Low Z target switching to increase tumor endothelial cell dose enhancement during gold nanoparticle-aided radiation therapy

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Purpose: Previous studies have introduced gold nanoparticles as vascular-disrupting agents during radiation therapy. Crucial to this concept is the low energy photon content of the therapy radiation beam. The authors introduce a new mode of delivery including a linear accelerator target that can toggle between low Z and high Z targets during beam delivery. In this study, the authors examine the potential increase in tumor blood vessel endothelial cell radiation dose enhancement with the low Z target.

Methods: The authors use Monte Carlo methods to simulate delivery of three different clinical photon beams: (1) a 6 MV standard (Cu/W) beam, (2) a 6 MV flattening filter free (Cu/W), and (3) a 6 MV (carbon) beam. The photon energy spectra for each scenario are generated for depths in tissue-equivalent material: 2, 10, and 20 cm. The endothelial dose enhancement for each target and depth is calculated using a previously published analytic method.

Results: It is found that the carbon target increases the proportion of low energy (<150 keV) photons at 10 cm depth to 28% from 8% for the 6 MV standard (Cu/W) beam. This nearly quadrupling of the low energy photon content incident on a gold nanoparticle results in 7.7 times the endothelial dose enhancement as a 6 MV standard (Cu/W) beam at this depth. Increased surface dose from the low Z target can be mitigated by well-spaced beam arrangements.

Conclusions: By using the fast-switching target, one can modulate the photon beam during delivery, producing a customized photon energy spectrum for each specific situation. © 2016 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4938410>]

Key words: radiation therapy, nanoparticle, dose enhancement, vascular disruption

1. INTRODUCTION

While nanoparticle-based cancer therapy has been an active area of research for several years, current approaches are beset by significant challenges including inadequate diffusion of nanoparticles into the tumor and the poor tissue penetration of the activating agent (optical, IR, UV, kV x-rays, etc.).^{1,2} The treatment concept described in this paper overcomes these challenges and offers a simple clinical workflow for improving cancer therapy in combination with high energy external beam radiation therapy.

We propose to target tumor blood vessels with gold nanoparticles (GNPs) prior to radiation therapy with a clinical linear accelerator. There is a growing body of evidence that vascular targets could be more important for anticancer therapy than clonogenic cell death alone.^{3–11} Garcia-Barros *et al.* proposed that damage to tumor vasculature during radiation therapy (specifically, apoptosis in the endothelial cells) may be a more important mechanism for tumor eradication than clonogenic cell death.³ A recent review by Park *et al.* enumerated the

experimental evidence that radiation-induced tumor vascular damage is contributing to the success of stereotactic radiation therapy procedures.⁴ Murphy *et al.* have shown that nanoparticle-mediated drug delivery to tumor vasculature can even have an antimetastatic effect.¹² Accordingly, for radiation therapy combined with GNP, a higher concentration of GNP near the vasculature provides a biological advantage over a homogeneous distribution throughout the tumor.¹³ Serendipitously, accumulation in the vasculature is expected for nanoparticles of a certain size.¹⁴ Nanoparticle concentration and duration in the tumor vasculature can be further optimized by molecular targeting.^{12,14}

The photoelectric interaction of low energy (<150 keV) photons with gold atoms leads to the emission of short-range electrons. Auger interactions occur at very low energies and emitted Auger electrons are quickly absorbed before contributing to the dose enhancement.^{15–17} Using Monte Carlo techniques, it has been found that the nanoscopic photoelectric dose enhancement for a clinical 6 MV photon beam can be many orders of magnitude, close to the GNP.^{18,19} Similarly,

endothelial cells in close proximity to GNP are expected to receive a highly selective boost, exceeding the predictions for homogeneously distributed GNP.²⁰

Chemical vascular-disrupting agents (VDAs) have been developed and tested clinically and preclinically. It has been shown that chemical VDA improves the effects of radiation therapy in preclinical models.^{21–23} However, recent human clinical trials of chemical VDA have resulted in unacceptable toxicities, limiting translation.^{4,5,11,24,25} By using biocompatible GNP, coupled with precise image-guided radiation therapy, we anticipate a reduction in associated normal tissue toxicities.

