



Article

AlphaGlue: A Novel Conceptual Delivery Method for α Therapy

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Abstract

Extensive research is being carried out on the application of α particles for cancer treatment. A key challenge in α therapy is how to deliver the α emitters to the tumour. In AlphaGlue, a novel treatment delivery concept, the α emitters are suspended in a thin layer of glue that is put on top of the tumour. In principle, this should be an easy and safe way to apply α therapy. In this study, the effectiveness of AlphaGlue is evaluated using GEANT4 and GEANT4-DNA simulations to calculate the DNA damage as a function of depth. Two radionuclides are considered in this work, ^{211}At and ^{224}Ra . The results indicate that, as a concept, the method offers a promising hypothesis for treating superficial tumours, such as skin cancer, when ^{224}Ra is applied directly on the tissue and stabilized with a glue layer. This results in 2×10^{-5} complex double strand breaks and 5×10^{-5} double strand breaks at 5 mm depth per applied ^{224}Ra atom. When applying a ^{224}Ra atom concentration of $(4.35 \pm 0.2) \times 10^{11}/\text{cm}^2$ corresponding to an activity of $(21.8 \pm 1)\mu\text{Ci}/\text{cm}^2$ on the skin surface, the RBE weighted dose exceeds 20 Gy at 5 mm depth. Hence, there is significant cell death at 5 mm into the tissue; a depth matching clinical requirements for skin cancer treatment. Given the rapidly falling weighted dose versus depth curve, the treatment depth can be tuned with good precision. The results of this study show that AlphaGlue is a promising treatment and open the pathway towards the next stage of the research, which includes in-vitro studies.



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Keywords: targeted alpha therapies; Geant4-DNA; DNA damage; ^{211}At therapy; ^{224}Ra therapy

1. Introduction

Radiotherapy is a standard treatment for many types of cancer. Alpha particle radiation therapy is a radiotherapy technique that involves applying α -emitting isotopes to treat tumours or metastatic cancer. Due to the high linear energy transfer (LET) of α particles, they deposit their energy over a very short distance ($\lesssim 100\mu\text{m}$), resulting in a highly localized dose. This localization is a critical factor for improving cancer treatment by minimizing damage to surrounding healthy tissue [1].

Several therapeutic approaches rely on α particles, including Targeted Alpha Therapy (TAT) [1,2], which uses isotopes such as ^{255}Ac [3–9] and ^{211}At [10–14], to precisely deliver α

radiation doses to tumours. Clinical studies have demonstrated the effectiveness of TAT in treating various malignancies, including leukemia, brain tumours, ovarian, and prostate cancers, underscoring the significant clinical potential of targeted α -emitter therapies.

In addition to TAT, ^{224}Ra has been utilized in Diffusing α -emitters Radiation Therapy (DaRT) [9,15–18], a novel therapeutic approach in which a small seeds containing ^{224}Ra are implanted into the tumour. As ^{224}Ra decays, it releases ^{220}Rn gas, which diffuses into the surrounding tissue and extends the range of alpha particle delivery, thereby achieving a greater treatment depth. Initial clinical results have demonstrated high efficacy in treating skin cancers, with complete response rates ranging from 89% to 100% [8,16,18,19]. While targeted α therapies have demonstrated clinical success, and DaRT has expanded the potential of α -emitter for treatments of solid tumours, it is still relatively cumbersome to apply as multiple seeds loaded with ^{224}Ra need to be inserted with less than 5 mm spacing [19]. The combination of the clinical success and the cumbersome application process, supports the relevance of exploring alternative delivery concepts such as AlphaGlue. Here we evaluate a novel concept of α therapy with α emitters suspended in glue. This is then applied to the skin to treat the tumour. In addition, AlphaGlue may offer a less invasive and potentially easier-to-use alternative, which could be particularly advantageous for sensitive areas such as facial skin cancers, but also anal, vaginal cancer or endometriosis. Similar approaches exploiting β -particles exist. Here radioactive patches are applied or loaded creams are used, for example ^{90}Y [20,21], ^{188}Re [22–25], ^{32}P [26] and ^{106}Ru [27]. The ranges of α 's and β 's and their DNA damage spectra are very different. A comparison study is out of the scope of this paper.

1.1. AlphaGlue

AlphaGlue is a novel delivery method for α therapy that involves applying a layer of glue loaded with α emitters to the surface of the skin. An unloaded second layer of glue may be applied to shield any potential other skin from the radiation, as discussed later in Section 2.1. Figure 1 shows a sketch of the concept.

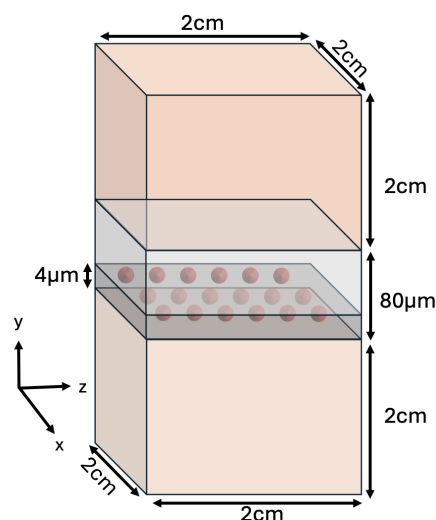


Figure 1. The glue layer loaded with ^{211}At or ^{224}Ra covers healthy tissue above and the tumour below.

In this study, the loaded glue contains either ^{211}At or ^{224}Ra . ^{211}At has two decay paths, and in either of them a single α is produced, as shown in Figure 2. In contrast, ^{224}Ra undergoes four α decays in its decay chain, as shown in Figure 3, resulting in multiple emissions that deliver a highly localized dose. To evaluate and compare the therapeutic

potential of ^{211}At and ^{224}Ra within the AlphaGlue framework, this study investigates the induced DNA damage through detailed Monte Carlo simulations. Melanoma invasion depth is typically between 1 and 4 mm, with thicker tumors exceeding 4 mm [28,29]. Therefore, we evaluate the effectiveness at these depths.

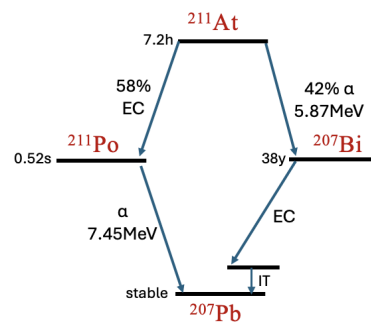


Figure 2. The decay chain of ^{211}At .

