.
brachytherapy application with in situ dose painting administered via gold nanoparticle eluters, for prostate cancer.

**Introduction**

A number of recent studies have concluded that administering gold nanoparticles (GNP) to cancer cells during brachytherapy could lead to significant dose enhancement to the tumor (1-4). However, delivery of sufficiently potent concentrations of nanoparticles into solid tumors remains a challenge (5-7). This is attributed mostly to the physiological barriers imposed by the abnormal tumor vasculature and the dense interstitial matrix, a complex assembly of collagen, glycosaminoglycan, and proteoglycans, which may hinder deep penetration of the nanoparticles (5, 7).

In an effort to overcome this challenge, a recent study (8) proposed a biological in situ dose painting approach in which inert brachytherapy spacers, routinely used for increasing spatial accuracy during brachytherapy, could be loaded with radiation-sensitizing drugs to be released or eluted in situ after implantation, to enhance therapeutic ratio. The study concluded that drug loading in implantable devices such as brachytherapy spacers provides new opportunities for therapy modulation via biological in situ dose painting.

Building on these concepts, this study explores the feasibility of a potential approach where GNP, which are relatively nontoxic (2, 8-12), would be loaded in the inert brachytherapy spacers instead of drugs. Such a gold-loaded brachytherapy spacer (GBS) could be produced by coating the inert spacers with polymer films containing GNP, similar to procedures for coating fiducials with polymer films loaded with poly(D,L-lactide-co-glycolide) (PLGA) nanoparticles (13). Alternatively, there is potential for producing GBS by incorporating GNP in PLGA polymer millirods during the gel phase of production (14). After implantation of the GBS, the polymer coating on the GBS would degrade, releasing the GNP in situ, which then diffuse into the tumor subvolume. The sustained release of GNP in situ from the GBS and consequent 3-dimensional intratumor biodistribution over time could then be customized by varying GNP size, initial concentration, and other factors to enhance brachytherapy effect in desired tumor subvolumes. Because implantation of inert spacers is already part of routine clinical practice, replacing the inert spacers with GBS would come at virtually no additional inconvenience to patients. The theoretical feasibility of this potential new approach is explored in this work by investigating the intratumor biodistribution and corresponding dose enhancement over time for GNP released from the GBS as a function of nanoparticle size for the different low-dose-rate (LDR) brachytherapy sources iodine-125 (I-125), palladium-103 (Pd-103), and cesium-131 (Cs-131).

**Methods and Materials**

An in vivo-determined diffusion coefficient, $D$, of $2.2 \times 10^{-8} \text{ cm}^2 \cdot \text{s}^{-1}$ for 10-nm nanoparticles (15) was used to estimate $D$ for other nanoparticle sizes (2, 5, 20, 30, 50, and 80 nm) by using the Stokes-Einstein equation (Equation 1), as follows.

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

Here, $r$ is the radius of the nanoparticles, $K_B$ is the Boltzmann constant, $T$ is the absolute temperature, and $\eta$ is the viscosity. Assuming a burst release of GNP from the GBS, diffusion of the GNP, given by the concentration $C(x, t)$ as a function of distance $(x)$ from the spacer over time $(t)$, can be calculated by applying Equation 2.

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

Equation 2 is a solution of Fick’s second law of diffusion for the given boundary conditions that the concentration of GNP in the tumor cells is $C_0$ (considered zero here) prior to burst release, whereas the concentration of GNP in the GBS is $C_s$. For simplicity in this initial study, $C_s$ was assumed to be 7 mg/g because this concentration has been used in previous in vivo studies of GNP (1, 16, 17). The term erf is the error function used in modeling 1-dimensional diffusion in the previous in vivo experimental work (15). The concentration profile calculations assumed steady release of GNP, with minimal elimination during treatment, and with the main mechanism of GNP motion being via diffusion (7). The assumption of burst release allows the use of 7 mg/g concentration of GNP present in voxels at the interface between the spacer and the tumor subvolume. The steady-state assumption implies that the number of nanoparticles released from the spacer per unit time remains constant so that voxels at the spacer—tumor interface always have at least 7 mg/g. The implications of these and other assumptions are discussed below (see Discussion). The concentration $C(x, t)$ was investigated for different sizes of GNP (2, 5, 10, 20, 30, 50, and 80 nm) over times relevant to the brachytherapy source lifetimes. The range of distances investigated was informed by previous studies of...
prostate tumors with a mean tumor radius of approximately 10 mm (18, 19) and possible high-risk (hypoxic) tumor subvolume sizes, which can be up to 50% of the tumor, with a corresponding radius of up to 8 mm (20).