The concept of GNP as vascular-disrupting agents when combined with external beam radiation therapy was first introduced in a theoretical study by Berbeco *et al.*¹³ An analytical calculation was performed based on a conservative geometry of a GNP localized adjacent to endothelial cells. The results of that study demonstrated the feasibility of providing substantial radiation dose enhancement to tumor endothelial cells during clinical radiation therapy procedures. Experimental evidence has also shown that gold nanoparticle aided radiation therapy can lead to increased cell death, *in vitro*,^{26–28} and increased tumor vascular damage, *in vivo*.^{29,30} A recent study by Kunjachan *et al.* demonstrated tumor vascular disruption after radiation combined with vascular-targeted gold nanoparticles in a multitude of experimental assays.³¹

Clinical radiation beams produced by a linear accelerator have substantial skin sparing and deep tissue penetration properties. However, an existing obstacle to gold nanoparticle-enhanced radiation therapy is the low proportion of low energy (<150 keV) photons in a clinical beam that will interact most strongly with the GNP. In a nominal 6 MV beam, only 8% of the photon spectrum is comprised of photons with energies less than 150 keV at 10 cm depth in tissue.

To overcome this obstacle, we propose a modification of the linear accelerator target to deliver more low energy photons—i.e., a “softer” beam. The goal is to design a target that balances increased GNP interactions with maintenance of normal tissue dose constraints. We will show that a 6 MV beam produced using a carbon target will almost quadruple the proportion of low energy (<150 keV) photons at 10 cm depth, which corresponds to 7.7 times the endothelial dose enhancement of a standard clinical beam. We will also show

that the corresponding 52% relative increase in surface dose is entirely mitigated by the use of multiple beam angles, a common practice in clinical radiation therapy.

A prototype switching target has been built and demonstrated on a clinical linear accelerator (Fig. 1). The device is compact, occupying, for testing purposes, a single port of the carousel of the linear accelerator (21iX, Varian Medical Systems, Inc.). The two targets included in the prototype are composed of copper/tungsten (Cu/W) and carbon (C), respectively. The switching mechanism operates at ~250 ms and is controlled externally. A complete description of the device will be presented in a separate publication. One application of the switching target is intermittent high contrast beam’s-eye-view (BEV) imaging during radiation therapy.^{32,33} However, a similar device can be used in the future to customize the photon energy spectrum for each treatment field, depending on the patient anatomy, target location, and geometry of normal tissues. In principle, both therapy and BEV imaging functions of the low Z switching target can be used simultaneously, a concept that is beyond the current scope of work. In the following study, we examine the dosimetric advantage of including a low Z linear accelerator target in gold nanoparticle aided radiation therapy.

2. METHODS AND MATERIALS

2.A. Monte Carlo photon spectrum generation

A Varian 2100EX Clinac was simulated using BEAMnrc. The model was modified from previous work,³² to account for changes present in the most recent High Energy Accelerator Monte Carlo Data Package provided by Varian Medical Systems under a nondisclosure agreement. These modifications largely consisted of the inclusion of the metal plating on the dielectric windows of the monitor chamber. To simulate the low Z target, the Cu/W target and flattening filter were removed and the carbon target placed 9 mm from the beryllium exit window. Directional bremsstrahlung splitting was used with a splitting radius of 10 cm for a jaw defined 10 × 10 cm,² at a source-to-surface distance (SSD) of 100 cm, with a bremsstrahlung splitting number of 2000. AE = ECUT and AP = PCUT values of 0.521 and 0.010 MeV, respectively, were used. Phase-spaces were scored at the water surface and at depths of 2, 10, and 20 cm. Dose was similarly calculated

FIG. 1. (A) The switching target (Cu/W and C) with electric motor and external control, (B) the switching target in the carousel of a Varian linear accelerator at Dalhousie University.

TABLE I. Thermal conductivity of target materials.

Target material	Thermal conductivity ($\text{W m}^{-1} \text{K}^{-1}$)
Diamond	900–2300
Graphite	119–165
Copper	401
Tungsten	173

at mentioned depths using DOSXYZnrc. BEAMdp was used to determine spectral distributions of the phase space files.