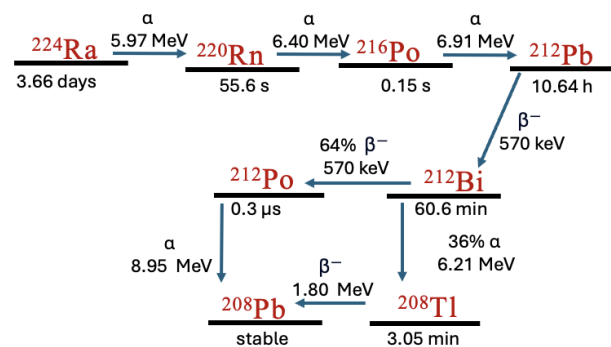


Figure 3. The decay chain of ^{224}Ra .

1.2. DNA Damage

In this study, the focus is on investigating DNA damage caused by the isotopes ^{224}Ra and ^{211}At when applied to the AlphaGlue, and comparing their effects. DNA damage, which can lead to cell death if not repaired by the cell, occurs through two primary mechanisms: direct and indirect. Direct damage takes place when particles interact with the DNA molecule and deposit their energy directly into it. Indirect damage occurs when particles interact with water molecules surrounding the DNA, producing free radicals that subsequently damage the DNA [30].

2. Materials and Methods

The DNA damage induced by ^{211}At and ^{224}Ra was simulated using Geant4 and Geant4-DNA, modeling both particle transport and nanoscale interactions within a cellular environment. The simulation process consists of two steps. First, the geometry of AlphaGlue, including radioactive decay and the generation of secondary particles, is modeled to calculate the particle spectrum at various distances from the source. This process is illustrated in Figure 4. Second, the DNA damage within a simplified cell nucleus is assessed based on this particle spectrum. Both stages of the simulation are performed using Geant4 (version 11.1) [31–33] and Geant4-DNA [34–38].

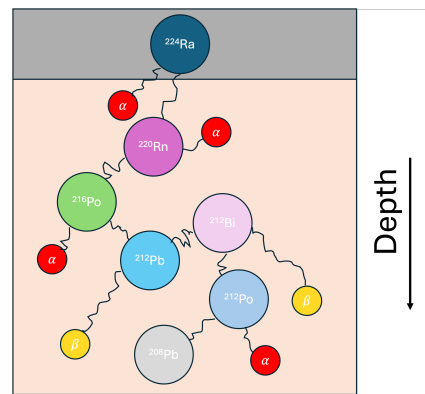


Figure 4. Schematic overview of the AlphaGlue decay calculation: ^{224}Ra isotopes decay producing an α and a ^{220}Rn . The ^{220}Rn will then decay to ^{216}Po producing another α . The ^{216}Po decays with the emission of another α to ^{212}Pb . ^{212}Pb undergoes β decay producing ^{212}Bi which also undergoes β decay to ^{212}Po . The ^{212}Po decay produces a final α . The random walk paths of the α 's, β 's and isotopes and the energy deposition along the paths is calculated using Geant4 to give the energy deposition as a function of depth.

2.1. Decay Simulation

The AlphaGlue model shown in Figure 1, was simulated using Geant4, see Figure 5. The glue model was represented as a cuboid structure with a thickness of 80 μm and dimensions of 20 mm in length and width. It was surrounded by two water boxes, the first positioned above and the second below, also measuring $20 \times 20 \times 20 \text{ mm}^3$. These water boxes contained 300 nm-thick thin shell layers divided into a series of voxels, which acted as detectors to record all decay products and secondary particles from the initial decay at specified distances for use in the DNA simulation component (see Section 2.2). A 4 μm layer of the glue was loaded, followed by a 76 μm layer of unloaded glue on top to limit radiation exposure in cases where healthy tissue may be adjacent to the treated area. The DNA damage in the tumour was calculated in the bottom water box. The top water box is used to calculate the damage coming from radiation leaking through the unloaded glue.

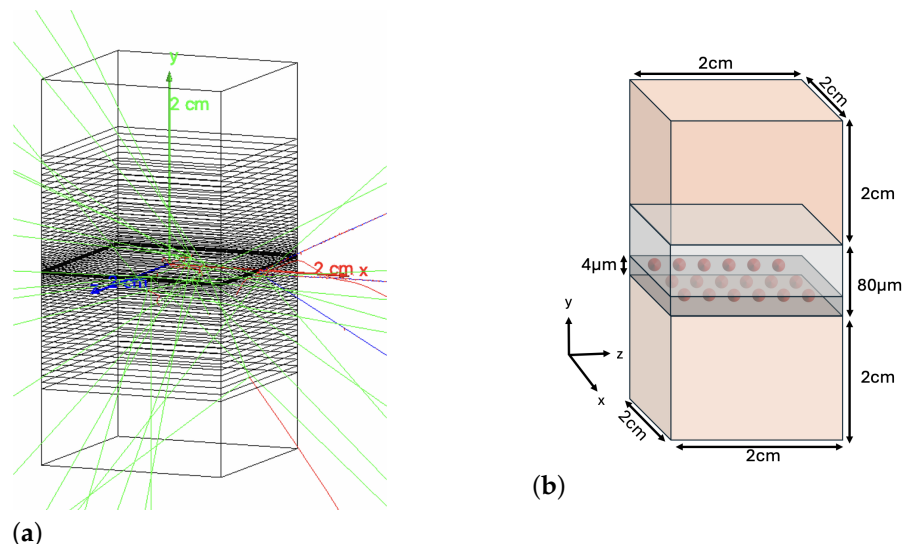


Figure 5. Visualization of the simulation geometry in Geant4 (a) for the AlphaGlue configuration (b). The two $2 \times 2 \times 2 \text{ cm}^3$ water volumes contain 300 nm-thick detector shells.

As Geant4-DNA supports DNA damage calculations only in water, this medium was chosen [36,38–40]. Water is also widely used as the reference medium in skin dosimetry,

for example VARSKIN [41,42] treats skin as a homogeneous block and uses absorbed energy distributions calculated in water. The same approach is applied and in ion-beam treatment planning, where soft tissues differ from water by less than 1% in stopping power ratio [41,43]. In addition, the diffusion constants for the isotopes are measured in water.

