Received: 1 December 2022 | Revised: 1 December 2022 | Accepted: 2 December 2022

DOI: 10.1002/mp.16155

RESEARCH ARTICLE

MEDICAL PHYSICS

Alpha dose modeling in diffusing alpha-emitters radiation therapy. Part II: Lattice studies

Guy Heger | **Mirta Dumančić** | **Arindam Roy** | **Lior Arazi**

Unit of Nuclear Engineering, Faculty of Engineering Sciences, Ben-Gurion University of the Negev, Be'er-Sheva, Israel

Correspondence
Lior Arazi, Unit of Nuclear Engineering, Faculty of Engineering Sciences, Ben-Gurion University of the Negev, P.O.B. 653
Be'er-Sheva 8410501, Israel.
Email: larazi@bgu.ac.il

Funding information
Alpha TAU Medical Ltd (ATM)

Abstract

Background: Diffusing alpha-emitters radiation therapy ("DaRT") is a new method, presently in clinical trials, which allows treating solid tumors by alpha particles. DaRT relies on interstitial seeds carrying μCi-level ^{224}Ra activity on their surface, which release a chain of short-lived alpha emitters that spread throughout the tumor volume primarily by diffusion. Alpha dose calculations in DaRT are based on describing the transport of alpha emitting atoms, requiring new modeling techniques.

Purpose: A previous study introduced a simplified framework, the "diffusion–leakage (DL) model," for DaRT alpha dose calculations, and employed it to a point source, as a basic building block of arbitrary configurations of line sources. The aim of this work, which is divided into two parts, is to extend the model to realistic seed geometries (in Part I), and to employ single-seed calculations to study the properties of DaRT seed lattices (Part II). Such calculations can serve as a pragmatic guide for treatment planning in future clinical trials.

Methods: We employ the superposition of single-seed solutions, developed in Part I, to study the alpha dose in DaRT seed lattices and investigate the sensitivity of the required seed activity and spacing to changes in the DL model parameters and to seed placement errors.

Results: We show that the rapid fall-off of the dose, which guarantees sparing healthy tissue already 2–3 mm away from the tumor, strongly favors a hexagonal, rather than square, seed placement pattern. Realistic variations in the seed manufacturing parameters (^{224}Ra activity and emission rate of its daughters) are shown to have a negligible effect on the required lattice spacing. On the other hand, tumor parameters (i.e., diffusion lengths and ^{212}Pb leakage probability), as well as seed placement errors, have a significant effect.

Conclusions: In most cases, hexagonal lattice spacing on the scale of ~3.5–4.5 mm using seeds carrying a few μCi/cm ^{224}Ra will enable overcoming realistic uncertainties in measured tumor environment parameters, as well as seed placement errors, and result in therapeutically relevant alpha dose levels.

KEYWORDS
alpha dose calculations, brachytherapy, DaRT, targeted alpha therapy

1 | INTRODUCTION

Diffusing alpha-emitters radiation therapy (DaRT) is a new method, which enables the treatment of solid tumors by alpha particles.[1] It relies on the insertion of multiple sources ("seeds") carrying a few μCi of ^{224}Ra below their surface into the tumor. As long as the seeds remain inside the tumor (typically $>$ 14 days), they release from their surface a chain of alpha emitters (progeny of ^{224}Ra), which diffuse over a few mm around each seed, leading to effective dose coverage of the entire tumor volume by their alpha decays. A simplified framework for DaRT alpha dose calculations, called "the diffusion–leakage (DL) model," was introduced and described in detail in a previous publication,[2] focusing on a point source as a basic building block for line-source configurations. In the present two-part publication, the discussion is extended to realistic seed geometries. In Part I, single-seed calculations were covered, including both analytical and numerical schemes for solving the DL model equations in one or two dimensions (called "DART1D" and "DART2D," respectively). Here, lattice calculations are the focus, showing the optimal grid geometry, the seed activities required to reach a target alpha particle dose, and finally, a comprehensive study of how the required lattice spacing is affected by uncertainties in the various model parameters.

2 | DaRT LATTICE CALCULATIONS

Studies of DaRT seed lattices are based on the single-seed calculations presented in Part I of this publication. The optimal arrangement of DaRT seeds is a hexagonal lattice, as it provides the highest packing density of circles in the two-dimensional Euclidean plane.[3] In this geometry, seeds are set at the vertices of a grid consisting of equilateral triangles of side a (the *lattice spacing*). Each seed occupies a hexagonal unit cell, of cross-sectional area $\sqrt{3}a^2/2$ formed by the bisectors to the lines connecting the seed to its six nearest neighbors (Figure 1). Equivalently, the unit cell can be defined as an equilateral triangle of side a formed by seed triplets. The minimum dose is found at the center of gravity of each triangle (the hexagon vertices).

Because of the very rapid fall off of the alpha dose, only the three seeds defining a triangle contribute to the dose inside it. In principle, if the seed spacing is comparable to their diameter, the dose should be calculated for the full geometry, with all three seeds included. However, for realistic seed diameters ($\leq$0.7 mm) and spacing ($>$3 mm), the dose can be calculated to subpercent accuracy by adding in superposition the contributions from each seed independently of the others. This is shown in Figure 2, where the results of a full 3D calculation with COMSOL Multiphysics™ are compared to a superposition of single-seed solutions obtained from a COMSOL 2D calculation, for a lattice with either 3 or 4 mm spacing. The comparison is done along a line from one of the seeds towards the center of gravity of the triangle.

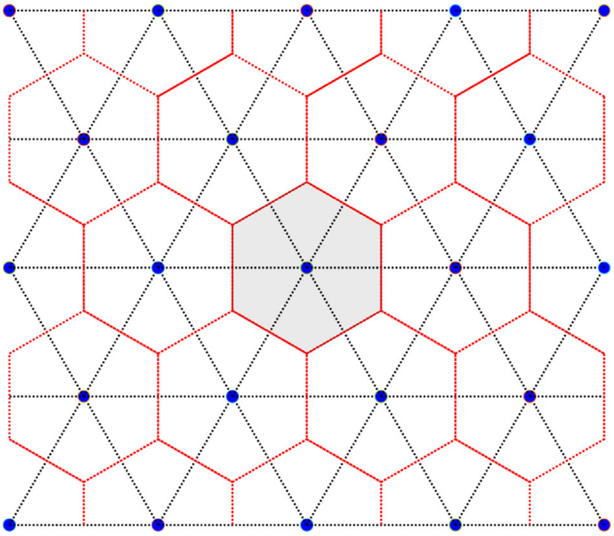

FIGURE 1 Hexagonal DaRT lattice geometry. Blue points mark seed centers. Each seed occupies a hexagonal unit cell (gray) of area $\sqrt{3}a^2/2$, where a is the distance between adjacent seeds. Equivalently, the unit cell can be defined as a triangle formed by three adjacent seeds.

Since the one-dimensional time-dependent solution provided by DART1D is accurate to within a few percent up to ~2 mm from the seed edge (as shown Part I), this approximation is used to study lattice properties in the plane perpendicular to the seed axis (away from the edge), allowing for fast parameter scans with sufficient accuracy. For actual treatment plans, however, one should rely on a superposition of 2D single-seed solutions, as done in conventional brachytherapy using TG-43-like lookup tables.[4] A recipe for casting the DaRT 2D dose model into TG-43-like format will be provided in a separate publication.