Previous theoretical and experimental investigations of beryllium ($Z = 4$) and aluminum ($Z = 13$) targets demonstrated the production of large amounts of low energy photons.³⁴ However, these target materials are not practical for clinical applications. For example, beryllium has a low neutron activation energy and is toxic/carcinogenic when machined. Aluminum is inexpensive and convenient to machine, but has a low melting point (660°C). In addition, it has been shown that reducing the atomic number of the target to values lower than carbon (e.g., beryllium) has the effect of increasing the relative photon content at very low energies leading to increases in surface dose without substantial low energy photons at clinically relevant depths.³²

For these reasons, we chose to investigate carbon in the current work. Carbon has a low atomic number ($Z = 6$) and no melting point (sublimes at $\sim 3600^\circ\text{C}$). Table I shows the thermal conductivity of potential target materials. Although the efficiency of bremsstrahlung is approximately Z^2 overall, within the bounds of the primary collimator (e.g., $\pm 14^\circ$), the dependence on Z is weak.^{35,36}

We generated Monte Carlo photon spectra for the following cases: (1) “standard” flat 6 MV beam with a Cu/W target, (2) flattening filter free (FFF) beam with a Cu/W target, and (3) FFF beam with a C target. This last beam is referred to as “6 MV (Carbon)” in this study. We used a 10×10 cm aperture at isocenter and 100 cm SSD for all beams. As the beams penetrate deeper in tissue, beam hardening (due to selective absorption of low energy primary photons) or softening (due to patient/phantom scatter) can decrease or increase the proportion of low energy photons. To study this effect, we generated spectra at 2, 10, and 20 cm depth in tissue. In addition to studying the relative endothelial dose enhancement, we also investigated the effect of the carbon target beam on entrance dose.

The Monte Carlo methods of photon beam generation with low Z targets used in this study have been previously validated experimentally.³² In those studies, photon depth dose measurements were acquired for both carbon and aluminum targets and excellent agreement with the Monte Carlo predictions was demonstrated.

2.B. An analytical calculation method for endothelial dose enhancement

We used a previously published method for estimating endothelial dose enhancement.^{13,37} Briefly, the tumor vascular endothelial cells are modeled as flat rectangular slabs.

FIG. 2. Simplified model of endothelial cell layer between intravascular cavity and tumor cells. The gold nanoparticles are attached to the vascular side of the endothelium. The range of photoelectrons generated within the GNPs is shown as a “sphere of interaction” with the nanoparticle at the center. The extra dose deposited in the nearest endothelial cell by GNP photoelectron emissions (shaded region) is used to calculate the dose enhancement. Reprinted with permission from Berbeco, Ngwa, and Makrigiorgos, *Int. J. Radiat. Oncol., Biol., Phys.* **81**(1), 270–276 (2011).

For the calculation, gold nanoparticles are placed just outside the endothelial cell (Fig. 2). This is a conservative model, as endothelial cell uptake of gold nanoparticles, previously demonstrated *in vitro* and *in vivo*, will increase the expected dose enhancement. Only photoelectric interactions are included as Auger effects will be extremely short range ($\sim$ several nanometer) and substantial self-shielding is expected. The photoelectric interaction cross section is provided in tables by NIST.³⁸ The range and dose deposition of emitted photoelectrons is calculated using the method of Cole.³⁹ The generation of photoelectrons will depend greatly on the energy of the incident photon. Photons above roughly 250 keV contribute very little to the dose enhancement. Only dose deposited within the “sphere of interaction” is included in the calculation.

Beam “softening” with a low Z target is expected to increase GNP therapeutic effectiveness.^{13,18,37,40–42} Our previous theoretical calculations combining Monte Carlo with the analytical microdosimetry calculation described above^{13,37} predict a roughly 50%–150% increase in dose to the tumor endothelial cells, for a 6 MV standard (Cu/W) beam. Factors that affect the therapeutic efficacy include depth in tissue,¹³ removal of the FFF, and the energy of the electron beam incident on the target.

