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Targeted alpha therapy with ^{212}Pb or ^{225}Ac: Change in RBE from daughter migration

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ABSTRACT

Targeted α-therapy (TAT) could be delivered early to patients who are at a high-risk for developing brain metastases, targeting the areas of the vasculature where tumor cells are penetrating into the brain. We have utilized a Monte Carlo model representing brain vasculature to calculate physical dose and DNA damage from the α-emitters ^{225}Ac and ^{212}Pb. The micron-scale dose distributions from all radioactive decay products were modeled in Geant4, including the eV-scale interactions using the Geant4-DNA models. These interactions were then superimposed on an atomic-scale DNA model to estimate strand break yields. In addition to ^{225}Ac having a higher dose per decay than ^{212}Pb, it also has a double strand break yield per decay that is 4.7 ± 0.5 times that of ^{212}Pb. However, the efficacy of both nuclides depends on retaining the daughter nuclei at the target location in the brain vasculature. The relative biological effectiveness (RBE) of ^{225}Ac and ^{212}Pb are similar when the entire decay chains are included, with maxima of 2.7 ± 0.6 and 2.5 ± 0.5 (respectively), and RBE values of about 2 to a depth of 80 μm. If the initial daughter is lost, the RBE of ^{212}Pb is completely reduced to 1 or lower and the RBE of ^{225}Ac is approximately 2 only for the first 40 μm.

1. Introduction

The favorable outcome of the phase 3, ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer Patients) trial has highlighted the use of α-emitting radionuclides for therapy [1]. In this context, ^{223}Ra, a calcium mimetic, was used in the treatment of patients with castration-resistant prostate cancer and bone metastases. Although this treatment exploits the natural accumulation of ^{223}Ra in areas of increased bone turnover in bone metastases, active targeting of cancer cells or tumor vasculature can also be achieved. This form of targeted α-therapy (TAT) relies on the binding of α-emitting radionuclides to molecular targets expressed on the target tissue [2]. The high relative biological effectiveness (RBE) affords α-particles an advantage over β-emitting radionuclides [3]. The short penetration depth in tissue (50–100 μm) and high linear energy transfer (LET) of 50–250 keV/μm allows the localized delivery of radiation ideal for the treatment of hematologic malignancies or micrometastatic residual disease [4]. These attributes provide the rationale for using α-emitting radionuclides in the treatment of brain cancer, either by intra-cavity delivery [5], receptor binding after local intratumoral injection [6], or by destroying tumor vasculature [7].

Brain metastases frequently arise from many types of cancer, including lung, breast, melanoma, renal, and colorectal [8]. It would be highly beneficial to create a therapeutic that targets brain metastases at the earliest stages of parenchymal penetration - that is, while the patient remains asymptomatic and before the micrometastases are detectable by imaging. Past work has shown that the vascular cell adhesion molecule 1 (VCAM-1) is highly expressed on μm endothelial cells during the very early stages of extravasation of circulating cancer cells into the brain [9]. Thus, VCAM-1 provides an ideal target for TAT. Indeed, we have recently evaluated the efficacy of a number of radionuclides including α-, β-, and Auger electron-emitters using a Monte Carlo (MC) model based on experimentally informed mouse brain vasculature and metastases penetration [10]. α-emitting radionuclides deposited approximately a 100 times the mean absorbed dose compared to β-emitting radionuclides over a depth of 50 μm, while their limited range assured that normal cells beyond the site of penetration were spared.

This MC approach has also been taken by others to investigate the efficacy of different nuclides in a concentric cylinder model

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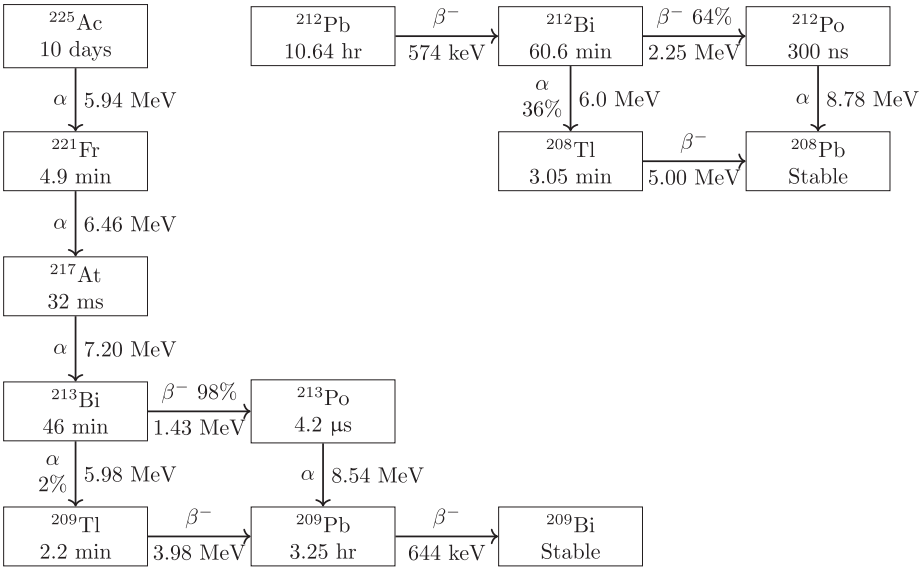