Figure 3 shows an example for a hexagonal DaRT seed lattice for a low-diffusion case $L_{Rn} = 0.3$ mm, $L_{Pb} = 0.1$ mm, with $P_{leak} = 0.5$, $L_{Bi} = 0.1L_{Pb}$, and $\alpha_{Bi} = 0$ (see Part I for a definition of the model parameters). The seeds carry 3 μCi/cm ^{224}Ra with $P_{des}(Rn) = 0.45$, $P^{eff}_{des}(Pb) = 0.55$. The calculation was done by a superposition of 2D single-seed solutions. The seed radius is $R_0 = 0.35$ mm. The lattice spacing is $a = 4$ mm. The total asymptotic alpha particle dose is shown in the seed midplane (a), and in a plane parallel to the seeds (b). The plane in (b) is chosen to pass through the points of the lowest dose (the center of gravity between three adjacent seeds). The minimal alpha dose between seeds (in the seed midplane) is 14.4 Gy. The dose falls off to negligible levels (<1 Gy) 3 mm away from the seeds. As shown in (b), the dose is lower close to the seed edges (between seeds). Roughly, the isodose pattern in

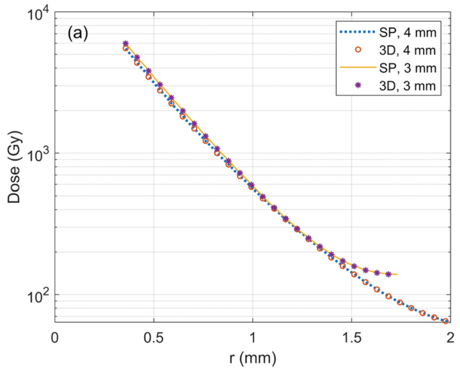

FIGURE 2 (a) Total alpha particle dose profiles calculated as a superposition (SP) of three DaRT seeds and a full 3D calculation of three such seeds, along a line from one seed towards the center of gravity of the triangle. The calculation was repeated for a lattice spacing of 3 and 4 mm, with the following model parameters: $L_{Rn} = 0.3$ mm, $L_{Pb} = 0.6$ mm, $P_{leak} = 0.5$, $L_{Bi} = 0.1L_{Pb}$, and $\alpha_{Bi} = 0$. The seeds carry 3 μCi/cm ^{224}Ra with $P_{des}(Rn) = 0.45$, $P_{des}^{eff}(Pb) = 0.55$. (b) Relative error between the superposition and 3D profiles shown in (a). The relative error is defined as $err = (SP - 3D)/3D$.

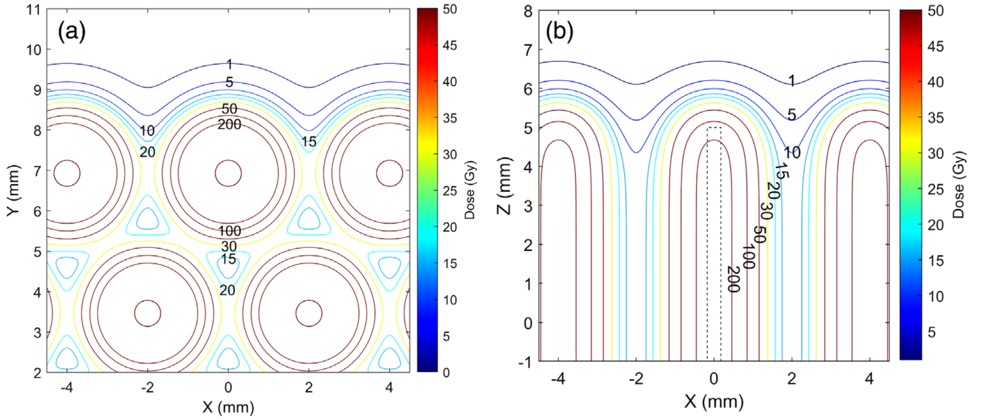

FIGURE 3 Example for a hexagonal DaRT seed lattice, representing a low-diffusion case: $L_{Rn} = 0.3$ mm, $L_{Pb} = 0.1$ mm, with $P_{leak} = 0.5$, $L_{Bi} = 0.1L_{Pb}$, and $\alpha_{Bi} = 0$. Seed activity is 3 μCi/cm ^{224}Ra with $P_{des}(Rn) = 0.45$, $P_{des}^{eff}(Pb) = 0.55$. The lattice spacing is $a = 4$ mm. Shown is the total asymptotic alpha particle dose in the seed midplane (a), and in a plane parallel to the seeds (b). The plane in (b) is chosen to pass through the points of lowest dose (the center of gravity of adjacent seeds). The dashed line in (b) represents a projection of the seed on this plane.

(a) suggests that the outermost plane of seeds (here, the top plane) should be inside the target volume, not more than ~1 mm from its edge, while (b) suggests that the seeds protrude ~1 mm out of the target volume. Specific clinical recommendations should depend on the required dose for a particular tumor type and the diffusion lengths considered to best describe the tissue close to the edge of the target volume.

Figure 4 shows the seed ^{224}Ra activity (per cm seed length) required for a minimal *nominal* alpha dose of 10 Gy (chosen as a convenient reference) in hexagonal lattices as a function of L_{Pb} for $L_{Rn} = 0.2, 0.3, 0.4$, and 0.5 mm. (The term "nominal" here means that uncertainties in the model parameters or seed positions are not considered.) For each value of L_{Rn}, we show a band of activities corresponding to the range $P_{leak}(Pb) = 0.2 - 0.8$, with the solid line representing $P_{leak} = 0.5$. (The lower edge of the band corresponds to $P_{leak}(Pb) = 0.2$ and the higher to $P_{leak}(Pb) = 0.8$.) The case $L_{Rn} = 0.5$ mm is included to account for the possibility of considerable vascular enhancement of the spread of ^{220}Rn. Three cases of lattice spacing are considered: 5 mm (a), 4 mm (b), and 3 mm (c). The other parameters are $P_{des}(Rn) = 0.45$, $P_{des}^{eff}(Pb) = 0.55$, $L_{Bi} = 0.1L_{Pb}$, $\alpha_{Bi} = 0$. Note that the dose at any point in the lattice is proportional to the seed activity. Therefore, if the desired minimal dose is other than 10 Gy, one can directly extract from these curves the required activity by multiplying the plotted value by a constant factor: $f =$ (desired dose in Gy)/10.

Figure 4a indicates that at 5-mm spacing, therapeutic dose levels (e.g., 10–20 Gy) can be reached with seed activities of a few μCi ^{224}Ra only for large values of the diffusion lengths (e.g., $L_{Pb} \gtrsim 0.5$ mm for $L_{Rn} \lesssim 0.3$ mm, or $L_{Rn} \gtrsim 0.4$ mm for any value of L_{Pb}). For low values of the diffusion lengths (e.g., $L_{Rn} \lesssim 0.3$ mm and $L_{Pb} < 0.2$ mm) at 5 mm spacing, the required seed activity is tens of μCi, while for the