The Monte Carlo generated spectra for the targets listed above are used to evaluate relative increase in endothelial dose enhancement. Like other reported calculations of gold nanoparticles in radiation therapy, this analytical calculation has not been validated *in vivo*. However, the concept of increasing DNA damage for larger proportions of low energy photons in a therapy beam has been validated *in vitro*.²⁷ Due to the lack of any clear absolute metric of the consequences of endothelial dose enhancement, we report our results as relative endothelial dose enhancement, where the standard Cu/W target is the reference. In this way, we are able to show the relative advantage of the lower atomic number linear accelerator target. The relative enhancement of each target is calculated at each depth, providing the increase in endothelial dose enhancement factor (EDEF) for the low Z target under the same treatment conditions as the conventional target. The explicit expression for the calculation

Fig. 3. Photon energy spectra at depth = 2, 10, and 20 cm for 6 MV delivery with a standard flat beam (Cu/W target), a FFF (Cu/W target) beam, and a carbon target beam. Note the substantial increase in low energy photons at all depths for the carbon target relative to the Cu/W target.

of the relative improvement in EDEF is $EDEF_{\text{new target}} / EDEF_{\text{standard flat (Cu/W)}}$.

3. RESULTS

The photon energy spectra calculated with the Monte Carlo for 6 MV standard (Cu/W), 6 MV FFF (Cu/W), and 6 MV (carbon) are shown in Fig. 3. These spectra are generated for depths of 2, 10, and 20 cm in tissue. Figure 4 shows the percentage of low energy photons (25–150 keV) for each target and depth combination. Relative to the 6 MV standard (Cu/W) beam, the 6 MV FFF beam shows a substantial increase in low energy photons for all depths. At 10 cm depth, the 6 MV standard beam is composed of 8% low energy photons compared to 11% for the FFF beam. The 6 MV carbon target beam has a much larger proportion of low energy photons at all depths than either of the Cu/W beams (standard or FFF). At 10 cm depth, the 6 MV carbon target beam is composed of 28% low energy photons. This is nearly four times the low energy photon content of the standard 6 MV beam and more than two and a half times that of the 6 MV FFF beam. Of note, the 6 MV carbon target beam becomes harder at greater depths whereas both 6 MV standard and FFF beams become softer at greater depths in tissue.

Fig. 4. The percentage of low energy photons (25–150 keV) for a standard (Cu/W target) beam, a FFF (Cu/W target) beam, and a carbon target beam.

Fig. 5. The expected increase in the EDEF for 6 MV FFF (Cu/W) and 6 MV (carbon), respectively. Results are shown relative to a 6 MV standard (Cu/W) beam. At 10 cm depth, the carbon target provides 7.7 times the EDEF.

As expected from the Monte Carlo photon energy spectrum results, the relative improvement in EDEF for the carbon target beam is substantial at all depths. The calculation of relative increase in EDEF is made independently for each depth condition, using the entire photon energy spectrum. Figure 5 shows the relative EDEF for the carbon target beam compared to the 6 MV FFF beam. At 2 cm depth, the carbon target beam provides 18.6 times the endothelial dose enhancement as a 6 MV standard beam. This reduces to 7.7 times at 10 cm depth and 4.0 times at 20 cm depth as the relative difference in the proportion of low energy photons decreases at the deepest depths. The 6 MV FFF beam would supply more than twice as much endothelial dose at 2 cm, decreasing to 1.5 times at 20 cm depth.

Due to the relative nature of the calculation in this paper, the size and concentration of the nanoparticles do not influence the results. In addition, no assumptions have been made about coating (e.g., PEG) or targeting (e.g., RGD).

The Monte Carlo data were also used to investigate the increase in surface dose and loss of penetration depth for standard and proposed beams. The percent depth dose (PDD) curves for the 6 MV standard (Cu/W), 6 MV FFF (Cu/W), 6 MV (carbon) normalized to deliver 100% dose at 10 cm

Fig. 6. PDD for 6 MV standard (Cu/W), 6 MV FFF (Cu/W target), 6 MV (carbon), 2.5 MV (C), normalized to 100% at 10 cm depth.

FIG. 7. Normalized percent skin dose as a function of number of parallel opposed treatment beams from different gantry angles. A 2.5 MV (carbon) beam requires eight beam angles to limit the surface dose to the same level as four beam angles of a 6 MV standard (Cu/W) beam (29.6%) while still delivering 100% dose to the tumor.

depth are shown in Fig. 6. We define the surface dose as the central axis dose at 1 mm as a percentage of $d_{\max}$.

