Broadband and Monochromatic X-ray Irradiation of Platinum: Monte Carlo Simulations for Dose Enhancement Factors and Resonant Theranostics

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Abstract—

Introduction: **X-ray irradiation of heavy-element (high-Z) nanomaterials as radiosensitizing agents should be extremely efficient for therapy and diagnostics (theranostics). However, broadband radiation from conventional X-ray sources results in unnecessary radiation exposure. Monochromatic X-ray sources are expected to be considerably more efficient. We present numerical simulations with platinum as an agent for killing cancerous cells via increased linear-energy-transfer (LET) and dose enhancement. We also describe a simple device for broadband-to-monochromatic (B2M) conversion.**

Materials and Methods: **Monte Carlo simulations for X-ray energy absorption and dose deposition in tissues were carried out using the Geant4 code for 100 kV, 170 kV and 6 MV broadband X-ray sources. Dose enhancements were calculated using platinum as the radiosensitizing agent. A broadband 100 kV source is used to produce monochromatic fluxes in the Kα,β lines from a zirconium target.**

Results and Discussion: **It is shown that X-ray energies in the range below 100 keV are most efficient in achieving both the required penetrative depths and deposition of energy. We confirm previous results that it is only the low-energy component around 100 keV from the 6 MV Linac that is most effective in dose-enhanced cell killing. Monochromatic x-rays such as obtained from B2M conversion should be most effective for theranostics, provided they can be tuned to resonant energies in the targeted material.**

Keywords— **X-rays, monochromatic, broadband, platinum, theranostics.**

I. Introduction

Conventional X-ray sources emit broadband radiation over a wide range up to their peak voltage. But X-rays at most of these energies are ineffective and result in unnecessary exposure for imaging and therapy. Despite some very low-energy filtration of X-rays with E ~ 10-20 keV, the remaining low-energy emission does not penetrate to sufficient depths. On the other hand, X-rays with energy more than a few hundred keV are largely Compton-scattered, which is ineffective. High-Z (HZ) radiosensitizing agents are therefore introduced to increase X-ray photoelectric absorption by heavy atoms. Among these agents are platinum compounds and gold nanoparticles. Although HZ material embedded in tissue increases dose absorption, the lack of specificity of broadband X-ray sources still results in radiation overdose. It is therefore proposed that monochromatic X-rays would be far more effective, as their energies can be precisely matched to atomic absorption cross sections, and the dosage determined with accuracy a priori.

However, there are two problems. First, a convenient monochromatic X-ray source must be developed. Second, a procedure for efficient photoabsorption of HZ material needs to be implemented. The underlying physical process is inner-shell ionization, leading to Auger cascades of secondary electrons. Up to 20 or more Auger electrons may be produced following a single primary K-shell photoionization of HZ elements such as Pt or Au via Coster-Kronig and Super-Coster-Kronig transitions [2]. Most of these electrons have relatively low energies of about 1 keV or less. Therefore their effective impact range is only on nanoscales comparable to the size of the cell nucleus. That localizes the linear-energy-transfer (LET) of Auger electrons resulting in cell killing without damage to surrounding cells.

While HZ compounds or nanoparticles may act as contrast agents, they cannot be effective for energies much higher than 100 keV. The reason is that after the K-shell jump, the photoabsorption cross sections decrease rapidly with energy. For example, Fig. 1 shows X-ray attenuation coefficients due to photoelectric absorption by platinum (Pt). The K-shell energies for the generally safe heavy elements are well below 100 keV; for example they are 81 keV and 78 keV for Au and Pt respectively. However, high-energy Linacs generating x-rays up to 6 to 18 MeV are commonly used for radiation therapy. It follows that for dose enhancement using HZ radiosensitizers only the relatively low-energy component around 100-200 keV from the high-energy Linacs is likely to be effective. Similar to earlier work on Au nanoparticles [1], we verify this hypothesis in the present study.