Dose enhancement or radiation boosting of a high-risk tumor subvolume with functional image voxels obtained via methods such as magnetic resonance imaging (MRI) or positron emission tomography (PET) imaging is customarily referred to as dose painting. In dose painting by numbers, dose is planned or assigned to each high-risk tumor voxel based on the local distribution of functional imaging parameters derived from the PET or MRI. A similar approach was used in this study, whereby a dose enhancement factor was assigned to each tumor voxel based on the local distribution or concentration of GNP. The DEF represents the ratio of dose to each tumor voxel with and without GNP. Detailed steps for calculating DEF due to radiation-induced photoelectrons (Auger electrons) emitted by GNP are described and validated with results using Monte Carlo simulations in previously published work (17, 21-23) involving tumor endothelial cells modeled as a rectangular slab (10 μm × 10 μm × 2 μm). The same steps were used here, except for the use of a slab 10 μm × 10 μm × 10 μm, representing a tumor voxel or subvolume containing a tumor cell of 10-μm diameter (Fig. 1). Briefly, photons from the LDR brachytherapy sources that would yield a given dose without GNP (eg from the treatment planning system), interact with the GNP associated with each tumor voxel via the photoelectric effect to yield photoelectrons/Auger electrons as illustrated in Figure 1. An emitted electron loses or deposits its kinetic energy, E, in the tumor voxel as described by the Cole formula (24) (Equation 3)

\[
\frac{dE}{dR} = 3.316(R + 0.007)^{-0.435} + 0.0055R^{0.33}
\]  

(3)

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

\[
R_{\text{tot}} = 0.431(E + 0.367)^{1.77} - 0.007
\]

(4)

The total energy (dose = energy/tumor mass) deposited in a tumor voxel is then calculated by simple integration of Equation 3 for the range of emitted photoelectron (Auger electron) energies. In the DEF calculations, it is considered that the local GNP concentration over immediately neighboring tumor voxels (highlighted in Fig. 1) is uniform or approximately the same as that of the investigated voxel. Hence, the specific location of the nanoparticle in the voxel does not influence the calculated DEF, with the energy deposited by photoelectrons (Auger electrons) in an adjacent voxel (“cross-fire”) accounted for. Given that the range of a photoelectron/Auger electron from GNP for the investigated brachytherapy sources is less than 10 μm, the micrometer-range dose enhancement from the electrons is expected to be more highly localized than brachytherapy radiation. This could allow for planned dose painting or subvolume radiation boosting without any significant increase in dose to the rectum and other organs at risk not containing GNP. The DEF profiles as a function of time for the different GNP sizes were investigated for 3 brachytherapy sources: Pd-103 (average photon energy of 21 keV; half-life of 17.2 days); I-125 (average photon energy of 27 keV; half-life of 59.4 days); and Cs-131 (average photon energy of approximately 30 keV; half-life of 9.7 days).

Results

The concentration-versus-distance profiles for the 10-nm particle with experimentally determined D is shown in Figure 2A for different times. The sample times considered were 1, 2, 5, 10 (half-life of Cs-131), 17 (half-life of Pd-103), 33 (number of days after which 90% of Cs-131 dose is delivered), 59 (number of days after which 90% of Pd-103 dose is delivered, and approximate half-life of I-125), and 200 days (number of days after which 90% of I-125 dose is delivered). Figure 2B shows DEF versus concentration plot for the different sources considered. Results highlight monotonic linear increase in DEF with concentration as would be expected. Despite higher average photon energies, which result in relatively fewer numbers of emitted photoelectrons, the DEF for Cs-131 for a given concentration is higher than those for I-125 and Pd-103. Closer analysis indicated that despite the fewer number of photoelectric interactions by Cs-131 photons, the photoelectrons produced with the L-edge of gold (approximately 13 keV) are more energetic than those produced by I-125 or Pd-103 photons. The higher overall energy deposited by the more energetic, albeit fewer, electrons resulted in higher DEF than the other sources, which had relatively higher numbers of emitted photoelectrons but with overall less energy.