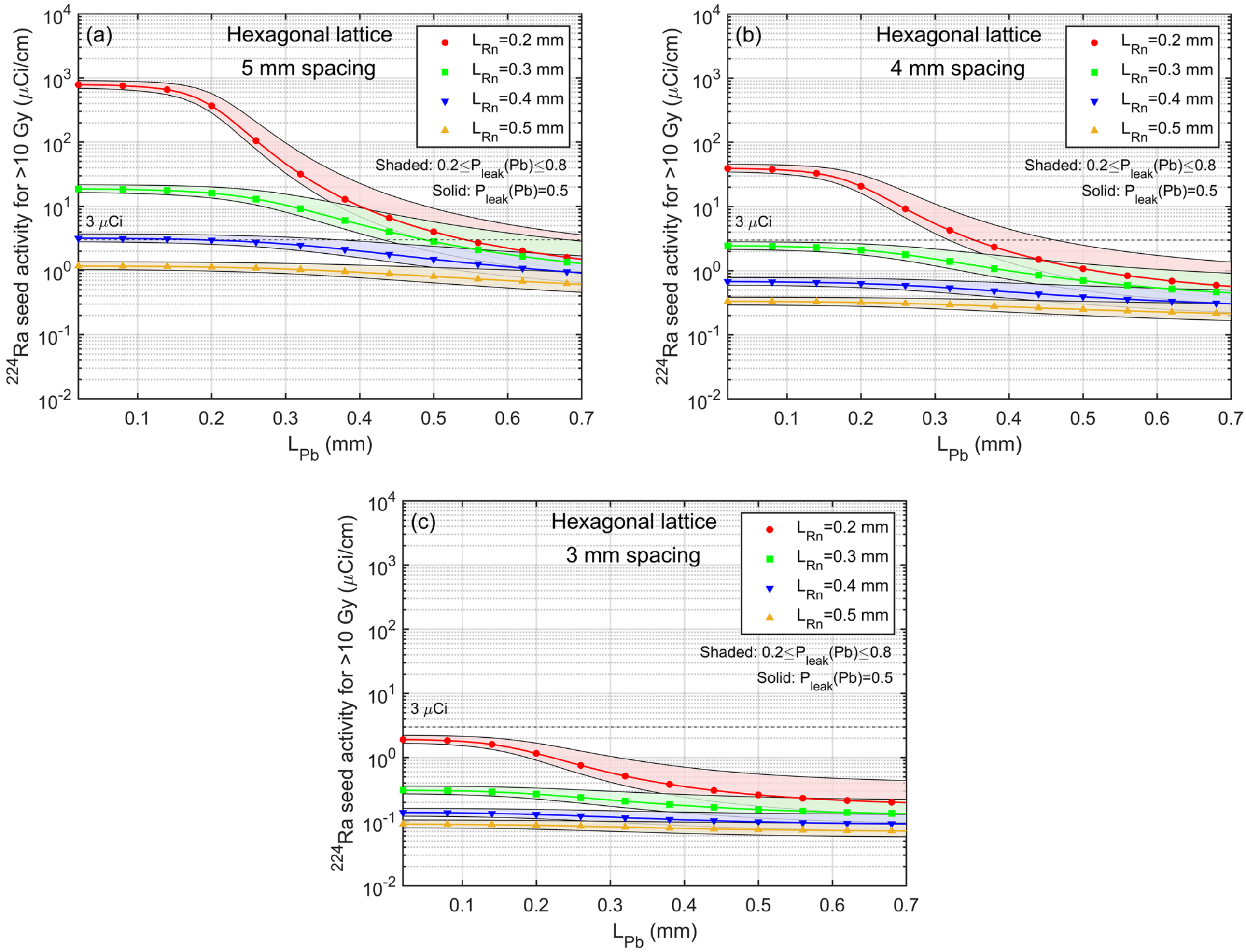

FIGURE 4 Hexagonal lattice calculations: ^{224}Ra seed activity (in μCi/cm) required to ensure a nominal alpha dose higher than 10 Gy throughout the lattice interior as a function of the ^{212}Pb diffusion length for varying values of the ^{220}Rn diffusion length for 5-mm spacing (a), 4-mm spacing (b), and 3-mm spacing (C). Individual bands correspond to $P_{leak}(Pb) = 0.2-0.8$ with the solid curves for $P_{leak}(Pb) = 0.5$. In all cases, $L_{Bi} = 0.1L_{Pb}$ and $\alpha_{Bi} = 0$. Seed radius is 0.35 mm, $P_{des}(Rn) = 0.45$, $P^{eff}_{des}(Pb) = 0.55$, and the treatment duration is 30 d.

extreme case $L_{Rn}, L_{Pb} \lesssim 0.2$ mm, it reaches hundreds of μCi. Such high activity values are unrealistic, and would significantly reduce the maximal tumor volume, which can be treated without systemic toxicity due to ^{212}Pb uptake in distant organs.[5] This situation can be mitigated by reducing the seed spacing to 4 mm, as shown in Figure 4b. Here we see that therapeutic dose levels can be reached with seeds carrying a few μCi ^{224}Ra if $L_{Rn} \sim 0.3$ mm, irrespective of L_{Pb}. However, the extreme case $L_{Rn}, L_{Pb} \lesssim 0.2$ mm can only be handled realistically at ~3- mm spacing, as shown in Figure 4c. (Additional calculations show that if $L_{Rn} = 0.25$ mm, the spacing can be relaxed to 3.5 mm for few-μCi seeds.)

As evident from Figure 4, reducing the seed spacing allows using lower-activity seeds to obtain the desired dose. Nontrivially, this has the additional benefit of lowering the required ^{224}Ra activity *per unit volume* of the tumor $(= \Gamma^{src}_{Ra}(0)/(\sqrt{3}/2\,a^2 l))$. Consequently, since the maximal tolerable activity of ^{224}Ra is limited by the dose to distant organs (and expected to be a few mCi[5]), working at small spacing allows treating larger tumors, or several distinct lesions. This is demonstrated in Figure 5 for the case $L_{Pb} = 0.2$ mm (a) and $L_{Pb} = 0.4$ mm (b), where the specific ^{224}Ra activity (in μCi/cm^3) required to guarantee a minimal nominal alpha dose of 10 Gy, as a function of the (hexagonal) lattice spacing, is shown for different values of L_{Rn}. The effect is especially pronounced for low-diffusion tumors. For example, for the case $L_{Rn} = 0.3$ mm and $L_{Pb} = 0.2$ mm, the required ^{224}Ra specific activity at 4.5-mm spacing (for 10 Gy) is 33.1 μCi/cm^3 (for $P_{leak}(Pb) = 0.5$), whereas at 3.5-mm spacing, it drops to 7.1 μCi/cm^3. Assuming, for example, a maximal ^{224}Ra activity of 3 mCi, the largest volume that can be treated at 4.5-mm spacing is ~90 cm^3, while at 3.5-mm spacing, it is ~420 cm^3. This effect becomes more pronounced for decreasing values of the diffusion lengths. In the extreme case of $L_{Rn} = 0.2$ mm and