Another serious problem in conventional theranostics is the use of broadband radiation that lacks specificity in its

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interaction with HZ material. Figure 1 shows the existence of features in the attenuation coefficients or cross sections for photoabsorption of x-rays by Pt. It is clear that these features can be targeted using monochromatic x-rays at resonant frequencies. In earlier works [2, 3] we have shown that monochromatic irradiation at resonant energies will allow the creation of inner-shell vacancies. In principle it is then possible to not only ionize the K-shell electrons that result in corresponding holes in all electronic shells, but also excite the Kα resonances. This combination of resonant K-shell ionization-excitation would *accelerate* the induced Auger effect and corresponding x-ray energy deposition. Numerical simulations for Au atoms show that HZ radiosensitization using x-rays tuned to these resonances can cause an 11-fold increase in the dose absorbed by the tumor [3].

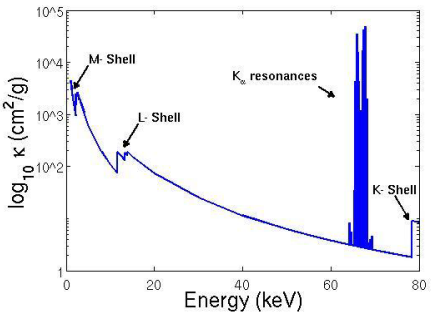

Fig. 1. X-ray attenuation coefficients for platinum as function of incident photon energy. In addition to the M-, L- and K-shell edges we also show the Kα resonances that may be targeted following K-shell ionization and Auger cascades that result in holes in the upper electronic shells. The region between the Kα and the K-edge is therefore filled with similar resonances that enhance photoelectric absorption by orders of magnitude above the otherwise low background [4].

Considerable work has also been carried out using Au nanoparticles in experiments and models [1].Simulations demonstrate that x-ray irradiation at about 100-200 keV has the highest dose enhancement factors (DEF) and is most effective in cell killing. In this study we examine the sensitivity due to Pt, which is commonly used in chemotherapy as cisPt, carboPt, and other compounds.

II. Methods and Materials

We consider three broadband X-ray sources in our simulations: 100 kV, 170 kV and 6MV. Their output spectra are shown in Fig. 2 for the former two devices and in Fig. 3 for a 6MV Linac. In Fig. 2 the Kα energy and the K-shell ionization energy of Pt are marked. Each K-shell ionization in a HZ atom generally results in K-alpha emission, triggering Auger electron cascades that create vacancies in upper L, M, N, O and P electronic shells of the platinum atom. Therefore, it is possible to resonantly excite electrons from the K-shell into higher shells. The large resonant coefficients for Kα excitation are shown in Fig. 1. The Resonant Nano-Plasma Theranostics (RNPT) methodology has been proposed to implement the Auger trigger and *in situ* enhancement of localized x-ray energy deposition via resonant excitation using monochromatic x-rays [2, 3].

Numerical Simulations: We adapted the Geant4 toolkit version 9.4 to simulate the deposition of X-ray energy through human tissue with the use of a 15 cm × 5 cm × 5 cm water phantom. A tumor was simulated using a 2 cm × 5 cm × 5 cm region located 10 cm into the phantom. This region was filled with a 7.0 mg/ml concentration of Pt homogeneously distributed in water to simulate the presence of Pt radiosensitizers in tumors.

The physical interactions of Pt and water with X-rays were governed by the atomic data built into Geant4. These atomic coefficients also determine the background photoabsorption by Pt as in Fig. 1. Photon fluence for each broadband source was determined using the spectra shown in Figs. 2 and 3. Energy intervals of 10 keV at low energies (<500 keV) and 500 keV for higher energies were used.

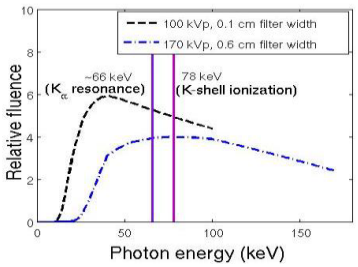

Fig. 2. The 100 kV and 170 kV bremsstrahlung spectra. The K-shell ionization energy and average energy of the Kα resonance resonance complex of Pt shown in Fig. 1 are marked.