The *G4EmPenelopePhysics* physics constructor was employed to describe electromagnetic interactions, with a low-energy production cutoff of 100 eV, corresponding to the model's low-energy limit [44]. To simulate the radioactive decays in the decay chain, the *G4RadioactiveDecayPhysics* constructor was activated. The daughter nuclei from the decay of ^{224}Ra which enter the tumour tissue diffuse. This diffusion is modeled as in [45]. The decay products are moved using a random walk using the diffusion constants $D_{220\text{Rn}} = 1.12 \times 10^{-3} \text{ mm}^2\text{s}^{-1}$, $D_{212\text{Pb}} = 1.22 \times 10^{-5} \text{ mm}^2\text{s}^{-1}$ and $D_{212\text{Bi}} = 6.78 \times 10^{-7} \text{ mm}^2\text{s}^{-1}$ from [46]. The ^{216}Po and ^{212}Po ions have relatively short half lives and therefore are assumed to decay at the same location as the parent nuclei. ^{212}Pb nuclei leak out of the tumour via vascular routes through interaction with surrounding molecules such as proteins. ^{212}Pb nuclei are removed at random, resulting in a leakage of 50%. The information for each particle entering the layer, including particle type, kinetic energy, initial position, and momentum, is calculated and saved in a phase space file. This file is used as input for the DNA damage simulation. Each particle is recorded in the phase space file upon entering the x or z face. This process is repeated for each particle track until the particle either exits the layer or loses all its kinetic energy. Secondary particles that exit one voxel and enter a neighboring voxel are saved to account for lateral scattering. Particles reentering the same voxel are not saved to avoid double counting in the DNA simulation. This is because scattered particles are explicitly tracked and accounted for within the DNA simulation.

2.2. DNA Damage Simulation

The DNA molecule is simulated within a 300 nm voxel, as shown in Figure 6. The DNA molecule structure was created using the “fractaldna” Python package (v0.6.0) [47], which generates short building blocks that can be repeated to create a continuous DNA structure.

Each straight chromatin fiber segment is 75 nm long, has a radius of 11 nm, and includes 33 nucleosomes. The positions of the deoxyribose-phosphate backbone (0.29 nm in diameter), histones (2.5 nm in diameter), and nucleotide base pairs are extracted from this model and represented as spheres, with nucleotide base pairs placed randomly with equal probability for each pair, achieving a density of 0.011 base pairs per cubic nm (bp/nm³), which is representative of a human cell nucleus [48].

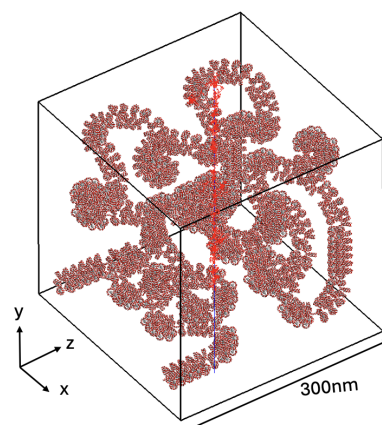


Figure 6. Simplified cell nucleus. An α -particle (blue) enters from the bottom and secondary electrons (red) are tracked.

The simulation tracks particles within the cell nucleus at the nanoscale using the Geant4-DNA low-energy extension cut of 100 eV. The *G4EmDNAPhysics_option7* physics constructor was used, as in [11,45], as *G4EmDNAPhysics_option7* combines low energy electron models with default Geant4-DNA electron models [37]. DNA damage yield is computed by simulating both direct and indirect DNA damage using a previously developed tool [49].

Direct and indirect damage can affect various components of DNA, including strand breaks in the double-helix backbone and damage to the bases. Strand breaks can result from both direct and indirect damage and are classified into three types: single-strand breaks (SSBs), double-strand breaks (DSBs), and complex double-strand breaks (cDSBs). We follow the classification of strand break clusters from [50]. As shown in Figure 7, SSBs occur when one strand of the DNA backbone is broken. These are typically non-lethal, as they are relatively easy for the cell to repair [51]. DSBs occur when both strands of the DNA backbone experience at least one break within 10 base pairs. Some DSBs are more complex, known as cDSBs, which involve additional strand breaks on either strand within 10 base pairs of the initial DSB. These cDSBs are the most challenging type of damage for the cell to repair [52].

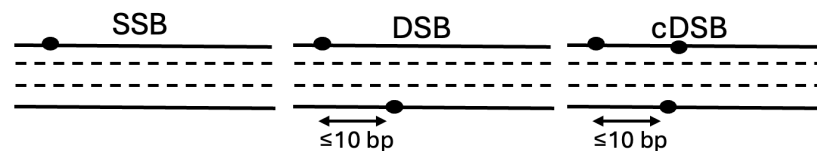


Figure 7. We follow the classification of strand break clusters from [50]. A SSB (Single-Strand Break) involves a break in only one strand of the DNA backbone. A DSB (Double-Strand Break) occurs when both strands experience breaks within ≤ 10 base pairs. A cDSB (Complex Double-Strand Break) represents a more complex form of DSB, involving additional strand breaks within ≤ 10 base pairs, making it more challenging to repair [53].

For indirect damage caused by particle interactions with water molecules and the resulting radicals, the radicals are tracked for up to 5 ns. Radicals located more than 9 nm away from the deoxyribose-phosphate molecules are removed from the simulation [54–56].

To calculate the direct DNA damage, the energy deposited within a radius of 0.35 nm from the deoxyribose-phosphate molecule is summed, and the linear damage model is applied [57]. In this model, energy deposits below 5 eV are assumed to cause no damage, while for deposits above 37.5 eV the damage probability is 100%. For energy depositions between these values a linear probability of damage occurring is applied. Indirect damage strand breaks are assumed to only occur due to reactions between the hydroxyl radical and deoxyribose-phosphate backbone. A 40.5% probability of such a reaction resulting in a strand break is applied [45,54,55,58].

3. Results

First the DNA damage when loading the 4 μm thick interface layer with ^{211}At was calculated. To load the glue, random locations were assigned for each of the ^{211}At atoms based on a uniform distribution such that the ^{211}At atoms were evenly spread throughout the $2\text{ cm} \times 2\text{ cm} \times 4\text{ }\mu\text{m}$ volume. Figure 8 shows the number of SSBs, DSBs, and cDSBs as a function of depth for the ^{211}At loaded layer. The shaded region represents the loaded glue, while the lighter region corresponds to the unloaded glue layer, which is applied to limit radiation exposure to any potential adjacent healthy tissue. DNA damage contributions from ^{207}Bi were neglected due to its long half-life of approximately 38 years.