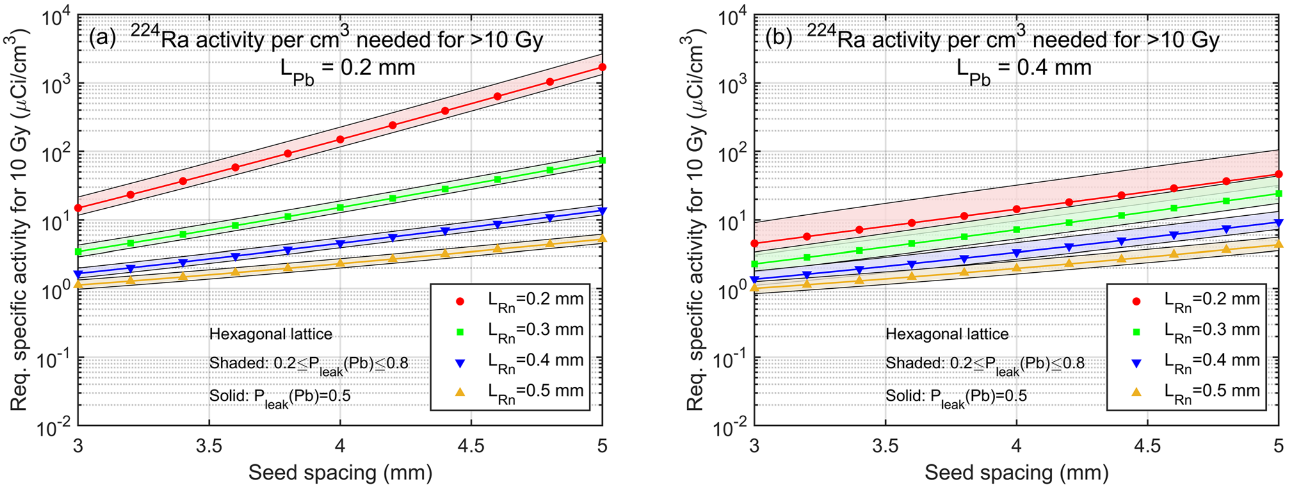

FIGURE 5 ^{224}Ra activity per unit volume (in μCi/cm^3) required to ensure a nominal alpha dose higher than 10 Gy throughout the lattice interior as a function of the seed spacing for varying values of L_{Rn}, and for a fixed choice $L_{Pb} = 0.2$ mm (a) and $L_{Pb} = 0.4$ mm (b). The bands correspond to $P_{leak}(Pb) = 0.2 - 0.8$, with the solid curves representing $P_{leak}(Pb) = 0.5$. The other parameters are $L_{Bi} = 0.1L_{Pb}$, $\alpha_{Bi} = 0$, $R_0 = 0.35$ mm, $P_{des}(Rn) = 0.45$, $P_{des}^{eff}(Pb) = 0.55$. Treatment duration is 30 d.

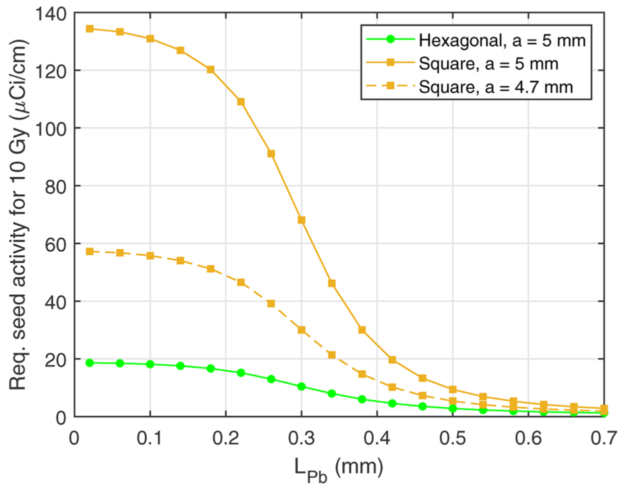

FIGURE 6 Hexagonal versus square lattices: ^{224}Ra seed activity (in μCi/cm) required to ensure a minimal nominal alpha dose higher than 10 Gy throughout the lattice interior as a function of L_{Pb} for $L_{Rn} = 0.3$ mm and $P_{leak} = 0.5$. The curves are for hexagonal and square lattices with 4-mm spacing and for a square lattice that has the same ^{224}Ra activity per unit volume as a hexagonal lattice with 4-mm spacing. The other parameters are $L_{Bi} = 0.1L_{Pb}$, $\alpha_{Bi} = 0$, $R_0 = 0.35$ mm, $P_{des}(Rn) = 0.45$, $P_{des}^{eff}(Pb) = 0.55$. Treatment duration is 30 d.

$L_{Pb} = 0.2$ mm, the maximal treatable volume grows from ~20 cm^3 at 4-mm spacing to ~260 cm^3 at 3-mm spacing (assuming a required dose of 10 Gy). As shown in (b), for larger values of L_{Pb}, the general behavior is qualitatively the same, but the slopes of the curves are smaller and the bands (defined by the range of $P_{leak}(Pb)$) become wider and begin to overlap.

The effect of lattice geometry on the required seed activity is addressed in Figure 6. The figure shows the ^{224}Ra seed activity (per unit length) required to ensure a minimal nominal alpha dose of 10 Gy as a function of L_{Pb} for a fixed choice $L_{Rn} = 0.3$ mm and $P_{leak}(Pb) = 0.5$. The results are compared for a hexagonal lattice with $a = 4$-mm spacing, a square lattice with 4-mm spacing, and a square lattice in which the cell cross-section area is the same as that of a hexagonal lattice with 4-mm spacing: $a' = (\sqrt{3}/2a^2)^{1/2} = 3.72$ mm. In low-diffusion tumors ($L_{Pb} \lesssim 0.3$ mm), for the same seed spacing, the hexagonal lattice requires ~4–4.5 less activity for the same dose when compared to a square one. For the same unit cell area (i.e., same ^{224}Ra activity per unit volume), the hexagonal seed arrangement requires $\sim 2 - 2.4$ less activity. The effect becomes smaller for high-diffusion tumors, but remains on the scale of ~1.5–2. Similar behavior is observed for other choices of lattice spacing, with the advantage of hexagonal geometry increasing with the ratio a/L_{Rn}.

3 | PARAMETER SENSITIVITY TESTS

In this section, we investigate the effect of variations in seed placement, seed properties, and tissue parameters on the required nominal lattice spacing for administering a therapeutic alpha dose. The analysis is based on fixing the seed ^{224}Ra activity to a constant value (initially 3 μCi/cm and later 6 μCi/cm) and finding the nominal spacing that guarantees a minimal alpha dose in the range 10–20 Gy with 90% confidence, for a given level of uncertainty in each parameter.

The lattice cell is nominally an equilateral triangle, and each case study involves random variations in one or two parameters for each of the three seeds defining the cell. For single-parameter studies the target dose is set

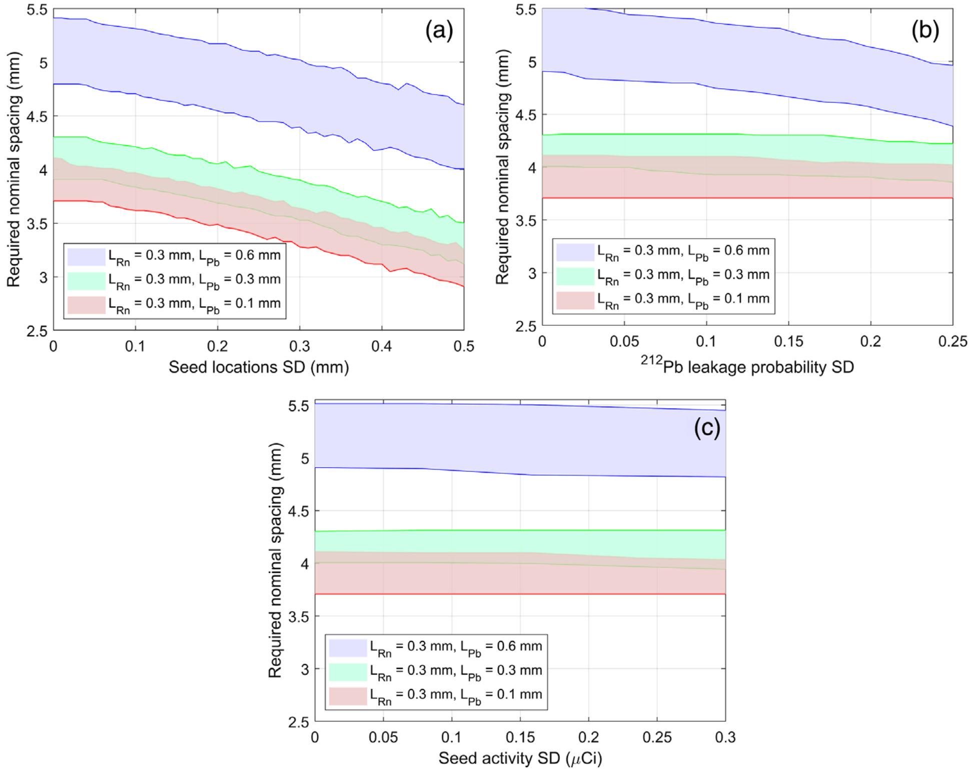

FIGURE 7 The nominal spacing required to ensure, with 90% confidence, that at least 10 Gy (upper limit of each filled range) or 20 Gy (lower limit of each filled range) are delivered in the cold-spot of a single triangular lattice cell as a function of uncertainties (standard deviations) in individual seed placement locations (a), ^{212}Pb leakage probability (b), and individual seed activities (c). The diffusion lengths are given in the plot. In all cases, $P_{des}(Rn) = 0.45$, $P_{des}^{eff}(Pb) = 0.55$, $L_{Bi} = 0.1L_{Pb}$. In (a) and (b), $\Gamma_{Ra}^{src}(0)/l = 3\,\mu$Ci/cm. In (a) and (c), $P_{leak}(Pb) = 0.5$.

to the range 10–20 Gy, while for two-parameter scans, it is fixed to 15 Gy for presentation purposes.