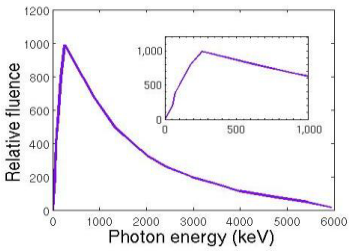

Fig. 3. The 6 MV LINAC bremsstrahlung spectrum. The peak around 300 keV results from filtering the lower energy x-rays.

III. Results and Discussion

Experimental results from a broadband-to- monochromatic (B2M) device are given, as well as modeling results from Geant4 simulations of DEFs using various broadband devices.

Monochromatic X-ray Source: We first report proof-of-principle results from a device to convert broadband radiation from a conventional X-ray source into largely monochromatic radiation at the Kα,β energies. This is achieved via fluorescent emission resulting from K-shell ionization of an element. For example, Fig. 4 shows experimental results using an ordinary 100 kV simulator and a zirconium target. The input spectrum is as in Fig. 2. The output spectrum in the top panel of Fig. 4 shows the Zr Kα,β lines above the scattered background; the isolated features after subtracting the background are shown in the bottom panel.

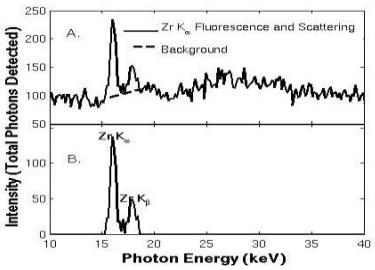

Fig. 4. Monochromatic Kα,β lines converted from a 100 kV broadband source. The top panel shows the monochromatic flux together with the Compton scattered background; the bottom panel shows the isolated features.

Using different HZ targets, it is possible to obtain monochromatic flux via Kα fluorescence at higher energies that would enable greater penetration in the human body.

Dose Enhancement: We calculated dose enhancement factors (DEF) for radiation therapy using a 6 MV Linac, compared to the relatively low energy range from the 100 kV and 170 kV. At each energy interval, the X-rays were tracked as they traveled through the phantom, with the total dose absorbed by the tumor model recorded. No difference in dose enhancement was seen with the tumor region located near the surface of the phantom compared to deep inside it. Dose deposition was determined for the tumor phantom containing either 7.0 mg/g or 0 mg/g, representing a tumor with and without radiosensitizers respectively. Dose enhancement due to Pt was then determined by dividing the dose in tumor with Pt over the dose delivered to the tumor without Pt.

Figure 5 shows the dose enhancements achieved using a 100 kV, 170 kV and 6 MV photon sources. As can be seen, dose enhancements peak at low energies (E < 100keV). The explanation for the double-peaked structure is as follows. The low energy x-rays in the otherwise bremsstrahlung spectrum are assumed to be filtered out. The combination of low-energy filter and L-shell ionization produces the first peak around 40 keV. The DEF decreases thereafter until the second peak at approximately 80 keV corresponding to the K-shelll ionization of Pt (Fig. 1). Dose enhancements decrease monotonically after K-shell ionization since there are no other absorption features in Pt photoabsorption cross section that induce another rise in the DEF. The interesting point however is that the DEF tends to a constant value at energies above 250 keV. At this and higher energies, Compton scattering predominates instead of photoelectric absorption [6]. Since there is little difference in attenuation due to largely elastic Compton scattering for both water and Pt, DEF's are small in the high-energy range E > 250 keV.

These results lead to two conclusions: first, dose enhancement characteristics of HZ radiosensitizers are largely due to photoionization and subsequent Auger ejections of electrons. That causes the enhancement in the DEFs shown in Fig. 5. The second is that elastic scattering dominates photoelectric absorption from about 200 keV onwards, and is relatively constant up to all higher energies even into the MeV range characteristic of Linacs. Therefore no further enhancement of DEF is possible. Also, these high-energy x-rays deposit very limited amounts of their energy to the tumor - the attenuation coefficients of HZ radiosensitizers at these energies are only slightly above that of normal tissue.

