Safety Evaluation of a Long-Lived Tumour-Specific Gadolinium (Gd)-Based Imaging Agent in Proton Therapy

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Abstract. We assessed the dosimetric safety of a potential diapeutic Gadolinium-based contrast agent for diagnostic MR imaging and MR-guided radiotherapy by calculating depth-dependent reactions rates in a spread-out Bragg peak (SOBP) in water. Energy-dependent cross-sections for inelastic proton reactions on Gadolinium were folded with proton energy spectra at depth. Particle transport, dose, and phase space scoring was performed using Geant4-based TOPAS Monte Carlo software. The isotopic Terbium yield at depth was calculated to be between $10^3$ to $10^5$ atoms/mmolnatGd per Gray SOBP dose in a 2.4 cm$^3$ volume. At currently achievable Gadolinium concentrations of 0.2 μmol/cm$^3$ this yields approximately 26 atoms/(cm$^3$ GySOBP), corresponding to less than 1 Bq activity. Additional dose from evaporation neutrons and subsequent capture gammas is on the order of 1 μSv/GySOBP. Thus, use of this long-lived contrast agent is dosimetrically safe at current concentrations and induced radioactivity is negligible.

1. Introduction
Development of long-lived tumour-specific magnetic resonance imaging contrast agents would enable continuous tumour identification and response assessment prior to, during, and after radiation treatment delivery including inter- and intrafraction tracking with MR-guided radiation therapy without the need for repeated injections of contrast agents. Additionally, predicted depletion of the contrast agent due to nuclear interactions in particle therapy could be used as a means for verification of absorbed dose complementing advances in in-vivo imaging during treatment. In this work, we aim to evaluate the possible dosimetric implications of a long-lived Gadolinium-based imaging agent in proton RT [1].

2. Materials and Methods
2.1. Proton Spread-Out Bragg Peak Simulation
Proton spectra were simulated using the Geant4-based TOPAS Monte Carlo software [2], with a parallel 5 x 5 cm$^2$ square beam with uniform distribution incident on a cubic water phantom with 50 cm edge length. The maximum proton kinetic energy was 150 MeV and the spread-out Bragg peak (SOBP) was created using TOPAS time features by changing the proton kinetic energy dynamically throughout the simulation [3]. The statistical kinetic energy uncertainty was set to a constant 0.1 MeV. Beam weights (or “durations” in TOPAS time features) were calculated using an analytical formula by Jette and Chen [4], based on the initial work by Borfeld and Schlegel [5]; its power-law parameters were tweaked for use with the Geant4 particle transport simulation.
Dose was scored along the central beam axis in a cylinder with 1 cm diameter with 1.25 mm bin thickness. Proton energy spectra were scored in 5 mm intervals from the distal end of the SOBP, \( R_0 = 15.4 \) cm, which was calculated as the range of a 150 MeV proton in water minus 4 mm. The total simulation time was chosen as 1 s with 1000 sequential times to allow fine changes in particle energy. In each time step 1000 histories were simulated for a total of \( 10^6 \) histories per run. The average SOBP dose was calculated for the depth range, \( d \in [10 \, \text{cm}, 15.5 \, \text{cm}] \).

2.2. Cross-Section Data

For isotopic inelastic proton cross-sections, \((p,Xn)\), with neutrons in the exit channel we used the TENDL 2017 database [6]. However, a major limitation of this database is that the maximum incident particle energy is limited to 30 MeV for the evaluated cross-sections, which is predominantly encountered in the Bragg peak, and hence at the end of the SOBP where the highest weighted Bragg peak is placed (see figure 1). To include reaction data for a larger portion of the SOBP, which corresponds to higher mean proton energies and broader energy spectra, we used published cross-section data for natural Gadolinium [7], with data available up to energies of 67 MeV. This dataset is limited to reactions producing \(^{151-156,160}\)Tb only; however, the isotopic yield for \(^{149,150,157-159}\)Tb should approximately be of the same order of magnitude as those of neighbouring isotopes.

2.3. SOBP Depth-Dependent Reaction Yields

The number of reactions in the volume \( S \Delta z \), centred at \( z \), is given by the product of the number of target atoms multiplied by the reaction’s cross-section and the incident particle fluence, \( R = N \sigma \phi \). However, both the cross-section and proton fluence (i.e. the proton spectrum) vary with energy. The proton fluence at depth was rebinned to match the cross-section binning, after which both were folded, yielding the number of reactions per Gray SOBP dose,

\[
\frac{R}{D_{SOBP}}(z) = \left( \rho \frac{N_A}{M_A} \right) S \Delta z \int dE \left[ \frac{\partial \phi}{\partial E} \right]_z \int dE \sigma(E) D_{SOBP}
\]

Where \( \rho N_A/M_A \) is the target atom density, i.e. the number of gadolinium atoms per millilitre; \( S \Delta z \) is the reaction volume centred at \( z \); the integral is the energy average of the fluence cross-section product per unit SOBP dose.