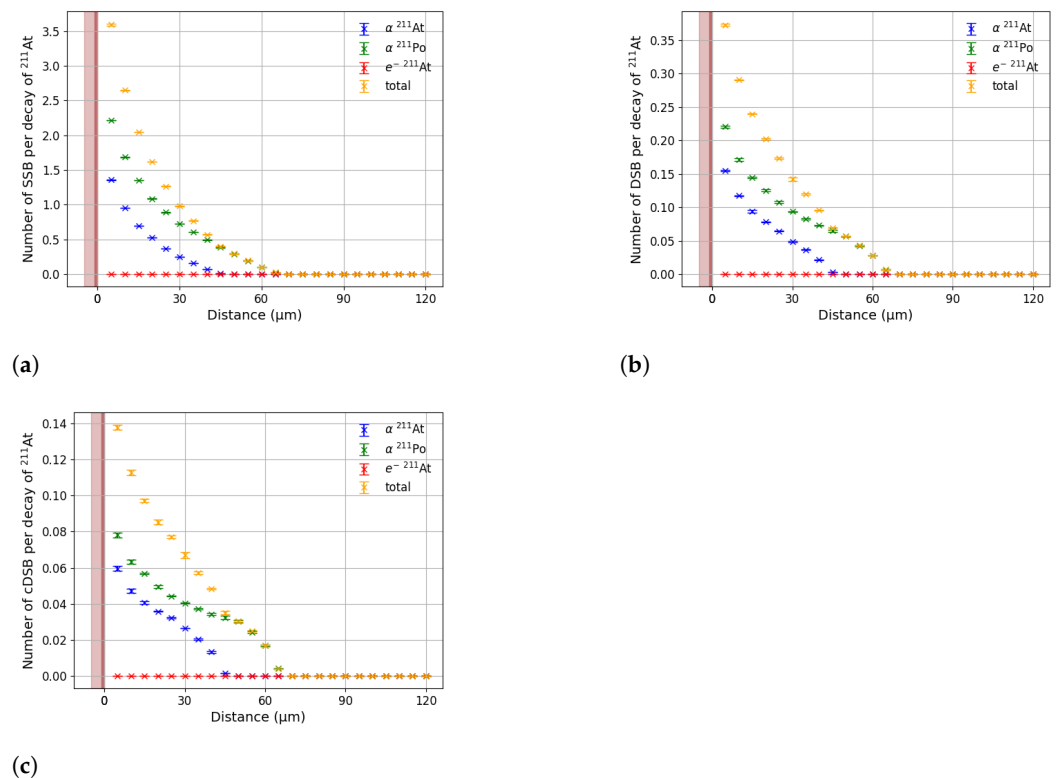


Figure 8. DNA damage caused by each particle in the ^{211}At chain: α particles from ^{211}At , α particles from ^{211}Po , and electrons from ^{211}At , along with the total of all these, as a function of distance: single strand breaks (SSBs) (a), double strand breaks (DSBs) (b) and complex double strand breaks (cDSBs) (c). Results are normalized per decay.

The results show that DNA damage is caused by α particles including all secondary delta electrons; the contribution of other electrons to breaks is negligible. ^{211}At has two possible decay paths, as illustrated in Figure 2. The probability of decaying via ^{211}Po is 58%, while the probability of decaying via ^{211}At is 42%. This is the main reason why there is more damage coming from the α from ^{211}Po compared to the α coming from ^{211}At . In addition, the α produced in the ^{211}Po decay has a higher energy of 7.45 MeV while the α originating in the ^{211}At decay has an energy of 5.87 MeV, leading to a larger range for the α coming from the ^{211}Po decay. The α from the ^{211}At has a range of only just over 40 μm in water, while the α from the ^{211}Po has a range of just over 65 μm . The slight bump in breaks towards the end of the range of each α is due to the Bragg peak.

On the opposite side of the glue, corresponding to the healthy tissue, no DNA damage is observed. This result confirms the treatment's ability to confine the radiation effects to a short, localized range while minimizing exposure to healthy tissue. This is important when the treatment is used inside a body cavity.

The results show that this treatment with ^{211}At works, but the range of the damage in the tissue is too limited. An alternative would be loading the glue with another isotope like for example ^{224}Ra . As mentioned before ^{224}Ra has a decay cascade, as illustrated in Figure 3, which includes ^{220}Rn . If the ^{220}Rn enters the tissue, it will diffuse leading to a much deeper treatment range [49]. The results when loading the glue with ^{224}Ra are presented in Figure 9. It shows the contribution to DNA damage from each isotope in the ^{224}Ra decay chain as a function of distance, for single-strand breaks (SSBs), double-strand breaks (DSBs), and complex double-strand breaks (cDSBs). Most of the α 's emitted have an energy of around 6–7 MeV and thus a similar range for their damage. The α emitted in the ^{211}Po decay has an energy of 8.95 MeV. The range for DNA damage of this α stretches to 90 μm . ^{212}Pb and ^{208}Tl only emit a β . Due to the sparse ionization along a β track compared

to an α track, β s only contribute to the generation of SSBs. When looking at the unloaded side of the glue, only very little damage is observed, demonstrating that shielding with a thin layer of glue is sufficient to protect other tissue. Application of a thicker layer of glue is possible to increase the shielding.