The basic procedure is as follows. For each parameter study, 1000 sets of values are randomly generated for each of the three seeds comprising the lattice cell. The values are generated independently for each seed, and in studies where two parameters are examined, both are generated independently. The values are sampled from a normal distribution around a nominal value with a given standard deviation (SD). For each generated set of random values, the dose map inside the lattice cell is calculated and the lowest ("cold-spot") dose is recorded. For each vector of cold-spot doses, the percentage of values above the target dose is saved. This is repeated for increasing lattice spacing. Finally, the minimal spacing, which yields the desired dose with 90% confidence, is recorded. The entire process is repeated with increasingly higher SDs, recording the required nominal spacing for each case.

In studies where seed parameters were examined (initial ^{224}Ra activity and desorption probabilities), the values of SDs were scanned over 0–10% of their nominal value. This is, in fact, more conservative than the quality control procedures of the seed manufacturer, which dictate rejecting seeds with deviations larger than 10% compared to the nominal value. In studies where physical parameters of the tissues were examined (diffusion lengths and ^{212}Pb leakage probability), the SDs were scanned over 0–50% of the nominal value. In the seed placement error study, the SDs of the x and y coordinates relative to the nominal seed location were increased from 0 to 0.5 mm, estimated as a reasonable level of uncertainty. All tests were repeated for three scenarios: low lead diffusion, with $L_{Rn} = 0.3$ mm and $L_{Pb} = 0.1$ mm, equal diffusion lengths, with $L_{Rn} = 0.3$ mm and $L_{Pb} = 0.3$ mm, and high lead diffusion, with $L_{Rn} = 0.3$ mm and $L_{Pb} = 0.6$ mm. In all scenarios, we set $L_{Bi} = 0.1L_{Pb}$ and $\alpha_{Bi} = 0$. Other nominal values used in all studies are $\Gamma_{Ra}^{src}(0)/l = 3\,\mu$Ci/cm, $P_{des}(Rn) = 0.45$, $P_{des}^{eff}(Pb) = 0.55$, $R_0 = 0.35$ mm, and $P_{leak}(Pb) = 0.5$. The treatment duration is 30 d.

It should be noted that except for the seed location study, which was done using the 1D numerical solution (DART1D), all dose maps were calculated, for the sake of computational efficiency, using the 0D closed-form approximation for an infinite cylindrical source. As shown in Part I, at a radial distance of ~2–2.5 mm from the seed, where the cold spot typically lies, this introduces an error of ~5% in the analysis of the high diffusion scenario, and negligible error for the others.

Figure 7 shows the required spacing as a function of uncertainties in individual seed placement locations (a), ^{212}Pb leakage probability (b), and individual seed activities (c). The filled colored bands in each panel

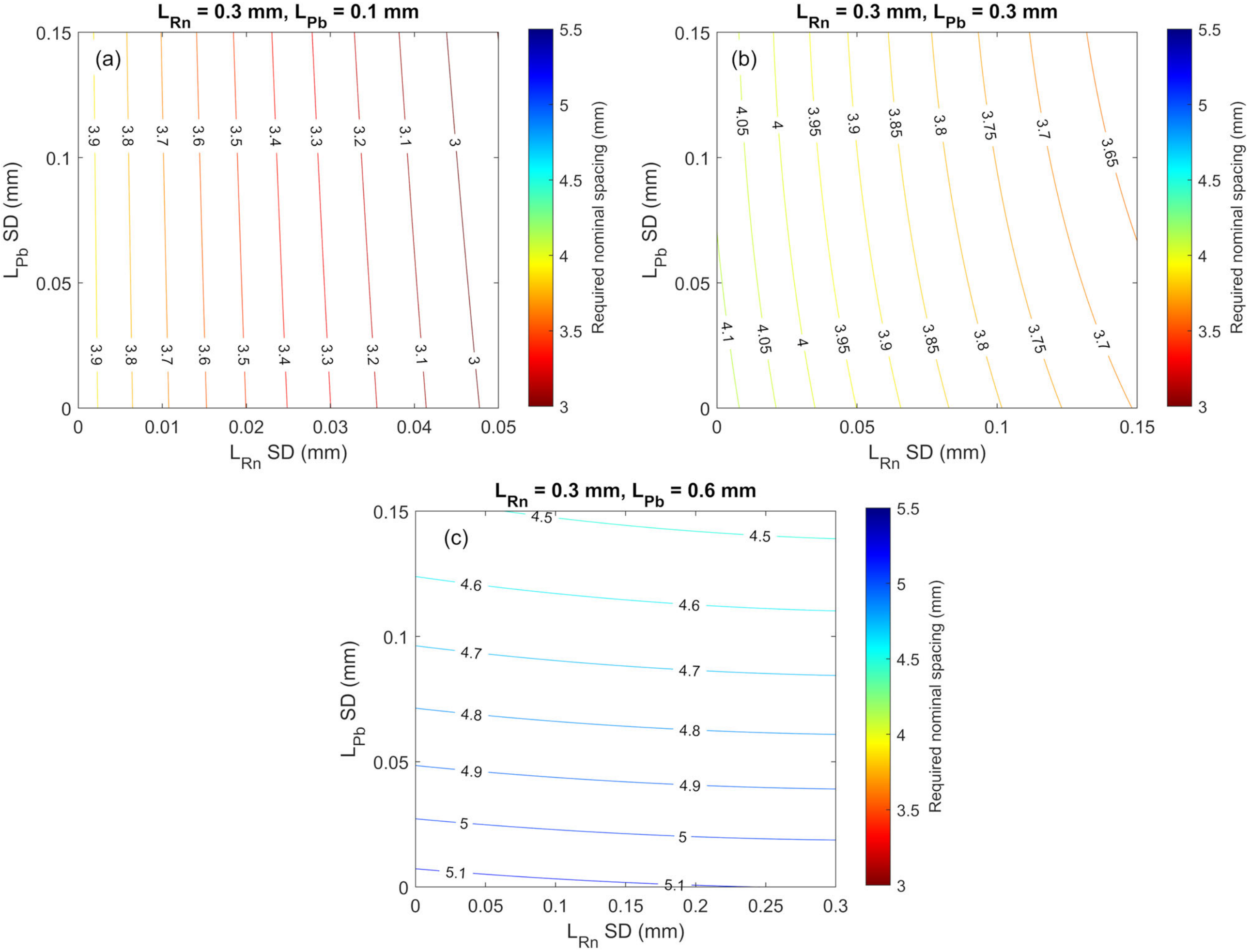

FIGURE 8 The nominal spacing required to ensure, with 90% confidence, that at least 15 Gy are delivered in the cold-spot of a single triangular lattice cell as a function of uncertainties (standard deviations) in the diffusion lengths for the low lead diffusion case (a), equal diffusion lengths case (b), and high lead diffusion case (c). In all cases, $\Gamma_{Ra}^{src}(0)/l = 3\,\mu$Ci/cm, $P_{leak}(Pb) = 0.5$, $P_{des}(Rn) = 0.45$, $P_{des}^{eff}(Pb) = 0.55$, $L_{Bi} = 0.1L_{Pb}$.

represent the 10–20-Gy range, with the lower edge corresponding to 20 Gy and the upper one to 10 Gy for each diffusion scenario. It is clear that seed placement errors have a significant effect on the required nominal lattice spacing: the observed decrease in the required spacing reaches up to ~0.8 mm for a SD of 0.5 mm in seed placement for the three diffusion length scenarios. Uncertainties in the ^{212}Pb leakage probability, as expected, only affect the required spacing in the case of lead-dominated diffusion (up to ~0.5 mm). Uncertainties arising from the variations in the initial seed activity have a completely negligible effect.