DEF versus distance profiles are shown in Figure 3 A-C for I-125, Pd-103, and Cs-131, respectively. In general, the results show that for any given position, the DEF increases over time, as would be expected, due to increased GNP concentration. The time evolution of the DEF is further
illustrated in Figure 4 for I-125 as a function of different GNP sizes, with D values ranging from \(11 \times 10^{-8} \text{ cm}^2 \text{ s}^{-1}\) to \(0.275 \times 10^{-8} \text{ cm}^2 \text{ s}^{-1}\). Results are shown for sample distances of 1, 5, 8, and 20 mm, with the generated profiles showing greater DEF over time for smaller GNP sizes at the distances considered due to faster diffusion. For example, significant DEF (>20%) could be achieved 5 mm from a spacer after 5, 12, 25, 46, 72, 120, and 195 days, respectively, for GNP sizes of 2, 5, 10, 20, 30, 50, and 80 nm when treating with I-125. Table 1 highlights these results in comparison to those obtained for Pd-103 and Cs-131 sources. It was observed that for Pd-103, significant DEF could be achieved at 5 mm after 5, 13, 27.5, 50, 77.5, 130, and >200 days, respectively, for 2, 5, 10, 20, 30, 50, and 80 nm GNP. For Cs-131, significant DEF could be achieved at the same position after 5, 11, 24, 42.5, 67.5, 110, and 176 days, respectively, for 2, 10, 20, 30, 50, and 80 nm GNP.

Table 1 shows the potential for customizing the DEF as a function of GNP size; the results provide preliminary indication of what range of GNP sizes may be appropriate when planning for the different brachytherapy sources at a given distance from a GBS. For example, the data suggest that significant DEF is achievable for any of the brachytherapy sources at very close distances (approximately 1 mm) from the GBS for any of the nanoparticle sizes considered. Meanwhile, using GNP of >50 nm to achieve
significant dose enhancement at 5 mm distance or greater may not be expedient, particularly during Cs-131 or Pd-103 brachytherapy, given their relatively shorter half-life values. Even GNP sizes of >20 nm may not be practical for Cs-131 for achieving significant DEF at distances of 5 mm or more, as more than 90% of the treatment dose (approximately 104 of typical 115 Gy) would already be delivered by day 34, and, hence, the DEF (>20%) would apply to very little remaining dose. Meanwhile, given the higher half-life of approximately 59 days, the use of I-125 as a source apparently may afford greater flexibility to customize the DEF as a function of GNP size.

Discussion

Altogether, the in silico results demonstrate the feasibility for prostate cancer, highlighting the potential to optimize treatment efficacy depending on GNP size for a given brachytherapy source. The choice of brachytherapy source for such an approach will ultimately also depend on the GBS polymer degradation rate. A recent study (14) investigating the degradation of PLGA polymer as a function of different polymer weight ratios indicated that many days may be needed for in vivo biodegradation to achieve steady-state release of a drug loaded in PLGA. Taking these factors into account, the preliminary results in this work indicate that there would be even less flexibility in the use of brachytherapy sources with short half-life like Cs-131 or Pd-103. Based on the results, such sources would likely need to be used mainly in conjunction with ultrasmall GNP with quick release GBS. The range of nanoparticle sizes available for customization of the dose enhancement would be more limited for such sources with shorter half-life.

The current study determined DEF profiles due to release of GNP from 1 GBS only. In practice, one would be able to use more than 1 GBS, which would allow for more flexibility or degrees of freedom for customization. Essentially, it may be more practical to load GNP in more spacers than to load just 1 spacer with a high concentration of GNP. The maximum loading capacity of GBS, in any case, remains to be determined experimentally. Also related to this, the starting concentration of GNP, which was 7 mg/g based on previous studies, may be variable. It may be possible to use higher concentrations, which could allow for higher DEF values over time for each tumor voxel compared to the results shown in this study. However, this initial study provides a useful reference when planning future, more extensive studies with 3-dimensional diffusion and with possible superposition of concentrations from neighboring spacers (typically 5 mm apart).

It is worth noting that such 3-dimensional diffusion would likely not be isotropic (7) and that D may depend on tumor type. Although the effect of using the Stokes-Einstein equation with the same viscosity coefficient may not be significant for GNP of <10 nm (25), restricted diffusion is expected to be significant for larger sizes, resulting in higher potential for nonisotropic diffusion.

Fig. 4. DEF as a function of time for differently sized nanoparticles at a distance of 1 mm (A), 5 mm (B), 8 mm (C), and 20 mm (D) from the GBS when using I-125. GBS = GNP-loaded brachytherapy spacers.
Also, the Stoke-Einstein formalism does not take into account potential variations in vascularization or higher interstitial pressure. These factors could influence the distribution of the GNP. A recent review (7) highlights possibilities that could minimize the influence of these variables, for example, normalization of the extracellular matrix, using matrix-modifying agents, which could also enable more uniform distribution. Planned studies would investigate optimal combination of these approaches for enhancing brachytherapy using GNP.