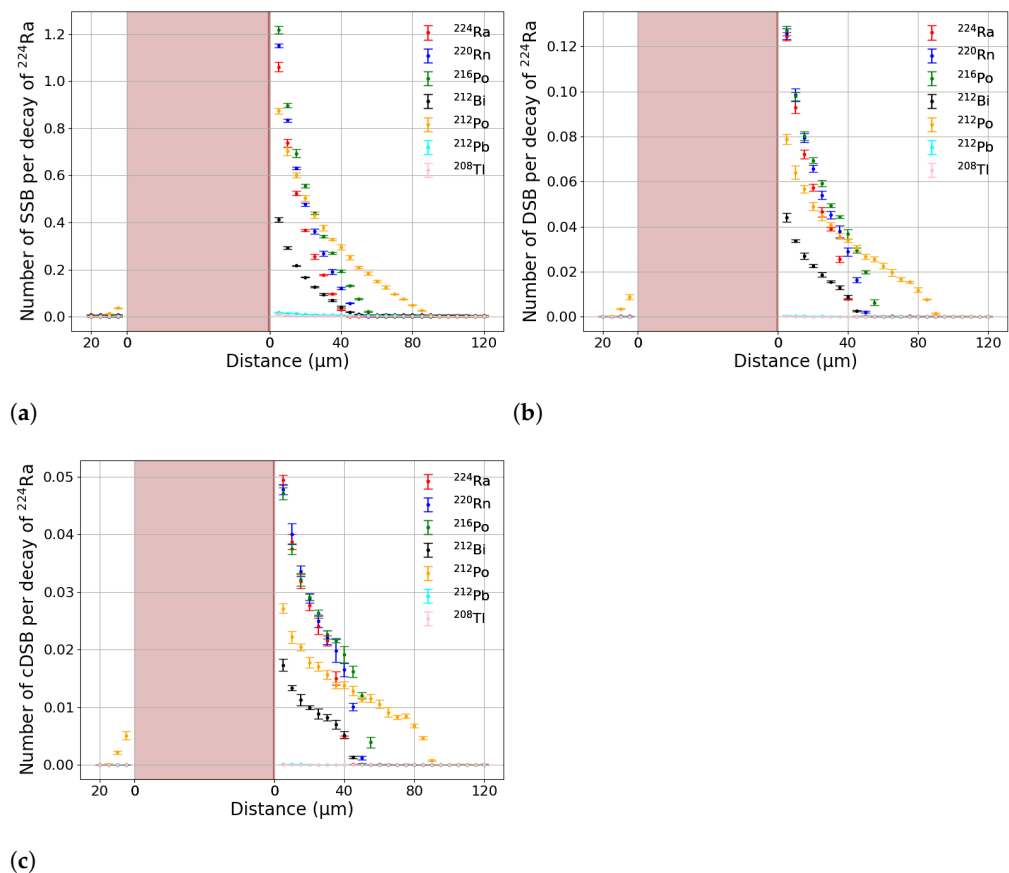


Figure 9. DNA damage caused by each particle in the ^{224}Ra chain as a function of distance: single strand breaks (SSBs) (a), double strand breaks (DSBs) (b) and complex double strand breaks (cDSBs) (c). Results are normalized per decay.

The results show that ^{224}Ra induces a higher number of DNA breaks compared to ^{211}At , as shown in Figure 10 as well, particularly at greater distances from the source. However, the maximum treatment depth using ^{224}Ra in this configuration is still too shallow, $\lesssim 90 \mu\text{m}$, for clinical applications where a greater treatment depth is required. This is because only very few ^{220}Rn isotopes can escape from the glue into the tissue. In DaRT, which uses a stainless steel seed, only isotopes that are located in the first $\sim 30 \text{ nm}$ can escape into the tissue [59]. Given that a $4 \mu\text{m}$ thick glue layer with the ^{224}Ra uniformly spread throughout is used, a negligible number of ^{220}Rn isotopes makes it into the tissue, limiting the treatment depth.

To enhance the effectiveness of the AlphaGlue treatment, in principle the ^{224}Ra can be applied directly on the skin after which glue is applied on top to keep it in place and shield potential healthy tissue. Despite potential practical issues with this as a treatment, it is nevertheless worthwhile exploring the difference in performance, as it provides a natural limiting case for treatment and there are ways to achieve this or something similar in the clinic.

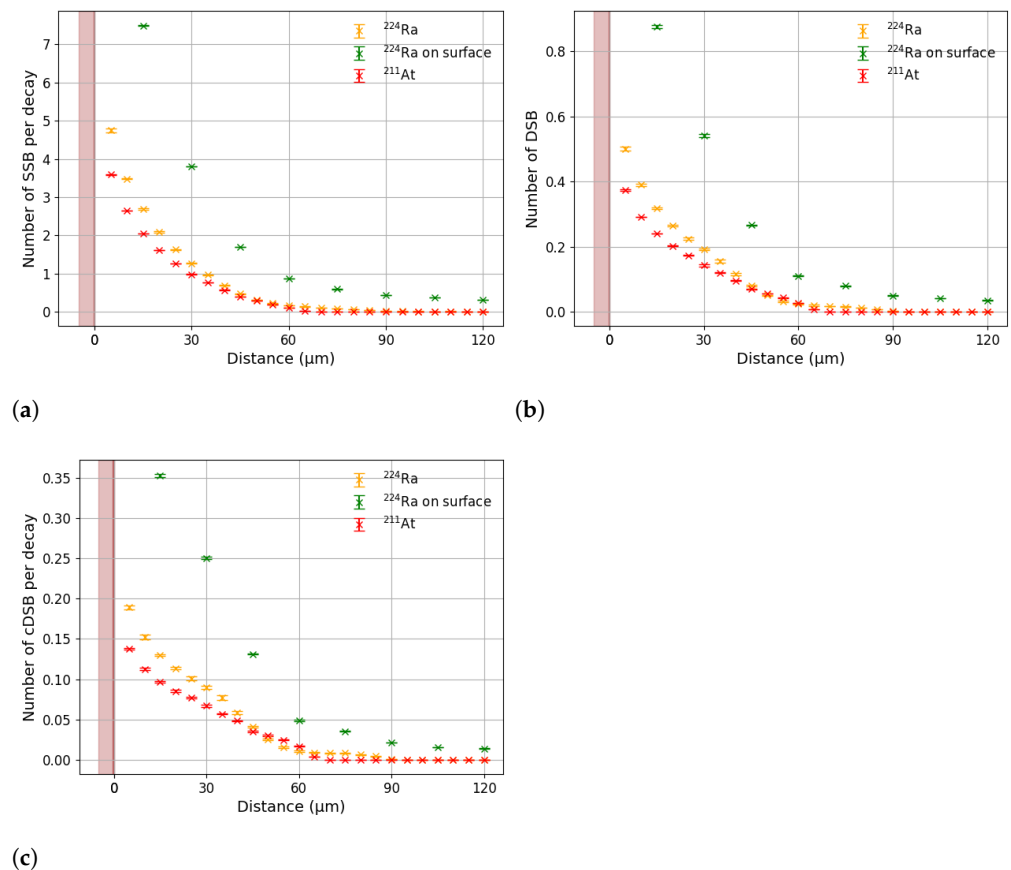


Figure 10. Comparison of the DNA damage caused by each particle in the ^{224}Ra -loaded and ^{211}At -loaded 4 μm thick glue layer and when ^{224}Ra is administered directly onto the skin, as a function of distance: single strand breaks (SSBs) (a), double strand breaks (DSBs) (b) and complex double strand breaks (cDSBs) (c). Results are normalized per decay.