Figure 8 shows a color map of the required spacing as a function of uncertainties in the two diffusion lengths for the three different scenarios described above (both L_{Rn} and L_{Pb} were sampled separately for each seed). Here, the target alpha dose was taken as 15 Gy. Uncertainties in the diffusion lengths are significant, but only in the dominant one of the two. In the radon-dominated, low-diffusion case ($L_{Rn} = 0.3$ mm, $L_{Pb} = 0.1$ mm), a SD of 50% (0.15 mm) in L_{Rn} would require reducing the nominal spacing from ~3.9 to ~3 mm. For the case of equal diffusion lengths ($L_{Rn} = L_{Pb} = 0.3$ mm), a SD of 50% in both parameters would require reducing the spacing from ~4.2 to ~3.7 mm. Last, for the high-diffusion lead-dominated scenario ($L_{Rn} = 0.3$ mm, $L_{Pb} = 0.6$ mm), a SD of 50% in L_{Pb} would require reducing the nominal spacing from ~5.2 to ~4.5 mm. Note, however, that—as discussed in a separate publication describing the experimental measurements of the diffusion lengths—typical SDs for a given cell line are not more than ~20%. This relaxes the required reduction in the nominal spacing to ~0.2–0.3 mm in all cases.

Figure 9 shows the nominal spacing required to ensure an alpha dose of 15 Gy with 90% confidence as a function of variations in the desorption probabilities for the three diffusion scenarios. Similarly to the seed activity, variations in the desorption probabilities have a negligible effect. Note that the color scale in Figure 9

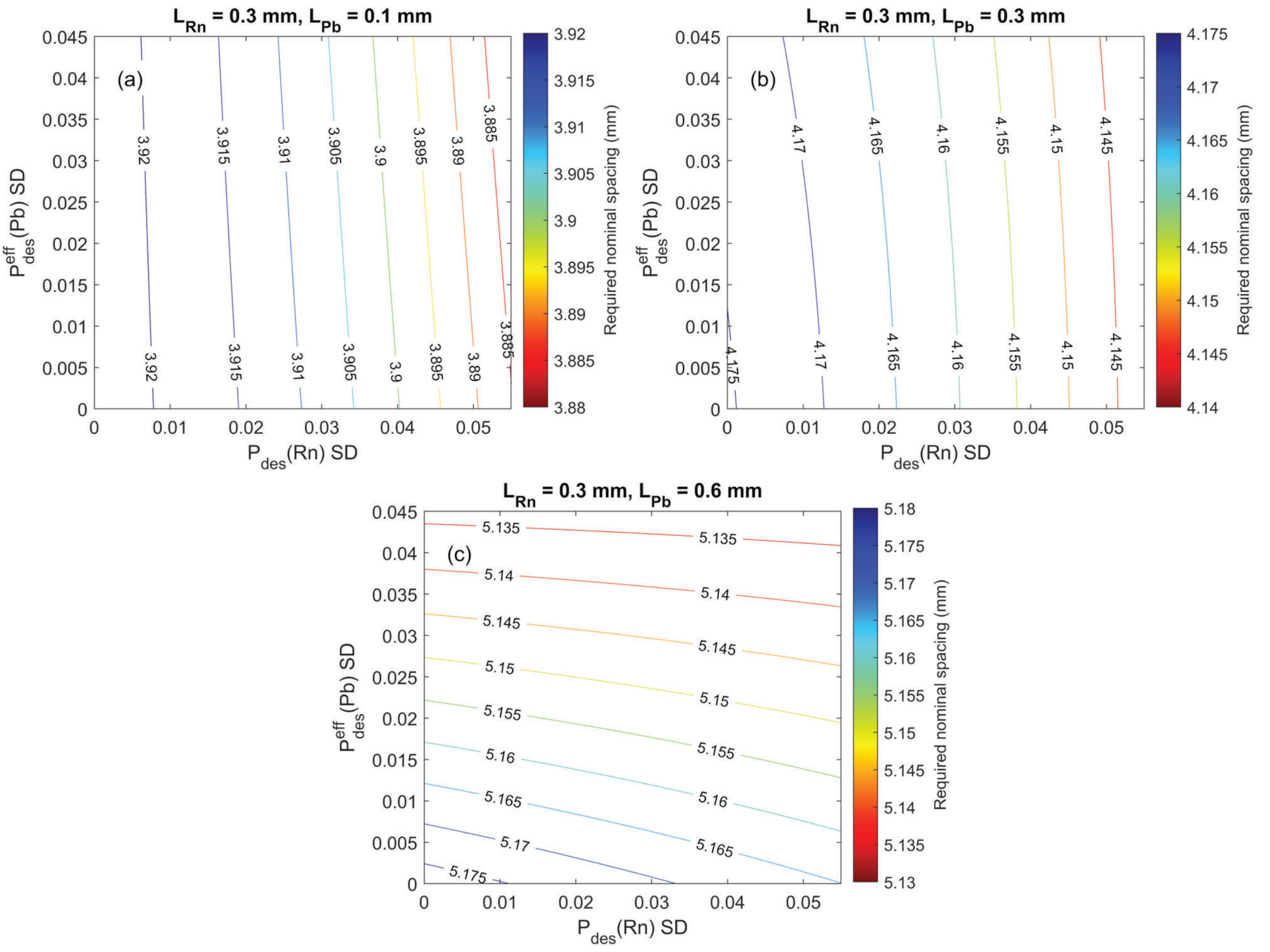

FIGURE 9 The nominal spacing required to ensure, with 90% confidence, that at least 15 Gy are delivered in the cold-spot of a single triangular lattice cell as a function of uncertainties (standard deviations) in desorption probabilities for the low lead diffusion case (a), equal diffusion lengths case (b), and high lead diffusion case (c). Note that the color scales are changed for each plot for presentation purposes. In all cases, $\Gamma^{src}_{Ra}(0)/l = 3\,\mu$Ci/cm, $P_{leak}(Pb) = 0.5$, $L_{Bi} = 0.1L_{Pb}$.

was changed for each plot in order to show the range of spacing variation.

As can be seen from all tests shown here, the two most significant parameters in the uncertainty analysis are the seed placement locations and the diffusion lengths, and in the case of diffusion lengths, only the dominant one is of importance. In light of this, a final set of plots is given in Figures 10 and 11, showing the required spacing as a function of uncertainties in both the seed location and the dominant diffusion length, for initial ^{224}Ra seed activities of 3 μCi/cm (Figure 10) and 6 μCi/cm (Figure 11). As before, the parameter scan is up to 50% uncertainty in the dominant diffusion length. Considering the full range of uncertainties in both parameters, the maximal required reduction in seed spacing is ~1.2 mm in all cases. However, when uncertainties in the diffusion length are limited to 20%, the required reduction in spacing is essentially dominated by seed placement errors and is limited to a maximal value of ~0.9 mm. As shown in Figure 11, increasing the initial seed activity to 6 μCi/cm relaxes the required seed spacing by ~0.4–0.5 mm compared to 3 μCi/cm seeds.