Based on the Terbium yields the induced instantaneous activity in the contrast agent was calculated by multiplying each produced radioactive Terbium isotope yield with its decay constant.

2.4. Neutron Production and Dose

The number of neutrons produced in an inelastic reaction, \( N = (A_{Gd,i} - A_{Tb,j} + 1) = (i - j + 1) \), depends on the initial and final atomic numbers. To estimate the number of neutrons produced we used the isotopic cross-section data from the TENDL database [6], following the same methodology outlined above. Each isotopic Terbium yield was multiplied with the appropriate number of neutrons in the exit channel. The average evaporation neutron kinetic energy was assumed to be approximately 2 MeV. As a conservative estimate it is assumed that the entire kinetic energy is deposited locally with a relative biological effectiveness (RBE) of 20. Once these neutrons have deposited most of their energy as they are captured by the tissue or agent nuclei; in either case the new nucleus will deexcite by emitting a cascade of gamma rays with a cumulative energy of about 10 MeV. Thus, for each produced neutron we assumed a maximum additional energy release of \( E_n = RBE_n \cdot T_n + E_\gamma = 50 \, MeV \) on average.
3. Results

The simulated proton energy distribution is most contracted close to the end of the SOBP with a mean and standard deviation of 17.3 MeV and 6.2 MeV, respectively. At 50 mm proximal to the end of the SOBP these values increase to 66.4 MeV and 18.7 MeV as demonstrated in figure 1. To limit the influence of missing cross-section data above 67 MeV on our calculations we calculated the reaction yields only in the first 30 mm proximal from the distal end of the SOBP. In figure 2 for $d = 0$ and $d = 30$ mm we show as an example the depth- and energy-dependent yield for $^{151}$Tb, while we have tabulated the cumulative terbium and neutron yields in table 1. These yields are per unit Gray SOBP dose and assuming 1 mmol/cm$^3$ natGd concentration. Using these yields we calculated the induced radioterbium activity to be approximately 930 Bq. Additionally, the additional dose in the calculation volume from evaporation neutrons and capture gammas is approximately $1 \text{ mSv}/(\text{Gy SOBP mmol}_{\text{natGd}})$.

![Figure 1](image1.png)

**Figure 1.** Proton energy spectra at 0 mm (blue/hatched) and 50 mm (red/dotted) from the distal end of the spread-out Bragg peak with mean energies of 17.3 MeV and 66.4 MeV, respectively. The $(p,Xn)$ threshold energy is at approximately 12 MeV. For natural Gadolinium we used available cross-section data up to 67 MeV.

![Figure 2](image2.png)

**Figure 2.** Differential terbium yields for $^{151}$Tb per Gray SOBP dose and millimole $^{154}$Gd per millilitre of tissue at $d = 0$ mm (blue/hatched) and $d = 30$ mm (red/dotted). The yield at the distal SOBP end ($d = 0$) is several orders of magnitude lower than the yield at $d = 30$ mm more proximal. This is due to the lower average proton energy and fluence towards the end of the SOBP.
4. Discussion and Conclusion

In this work, we have evaluated some of the dosimetric implications of a long-lived Gadolinium-based imaging agent in proton RT [1]. The use of contrast agents containing high atomic number elements allow for a dose enhancement effect in both, photon and particle RT through enhanced Auger electron production. A dose enhancement effect due to the presence and retention of a long-lived diagnostic contrast agent converts such an agent into a diapeutic. However, in particle therapy the additional dose from secondary particles, most notably neutrons, prompt gamma rays, and radioactive decay due to induced radioactivity needs also to be considered in order to safely use such an agent in standard clinical practice.

At 1 Gy SOBP dose and millimolar concentrations of the Gd-based contrast agent radioterbium yields are below 1 kBq and additional dose from evaporation neutrons and capture gammas is approximately 1 mSv. For the investigated agent the concentrations currently achievable in small animals are three orders of magnitude lower. Thus, any dose to the patient or the general public from both, induced radioterbium activity and secondary particles would be negligible, demonstrating the safety of this long-lived contrast agent for use in proton radiotherapy. Further studies will investigate short-range dose enhancement effects due to enhanced Auger electron production [8].

5. References

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