Figure 10 shows the DNA damage distributions for three cases: ^{224}Ra -loaded glue, ^{211}At -loaded glue and ^{224}Ra directly applied on the surface. For the ^{224}Ra -loaded glue and the ^{211}At -loaded glue, the isotopes were uniformly loaded within the glue and evenly spread over the $2 \times 2 \text{ cm}^2$ area. For the ^{224}Ra directly applied on the surface, the isotopes were uniformly spread over the $2 \times 2 \text{ cm}^2$ area. Surface application of ^{224}Ra significantly increases DNA damage at greater distances compared to both embedded ^{224}Ra and ^{211}At by a factor 3–4 at small distances. The increase in damage when applying the ^{224}Ra on the surface is not just by having more α particles entering the tissue. This can be seen in Figure 11, which shows the ratio of DNA damage occurring for the loaded glue and the DNA damage occurring for the case of applying ^{224}Ra directly on the surface. For all three types of damage, this ratio is not a constant with depth as it would be if it is just an effect of the number of α 's, but it decreases rapidly, demonstrating that applying ^{224}Ra directly on the surface yields more damage at depth. The increase in damage at depth for ^{224}Ra on the surface originates from more ^{220}Rn entering the tissue and diffusing before decaying. This enhances the depth profile of the treatment significantly. Figure 12 shows the number of DSBs and cDSBs as a function of depth for surface-applied ^{224}Ra over a much larger depth range. The results show that the DNA damage can extend beyond 2–4 mm beneath the skin [60] making it feasible as a skin cancer treatment.

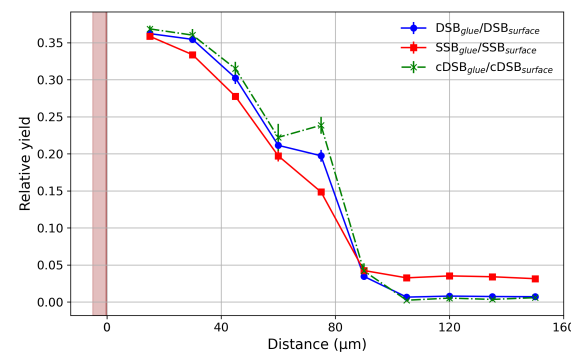


Figure 11. Ratio of DNA damage yield (DSB, SSB, and cDSB) from ^{224}Ra embedded in glue relative to ^{224}Ra applied on the surface, as a function of depth.

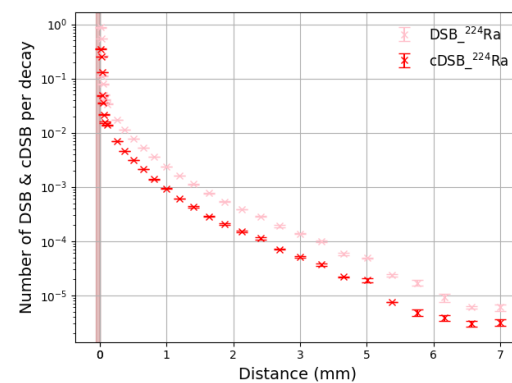


Figure 12. Double-strand breaks (DSBs), and complex double-strand breaks (cDSBs) as a function of depth per decay.

3.1. Effective Treatment Depth

^{224}Ra applied on the glue surface produced the most extended DNA damage profile. The actual amount of DNA damage at a certain depth depends on the number of ^{224}Ra isotopes used; enough ^{224}Ra isotopes need to be provided to get enough DNA damage at depth to eradicate the tumour. When using photon therapy, tumours can usually be eradicated by a single fraction of photons amounting to a typical dose of 20–25 Gy [61]. The damage per dose for α particles is much higher than for photons. This is expressed in the relative biological effectiveness (RBE). RBE is defined as

$$\text{RBE} = \frac{D_{\text{end point/photon}}}{D_{\text{end point/quantity}}} \quad (1)$$

where the endpoint is a biological quantity of interest. In this study two end points DSBs and cDSBs have been used. ^{60}Co was used as the photon reference [45]. The RBE-weighted dose, D_{RBE} is the product of the RBE and the absorbed dose [62]. The D_{RBE} allows dose thresholds to be compared between treatment types.

$$D_{\text{RBE}} = \text{RBE} \times D \quad (2)$$

Figure 13 shows the RBE as a function of distance from the surface, calculated using both DSB and cDSB yields relative to a ^{60}Co reference. The ^{60}Co simulation was performed by irradiating a spherical water volume with photons of 1.17 and 1.33 MeV energies at 5 mm from the centre of the DNA target ensuring charged particle equilibrium [63]. This simplified spherical isotropic setup was chosen to provide a reproducible photon reference, consistent with previous Geant4-DNA studies [11,45]. In contrast, α -particles deposit their

dose over sub-mm ranges without reaching equilibrium, which necessitates a different geometry for the AlphaGlue calculations. RBE_{DSB} and RBE_{cDSB} were then obtained by comparing the DSB and complex DSB yields from ^{224}Ra on the surface to those from ^{60}Co . Near the source, RBE_{cDSB} reaches up to 7, drops to 5 at 1 mm and then falls slowly at larger distances but remains between 4 and 5. At small distances, the RBE_{DSB} is just over 2 and drops to 2 around 1 mm. After 1 mm, the value changes but remains between 1 and 2.