4 | DISCUSSION

In this work, which constitutes the second part of a two-part publication, the single-seed calculations described in Part I were utilized to study the properties and key dependencies of DaRT seed lattices.

As a starting point for the discussion of DaRT lattices, we showed that for a uniform medium, one can accurately calculate the dose from multiple seeds by simple superposition. This is a major simplification, since complete 3D finite element solutions for multiple-seed configurations are extremely time consuming. With superposition validated, we showed that the rapid fall off of the DaRT alpha dose ensures that in an array of seeds of μCi-scale ^{224}Ra activity, the dose drops to negligible levels already ~2–3 mm away from the outermost

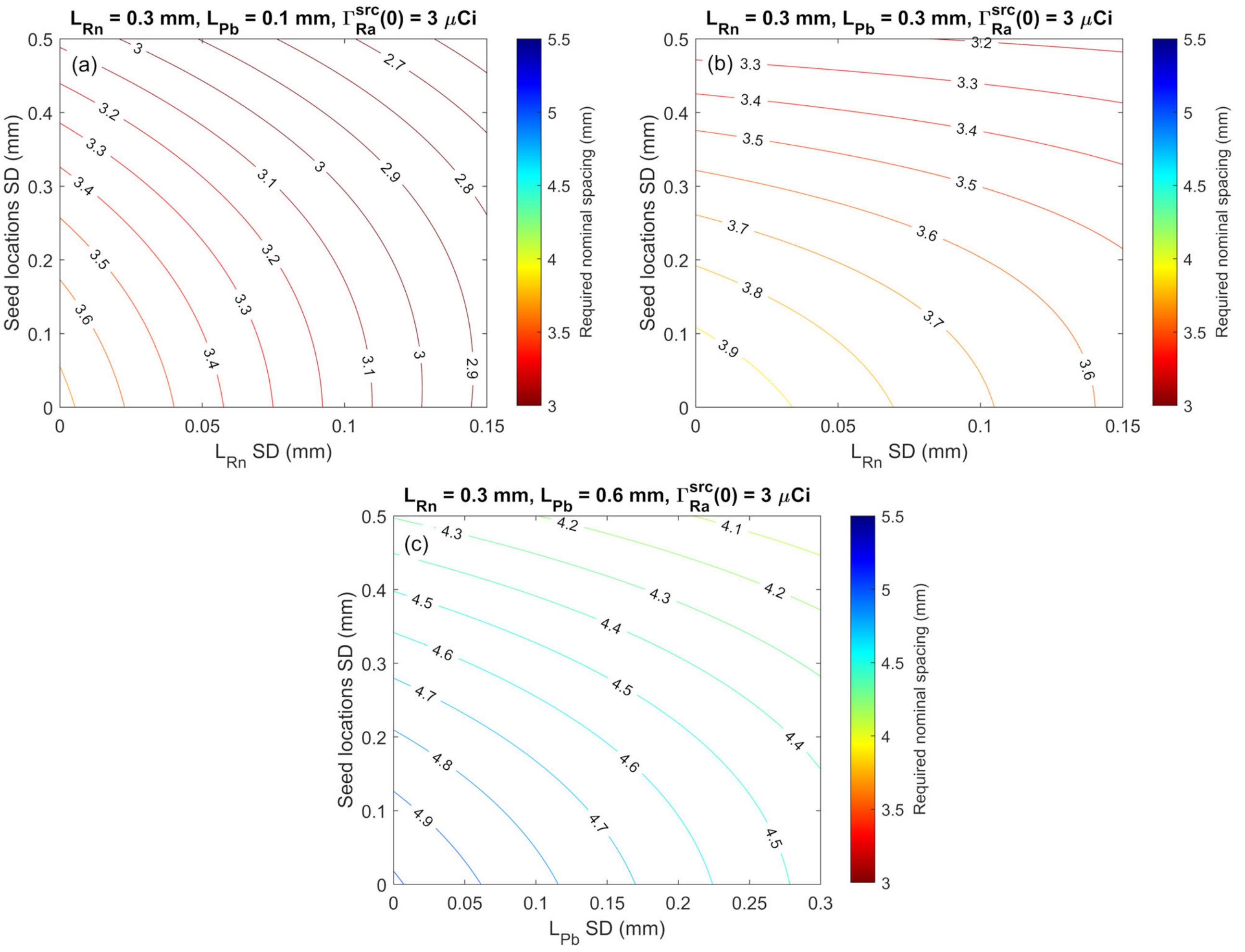

FIGURE 10 3-μCi/cm seeds: the required nominal spacing in order to ensure, with 90% confidence, that at least 15 Gy are delivered in the cold-spot of a single triangular lattice cell as a function of uncertainties (standard deviations) in seed locations and the dominant diffusion length for the low lead diffusion case (a), equal diffusion lengths case (b), and high lead diffusion case (c). In all cases, $P_{leak}(Pb) = 0.5$, $P_{des}(Rn) = 0.45$, $P^{eff}_{des}(Pb) = 0.55$, $L_{Bi} = 0.1L_{Pb}$.

seeds, leading to excellent conformity and ensuring that adjacent healthy tissue is spared. A useful consequence of this rapid fall off is that for alpha dose calculations, one needs to consider contributions only from seeds up to a distance of $\lesssim$3 mm from the point of interest.

The accuracy of the 1D solution for an infinite cylindrical source up to ~2 mm from the seed edge, together with the need to consider contributions only from adjacent seeds, served as the basis for efficient lattice calculations, which allowed us to identify the key parameters affecting the lattice properties—namely, the interplay between the seed activity and spacing required to ensure sufficient coverage of the tumor with therapeutic dose levels.

Hexagonal arrangements of seeds—which can be expected a priori to be the optimal geometry—were indeed shown to be much more efficient in utilizing the seed activity than square lattices, even if the spacing of the latter is reduced to maintain the same ^{224}Ra activity per unit volume. Therefore, it is recommended that, when possible, seeds are inserted using a hexagonal grid, rather than a square one as is commonly done in low-dose-rate brachytherapy.

The most important parameters affecting the DaRT dose field are the diffusion lengths of ^{220}Rn and ^{212}Pb, with a less significant contribution by the ^{212}Pb leakage probability. Assuming, as a starting point, an ideal lattice geometry (i.e., perfect seed placement on the hexagonal grid points) and a uniform medium, we investigated the dependence of the seed activity required to guarantee a nominal alpha dose of 10 Gy (as a convenient reference for a therapeutic alpha dose) on the diffusion lengths for a given seed spacing. We found that the spacing must be adjusted based on the diffusion lengths to allow for therapeutic dose coverage with μCi-scale seeds. A spacing of 5 mm can be used for high-diffusion tumors (e.g., $L_{Pb} \gtrsim 0.5$ mm or $L_{Rn} \gtrsim 0.4$ mm) using few-μCi seeds, but requires 10-fold higher seed activities for low-diffusion tumors (e.g., $L_{Rn} \lesssim 0.3$ mm and $L_{Pb} < 0.2$ mm). Such tumors can be effectively covered