Fig. 1. Decay chains of ^{225}Ac and ^{212}Pb. The energies shown are Q-values for the specified decay channel.

representing vasculature geometry [11,12]. However, these studies did not include the RBE of the different types of radiation. Calculating absorbed dose on the scale of a few micrometers does not capture whether energy is deposited at radiation sensitive sites, such as the DNA. Double strand break (DSB) yield, a significant factor for cell survival, depends on the LET of the incident radiation [13]. By coupling a track-structure simulation of radioactive decay and a geometrical model of DNA, we can predict the relative DNA damage from potential TAT nuclides [14,15]. A critical aspect that has to be considered when evaluating α-emitting radionuclides for TAT, especially when directed towards treating early brain metastasis, is the possibility that daughter nuclides could migrate away from the target site [16]. Of particular concern would be the use of α-emitting radionuclides where the decay chain involves the transition between multiple radioactive daughters.

We have previously postulated that ^{212}Pb has a favorable dose profile in treating early brain metastasis, while ^{225}Ac provided the highest dose per decay in a cylindrical vessel geometry [10]. However, both radionuclides have multiple α-emitting daughters in their decay chain, as shown in Fig. 1. In this manuscript we describe our approach of using a two-stage Monte Carlo simulation to model ^{212}Pb and ^{225}Ac. We calculate the biological efficacy in terms of DSB yield and RBE, and in addition we examine the impact of losing radiation-emitting daughters after the decay of the parent radionuclide.

2. Materials and methods

2.1. Geant4 simulation

We simulated the overall geometry, radioactive decay, secondary production, and energy deposition using the Geant4 toolkit version 10.02.p02 [17–19]. The Geant4 simulation could be run in one configuration for directly scoring dose on a micrometer-scale, or the primary mode for subsequent processing in the DNA damage simulation [20].

The geometry was defined to be flexible and efficient. We have previously reported the biological measurements that motivated our geometry parameters [10]. A central cylinder represented the blood vessel, with a radius that was specified in a configuration (macro) file at run-time. The space outside of this cylinder represented brain tissue. Placement of the radionuclide was specified along a cylindrical shell, corresponding to the inner diameter of the blood vessel. Our previous report showed the minimal impact of varying the length of vessel along which the radionuclides are placed; in this work, we use an active length of 40 μm. The material throughout the entire volume was defined as water, scaled to a density of 1.06 g/cm^3.

The simulation included the entire decay chain of either ^{212}Pb or ^{225}Ac, as shown in Fig. 1. All decay parameters and probabilities were specified by the Geant4 datasets RadioactiveDecay4.3.2 and G4ENSDFSTATE1.2.3. Due to an error in these files (corrected in later versions), we modified the ^{225}Ac data files to have the correct mean life time of 1.236554×10^{15} ns.

Interactions were recorded in a thin cylinder, placed at the midpoint of the radioactive distribution, as shown in Fig. 2. The thin cylinder had a width of 3.5 μm and extended from the vessel to an outer radius of 110 μm. For the Geant4-based radial dose calculations, the entire cylinder was used. However, the simulation of DNA damage requires events to be defined within quasi-cubic regions of interest (ROI). In this mode, interactions were recorded within radial rectangular prisms. These were inscribed within the thin cylinder, having a width and thickness of 3.5 μm. The length was calculated based on the vessel radius so that the outer edge did not extend past a radial distance of 110 μm. Multiple rectangular prisms were defined within the cylinder, placed with equal angular spacing. The number of prisms depended on the vessel radius and was calculated to be the maximal number with no overlap between the prism volumes.

The physics models were chosen to balance computational efficiency with the required spatial accuracy. Low Energy (Livermore) models were used, except in the volumes used for DNA damage scoring and buffer-regions around the scoring volumes, where the Geant4-DNA models were enabled. This approach demands lower computational

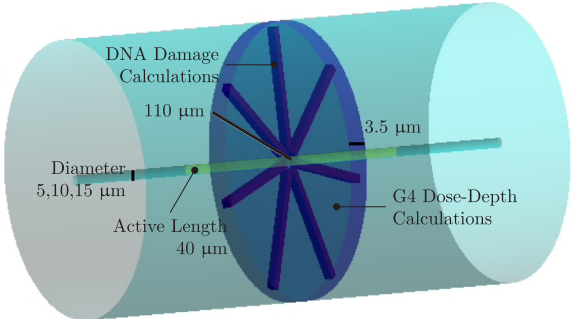

Fig. 2. The Geant4 simulation geometry, showing the vessel geometry and the two possible volumes in which interactions were recorded.