Figure 14 shows the D_{RBE} for AlphaGlue loaded with 3 μCi of ^{224}Ra , which corresponds to 5.06×10^{10} ^{224}Ra isotopes, at the surface. It is clear that the weighted dose decreases sharply with depth and reaches the 20 Gy threshold at approximately 1 mm for the end point using DSBs and at approximately 1.6 mm for cDSBs. This depth can be tuned by selecting a different number of ^{224}Ra isotopes. This is shown in Figure 15, where the 20 Gy depth is shown for different numbers of ^{224}Ra isotopes. The results show that tumour eradication can happen at clinically relevant depths of up to 5 mm by using $(1.74 \pm 0.08) \times 10^{12}$ ^{224}Ra atoms evenly spread over the $2 \times 2 \text{ cm}^2$ area on the skin surface corresponding to an activity of $(87 \pm 5) \mu\text{Ci}$ when using the cDSBs for the RBE calculation and $(2.6 \pm 0.2) \times 10^{12}$ ^{224}Ra atoms evenly spread over the $2 \times 2 \text{ cm}^2$ area on the skin surface corresponding to an activity of $(135 \pm 13) \mu\text{Ci}$ when using the DSBs for the RBE calculation. This is equivalent to a ^{224}Ra atom concentration of $(4.35 \pm 0.2) \times 10^{11} / \text{cm}^2$ or an activity of $(21.8 \pm 1) \mu\text{Ci} / \text{cm}^2$ when using the cDSBs for the RBE calculation and $(6.50 \pm 0.5) \times 10^{11} / \text{cm}^2$ or an activity of $(34 \pm 3) \mu\text{Ci} / \text{cm}^2$ when using the DSBs for the RBE calculation.

Given the rapidly falling weighted dose versus depth curve, the treatment depth can be tuned with good precision by decreasing the number of ^{224}Ra isotopes. The number of required ^{224}Ra isotopes to achieve cell death at clinically relevant depths is not excessive; a vial of Xofigo [64], which is an approved α therapy exploiting ^{223}Ra , that is used to treat adults with cancer of the prostate when the cancer has spread to the bones [65,66], contains 9.4×10^{12} ^{223}Ra atoms.

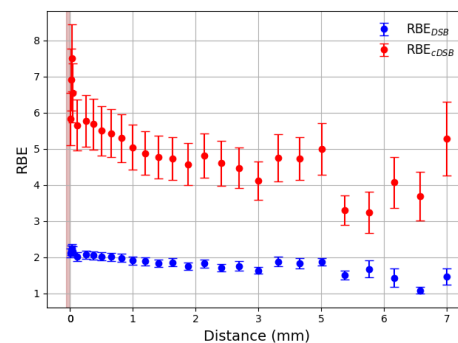


Figure 13. RBE as a function of distance, based on DSB and cDSB yields relative to ^{60}Co .

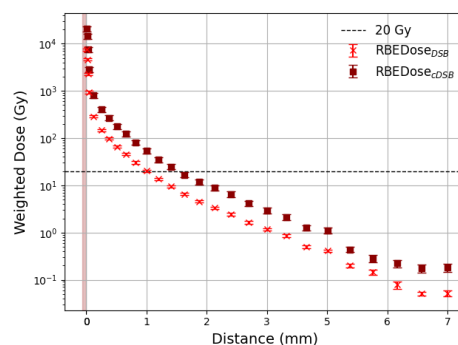


Figure 14. RBE-weighted dose as a function of distance for AlphaGlue loaded with 3 μCi of ^{224}Ra .

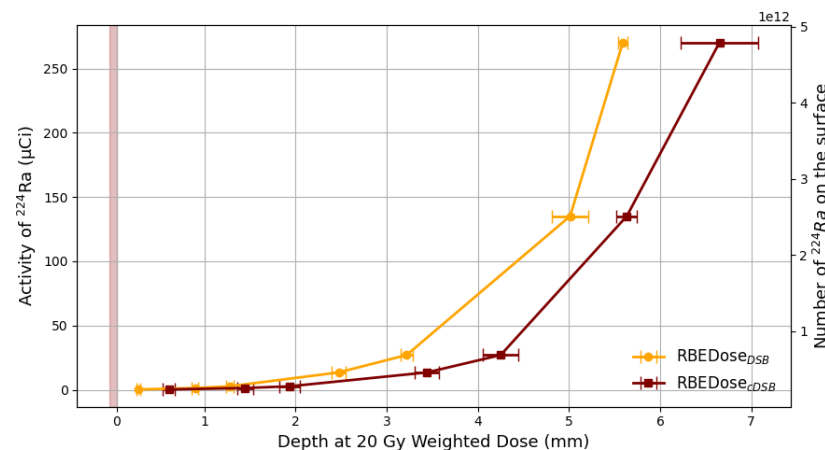


Figure 15. Required activity of ^{224}Ra (in μCi) as a function of depth to reach a 20 Gy weighted dose.

3.2. Comparison with DaRT

Both DaRT and AlphaGlue use ^{224}Ra but the delivered radiation pattern is different due to the different source geometry. Figure 16 shows a comparison of the RBE weighted dose as a function of depth. The RBE weighted dose for DaRT was calculated in [45]. For AlphaGlue the ^{224}Ra activity is spread over a larger area while in DaRT the ^{224}Ra activity is spread over the small surface of the seed. The initial drop in weighted dose is due to the α 's produced in the ^{224}Ra decay and subsequent decays due to ^{220}Rn isotopes and their daughter isotopes that do not enter the tissue and thus not diffuse. This is limited to a depth $\lesssim 100\ \mu\text{m}$. Subsequently, the weighted dose drops faster for DaRT than for AlphaGlue. This is because the initial emission for the cylindrical seed leads to a particle density decrease following $\sim \frac{1}{R}$ in addition to the decrease due to particle decay. The RBE weighted dose in AlphaGlue decreases mainly due to particle decay. Hence, it drops slower than for DaRT and the RBE weighted dose graphs become parallel when the decrease is dominated by the decay of the diffused particles. At a radial distance of 5 mm from the seed centre, the RBE_{cDSB} -weighted dose decreases to approximately 1 Gy. In our AlphaGlue surface model, the RBE_{cDSB} -weighted dose at 5 mm is likewise about 1 Gy. This agreement at depth, despite the different geometries (interstitial seed versus surface application), provides further confidence in the conceptual validity of the AlphaGlue approach and opens the pathway towards subsequent in-vitro and, eventually, in-vivo investigations that will allow the proposed solution to be assessed in a more realistic context.