Figure 6 illustrates these two points and the low and high energy behavior of the Pt DEF using a 6 MV Linac. Following the peak around 200 keV the DEF falls rapidly to a constant value with very little enhancement up to the maximum energy 6 MeV. The drop thereafter is due to negligible interaction of x-rays with atomic species and the final limiting value of DEF is unity.

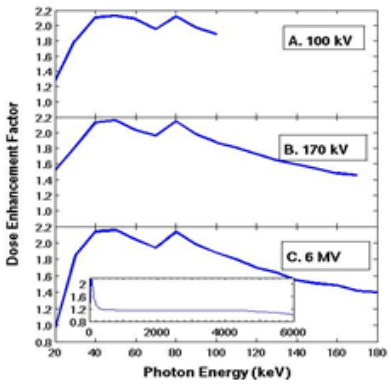

Fig. 5. Similarities in dose enhancement factors with platinum radiosensitization and x-ray irradiation from different broadband sources: A. 100 kV, B. 170 kV, C. 6 MV

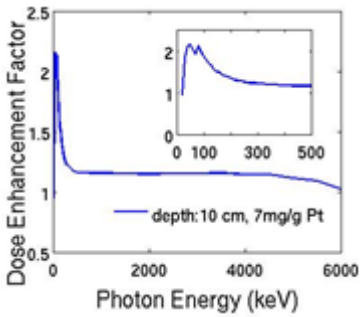

Fig. 6. DEF with a 6 MV source and Pt reagent. The DEF peaks at approximately 100 keV and then drops to constant values at high energies

Experimental X-ray Irradiation: The numerical simulations presented herein will be tested experimentally. The experiments are in progress in two stages. First, specific cancer cell lines are prepared after being treated with Pt compounds such as platinated dendrimers, cisPt or carboPt. These would then be irradiated using a 168 kV and 6 MV sources to measure the cell survival fractions to validate the models and the conclusion that it is the low energy component of the broadband spectrum that results in effective cell killing; the high energy component has little effect on the DEF and survival fractions.

Fig. 4 demonstrates that conversion of x-rays from a broadband source to largely monochromatic spectrum is feasible. Moreover, Kα fluxes can be produced at a range of desired energies by selecting different HZ targets. However, the intensity is still insufficient to enable imaging and therapy to the extent needed for clinical applications and more experimental work is required. The B2M conversion efficiency is estimated to be around 0.02. Much lower monochromatic flux is required to activate the targeted features in photoabsorption (Fig. 1) than from broadband sources such as simulated in this report. The resulting DEFs from monochromatic x-ray irradiation should be considerably higher than obtained herein (Fig. 5).

IV. Conclusion

Based on the numerical simulations presented in this report, the following conclusions may be drawn:

1. Heavy elements such as Pt or HZ compounds are subject to Auger decays of secondary electrons upon x-ray irradiation which can efficiently kill malignant cells with minimal collateral damage.
2. A general pattern is demonstrated in the behavior of the DEF with a peak of ~2.2 close to the L- and K-edges of HZ material. The low energy range E < 100 keV is most effective, and drops substantially to a constant value of ~1.2 for E > 250 keV.
3. The results confirm earlier studies using Au nanoparticles [1,5,6]. These studies on both Au and Pt should be of considerable interest to the biomedical community pertaining to the use of high-energy megavoltage radiation up to 6-10 MV in conjunction with HZ radiosensitization.
4. Monochromatic x-ray sources would obviously be most efficient since they can be tuned resonantly to specific features that enhance photoabsorption. While we have presented first results from a proof-of-principle device for B2M conversion, more experimental work is needed to generate required monochromatic fluxes.
5. These conclusions are embodied in the new RNPT methodology that exploits monochromatic x-ray ionization-excitation of HZ nanomaterials.

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