The current study did not consider possible elimination of GNP from the tumor during the treatment. This would, in principle, potentially reduce the available GNP for dose enhancement and hence DEF values. Studies show that any elimination would depend on nanoparticle size and shape and on whether it is functionalized or not. Functionalization to actively bind to tumor cells or facilitate GNP tumor cell uptake would minimize elimination but also reduce GNP diffusion distance (7, 15); hence, more work would be needed to find the right balance. In general, an advantage of using nanoparticles in nanomedicine is their enhanced retention in tumors and ability to functionalize the nanoparticle, and so it should be possible to find the optimal balance. Experimental studies providing information on the uptake, retention/elimination rates of nanoparticles in tumors as a function of nanoparticle size and other factors would benefit further work.

Although the current study used analytically calculated DEF, in principle, DEF values from other studies as a function of concentration could also be used, including dose enhancement calculated via Monte Carlo simulations. Montenegro et al (26), Pradhan et al (27), and Nahar et al (28) proposed a resonant nanoplasma theranostics method using Monte Carlo simulations to calculate the dose enhancement from high-Z nanoparticles. Their results also showed significant enhancement by GNP for photon sources in the kV energy range. Other investigators (1, 2, 24) have also used the Monte Carlo method to calculate dose enhancement values due to GNP for the studied concentration. The analytical approach used here to calculate the DEF values was validated in comparison with Monte Carlo results in previous publications (17, 22-24).

The uncertainties in DEF for the analytical approach are estimated to be within 10% (22). Despite the small (micrometer range) tumor voxel/subvolume considered (Fig. 1), the local concentration of GNP may not be homogeneous. DEF calculations showed that variations in local concentrations as small as 1 mg/g would still achieve a significant dose enhancement of more than 20% for all brachytherapy sources considered. Also, the DEF values were calculated without considering the specific location of the GNP in the voxel or cell. Hence, the dose enhancement to the nucleus (damage to DNA) is expected to be higher for GNP closer to the nucleus and lower for GNP farther away from the nucleus, given the shorter range of Auger electrons. Recent research has indicated that nuclear targeting of GNP in cancer cells is feasible (29). Such targeting could help localize more GNP near the nucleus, minimizing this uncertainty while maximizing dose enhancement to the nucleus. In addition to targeting, other design parameters, for example, GNP size (which also determines uptake into the cell) or spacer location could be considered in minimizing uncertainties or ensuring sufficiently potent GNP concentration in target tumor subvolume. Ultimately, because of the complex interplay of these different factors, experimental studies are needed to determine the optimal parameters for maximizing the dose enhancement to target tumor subvolume.

Figure 5 schematic highlights the potential clinical impact if the GBS approach can be developed. The colored area in Figure 5A illustrates the dose distribution prescribed by a physician’s treatment plan for a patient, using I-125 seed irradiation only. Red areas have the highest dose, followed by that in pink areas. The circle is a hypothetical high-risk tumor subvolume or region of interest identified by MRI or PET that needs a dose boost, which cannot be achieved without increased dose (toxicity) to the rectum. In comparison, Figure 5B illustrates potential dose distribution using this approach when the GBS is used instead of

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**Abbreviations:** DEF = dose enhancement factor; GBS = gold nanoparticle-loaded brachytherapy spacers.
the usual inert spacer. The I-125 radiation plus additional dose from radiation-induced photoelectrons/Auger electrons from the released GNP leads to dose boost (red color) to the high-risk region of interest without increased toxicity to urethra or rectum. If such an approach can be successfully developed, it could potentially be used during initial treatment of locoregional prostate cancer for subvolume radiation boosting to high-risk tumor subvolumes while minimizing dose to neighboring organs at risk. Kuban et al (30) recently reported that if dose to normal tissue like the rectum can be minimized, even moderate radiation boosting would significantly decrease prostate cancer recurrence.

Conclusions

In situ administration of GNP would potentially be more cost-effective than intravenous administration. In situ administration with the GBS also circumvents the central problem in the use of nanoparticles, that is, directing a substantial amount to the intended treatment site or tumor subvolume. The findings in this work provide impetus for further work toward development of a potential GNP-aided brachytherapy application, employing GBS for customizable and sustained in situ administration of the GNP.

References