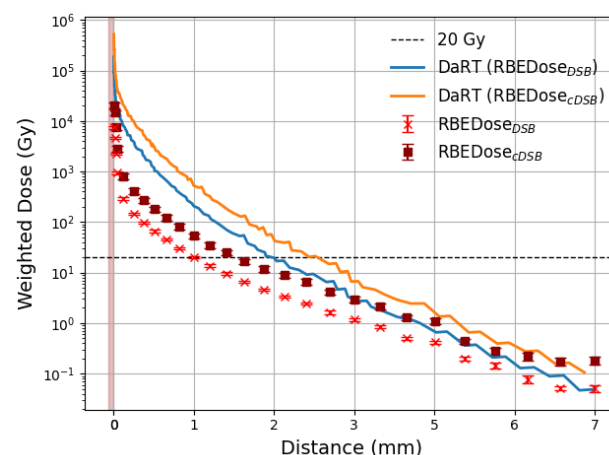


Figure 16. RBE-weighted dose as a function of distance for AlphaGlue and DaRT loaded with $3\ \mu\text{Ci}$ of ^{224}Ra . The DaRT data are taken from [45].

4. Discussion

This study focused on the characterisation of a novel α -therapy delivery concept, called AlphaGlue. In AlphaGlue, α -emitters are suspended in glue which is directly applied to the skin-tissue. A layer of unloaded glue can be applied on top to shield the radiation. A Monte Carlo simulation study using GEANT4 and GEANT4-DNA was done to calculate the DNA damage as a function of depth. A configuration with a 4 μm thick loaded glue layer covered with a 76 μm layer of unloaded glue was explored. Two isotopes, ^{211}At and ^{224}Ra , were studied. The results showed that, in the standard loaded glue configuration, DNA damage induced by ^{211}At was confined to approximately 70 μm , while using ^{224}Ra extended the damage range slightly further to around 90 μm from the glue layer. The key reason for the limited range is that there is only damage due to the emission of α particles that enter the tissue. Applying ^{224}Ra on the surface of the tissue and using a glue layer to keep it in place and shield potential tissue on the far side, significantly enhanced the treatment depth, with DSB and cDSB damage produced beyond 5 mm into the tissue; a depth exceeding the clinical requirements for nasal carcinoma treatment.

The calculated activity provides a reference for how much material would be required to achieve a clinically relevant dose at depth. For instance, an activity of $(34 \pm 3) \mu\text{Ci}/\text{cm}^2$ was needed to reach 20 Gy at 5 mm in our model, which is comparable to the activity levels of existing clinical treatments such as Xofigo [64], which exploits ^{223}Ra dichloride, administered at approximately 30 μCi (1100 kBq/mL) for prostate cancer. This supports the plausibility of the AlphaGlue concept. Specifically, to achieve cell death at 5 mm depth, a ^{224}Ra atom concentration of $(4.35 \pm 0.2) \times 10^{11}/\text{cm}^2$, corresponding to $(21.8 \pm 1) \mu\text{Ci}/\text{cm}^2$ using cDSB-based RBE, or $(6.50 \pm 0.5) \times 10^{11}/\text{cm}^2$, corresponding to $(34 \pm 3) \mu\text{Ci}/\text{cm}^2$ using DSB-based RBE, is required.

Looking Towards the Future

The presented study is based solely on Monte Carlo simulations and designed to explore the feasibility of the AlphaGlue concept in ideal circumstances. A direct comparison with DaRT [45], see Section 3.2, further shows that both approaches can deliver an RBE_{cDSB} -weighted dose of approximately 1 Gy at 5 mm, despite their different geometries (interstitial seed vs. surface application). This shows that the AlphaGlue concept can yield similar clinical outcomes as a successful alternative α -particle based treatment for superficial tumours, highlighting the clinical relevance of the concept explored here.

In-vitro experimental studies are being planned, and improvements to the models will include the implementation of more realistic skin geometries and the incorporation of heterogeneous tissue layers.

Towards clinical deployment, many safety and engineering aspects need to be addressed. However, comparable approaches such as β -emitting skin patches have already demonstrated that radionuclide delivery to superficial tumours is clinically feasible and safe [20–25]. Clinical deployment of DaRT, which also relies on ^{224}Ra , has already demonstrated that this isotope can be used safely and effectively for skin cancer [8,18]. Similarly, Xofigo, a ^{223}Ra based α -therapy, is widely used in routine practice [65,66]. A practical approach for AlphaGlue could involve a two-component glue system, with an additional unloaded protective layer on top. One of the glue components would be pre-mixed with the ^{224}Ra . The contents of the vial with the pre-mixed component can be sucked into a syringe which already has the second glue component in it. Simulations show that an 76 μm unloaded glue layer on top of the loaded glue is sufficient to contain α -radiation, while a thin gas-tight foil can prevent ^{220}Rn escape. Such a procedure would be conceptually similar to existing deployment of Xofigo, and the short range of α -radiation makes it straightforward to ensure safety for both patients and medical staff. Furthermore, the

decay of ^{224}Ra (half-life 3.6 days) means that if the glue remains in place for a few weeks, residual activity falls to negligible levels, avoiding long-term radioactive waste.

5. Conclusions

A key challenge in α therapy is how to deliver the α emitters to the tumour. In this study, the effectiveness of a novel treatment delivery concept, AlphaGlue, is evaluated. In AlphaGlue the α emitters are delivered using a thin layer of glue that is put on top of the tumour. This may offer a less invasive and potentially easier-to-use alternative, which could be particularly advantageous for sensitive areas such as facial skin cancers, but also anal, vaginal cancer or endometriosis. The DNA damage as a function of depth is calculated using GEANT4 and GEANT4-DNA simulations using ^{211}At and ^{224}Ra . It is shown that significant cell death at 5 mm into the tissue can be achieved when applying a ^{224}Ra atom concentration of $(4.35 \pm 0.2) \times 10^{11}/\text{cm}^2$, which corresponds to a local activity of $(21.8 \pm 1) \mu\text{Ci}/\text{cm}^2$, when using the cDSBs for the RBE calculation and $(6.50 \pm 0.5) \times 10^{11}/\text{cm}^2$, which corresponds to a local activity of $(34 \pm 3) \mu\text{Ci}/\text{cm}^2$, on the skin surface when using the DSBs for the RBE calculation. This study has shown that there is good potential to develop the AlphaGlue style treatment further and opens the pathway to in-vitro experiments.

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Abbreviations

The following abbreviations are used in this manuscript:

LET	linear energy transfer
TAT	Targeted Alpha Therapy
DaRT	Diffusing α -emitters Radiation Therapy
SSB	Single Strand Break
DSB	Double Strand Break
cDSB	Complex Double Strand Break
RBE	relative biological effectiveness

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