The loss of penetration depth and reduced skin sparing effects of beams with more low energy photons contribute to higher entrance dose. Beams of 6 MV FFF (Cu/W) and 6 MV (carbon) contribute 21% and 52% more surface dose than a standard flat 6 MV beam, respectively. However, Fig. 7 shows the reduction in surface dose by the use of treatment plans consisting of multiple angles, as are most commonly used clinically. We simulated parallel opposed beams to include both entrance and exit doses, representing a worst-case scenario. Cylindrical symmetry is assumed with a separation of 20 cm. The normalization is 100% to a point on the central axis at 10 cm depth. To achieve the same or less surface dose (29.6%) as a 4-field standard flat 6 MV delivery, a 6 MV (carbon) beam requires five beams to reach the same level of skin sparing as a 4-field 6 MV standard

(Cu/W) delivery, while still delivering 100% dose to the tumor at 10 cm depth. In these figures, we also show the results for a 2.5 MV (carbon) beam. Currently, used for imaging only, this beam could have therapeutic use in the future.

4. DISCUSSION

In this study, it has been demonstrated that a 6 MV photon beam generated using a clinical linear accelerator with a carbon target will provide a substantial increase in low energy photons compared to conventional beams with a Cu/W target. These additional low energy photons will translate into a multifold increase in endothelial dose enhancement when incident upon gold nanoparticles in close proximity. A full study of 3D treatment planning with a 6 MV carbon target beam will be the subject of a future study.

One potential application of this work is the use of a fast-switching target (FST) to generate custom photon energy spectra. Different clinical scenarios of gold nanoparticle-aided radiation therapy will call for different mixes of low/high energy photon spectra. This will depend on beam angle, field size, patient thickness, and proximity of normal tissues, dose fractionation, and other clinical parameters. Toggling between different targets during beam delivery will generate a customized photon energy spectrum (Fig. 8). The optimal spectrum can be determined prior to treatment delivery similar to the modulation of multileaf collimators in intensity-modulated radiation therapy.

This study is focused on photon beams with a peak energy of 6 MV. Lower energy beams with alternative targets could offer similar advantages in increased proportion of low energy photons. Some currently available linear accelerators are able to deliver imaging beams of 2.5 MV using a low Z target. Previously published studies have shown that 40%–50% of the primary photons from a 2.5 MV (carbon) beam are in the diagnostic range.³³ However, these beam lines are not approved for human radiation therapy and will also likely

FIG. 8. Conventional delivery (left) is contrasted with FST delivery (middle and right). These drawings depict incoming 6.5 MeV electrons colliding with the linear accelerator target, generating photons for radiation therapy. The resultant photon energy spectra for 10 cm depth in tissue are shown for each delivery mode, respectively. These spectra are shown in greater detail in Fig. 3. (Left) Conventional (conv-Cu/W) delivery is shown with the standard Cu/W target and a flattening filter. (Middle) FST delivery with only the high Z (FFF-Cu/W) target, the flattening filter is removed. (Right) FST delivery with only the low Z (FFF-C) target, the flattening filter is removed.

suffer from a low dose-rate. An additional challenge will be the balance of tumor coverage and skin sparing for deep-seated tumors. Simulated PDD and surface dose calculations are shown in Figs. 6 and 7 for comparison with the 6 MV beams.

Collateral advantages of the fast-switching target research include novel clinical imaging concepts. We anticipate that both volumetric and planar imaging with the therapy beam will be greatly improved by the target modifications presented here, resulting in improved patient setup and beam's-eye-view in-treatment imaging.^{34,43–45} For example, fast and periodic imaging of a lung tumor with a low Z target could be used to update predictive models of respiratory motion, without interruption of the treatment delivery. Previously published imaging work with low Z targets demonstrated a marked improvement in image contrast using a 2.35 MV beam with a carbon target.³³

5. CONCLUSION

Our results indicate that replacing the Cu/W target with a carbon target in a clinical linear accelerator should result in a multifold increase in the radiation dose enhancement to tumor blood vessel endothelial cells when GNP is in close proximity. The resulting disruption of tumor vasculature can provide a new therapeutic tool for clinical situations where the deliverable radiation dose is limited by adjacent normal tissue. The concept of customizing photon spectra via a fast-switching target is a novel concept which could offer a further personalized solution for each unique clinical scenario.

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