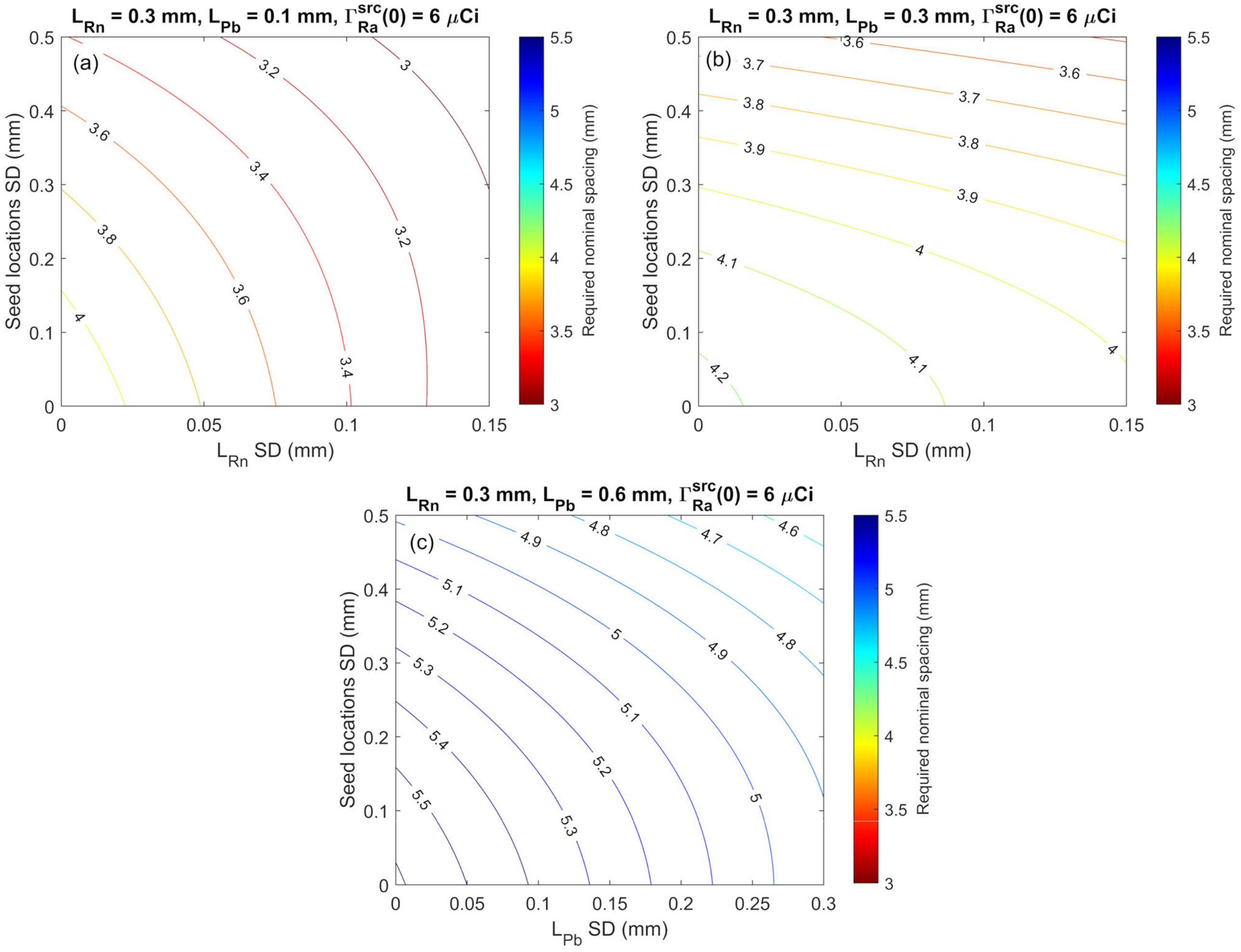

FIGURE 11 6-μCi/cm seeds: the required nominal spacing in order to ensure, with 90% confidence, that at least 15 Gy are delivered in the cold-spot of a single triangular lattice cell as a function of uncertainties (standard deviations) in seed locations and the dominant diffusion length for the low lead diffusion case (a), equal diffusion lengths case (b), and high lead diffusion case (c). In all cases, $P_{leak}(Pb) = 0.5$, $P_{des}(Rn) = 0.45$, $P^{eff}_{des}(Pb) = 0.55$, $L_{Bi} = 0.1L_{Pb}$.

by few-μCi seeds if the spacing is reduced to ~4 mm. Reducing the spacing has an additional benefit: it allows using a significantly lower ^{224}Ra activity per unit volume, and therefore, enables the treatment of significantly larger tumors or several lesions without reaching systemic toxicity due to ^{212}Pb uptake in distant organs. The feasibility of seed insertion at 4-mm spacing, including the use of hexagonal grids, has already been demonstrated in ongoing clinical trials, that will be described in separate publications.

The nominal lattice calculations were followed by a sensitivity analysis, aimed at understanding how uncertainties in the model parameters affect the required lattice spacing. These were performed for three representative scenarios: low lead diffusion, high lead diffusion, and equal diffusion lengths. The results show that uncertainties in desorption probabilities and initial seed activities, under the quality control procedures of the manufacturer, have negligible effect on the required lattice spacing. The ^{212}Pb leakage probability has a stronger effect, but only in the lead-dominated diffusion scenario. In all studies, the strongest dependence was observed for uncertainties in the seed locations and diffusion lengths. Compensation for the leading uncertainties can be done by reducing the nominal seed spacing, typically by $\sim 0.8 - 1$ mm, or by increasing the initial ^{224}Ra seed activity, for example, from 3 to 6 μCi/cm (which relaxes the required spacing by $\sim$ 0.5 mm). The importance of seed placement accuracy again motivates the use of hexagonal grid templates to physically guide seed insertion.

The randomization process employed in this work is simplistic, in the sense that each random parameter is assigned a single value per seed, ignoring nonuniformities in the activity and desorption probabilities over the seed surface and local (voxel-by-voxel) variations in the tissue parameters (diffusion coefficients and clearance rate constants). Another simplification is the assumption that the seeds remain parallel to each other. Global variations in the seed parameters have—as shown above—a negligible effect on the required seed spacing. In practice, actual local variations over the seed surface are within ∼ 10% of their average values, and are, therefore, "covered" in the present analysis. Local variations in the tissue parameters are harder to model realistically and require a full 3D simulation, and angular variations in seed orientation call for a different analysis scheme than the one employed here. We defer the treatment of both issues to future studies.

Treatment plans should take into account that the diffusion lengths and ^{212}Pb leakage probability are likely not uniform, on the macroscopic scale, throughout the tumor volume. The well-vascularized regions close to the tumor edge are expected to display higher leakage and less diffusion than the tumor interior, due to the rapid clearance of ^{212}Pb by the blood and the absence of necrotic domains. Assuming a fixed lattice spacing, this requires treatment plans to adopt conservative assumptions regarding the values of the diffusion lengths and the leakage probability. This way, a plan aiming at sufficient dose coverage in outer tumor regions can be expected to yield much higher alpha doses in the interior.

The target alpha dose in the tumor periphery can be estimated based on clinical experience with low-LET radiation, by aiming for a biologically effective dose (BED) known to achieve a high rate of tumor control, with an appropriate choice of relative biological effectiveness (RBE) value for alpha particles. To compensate for uncertainties in the RBE, seed placement errors (relative to the ideal grid) and local variations in the diffusion lengths, it may be advisable to plan for a higher alpha dose than the nominal value BED considerations require.

The current study does not consider additional contributions from the beta and gamma dose in DaRT lattices, which will be addressed in a separate publication. For 3-μCi/cm seeds, typical levels of the low-LET dose are $\sim 10-20$ Gy at the center of gravity of seed triplets, depending on the lattice spacing and the ^{212}Pb leakage probability. This extra dose, although subdominant compared to the alpha dose with its associated high RBE, can, in fact, have a non-negligible effect on local tumor cell survival, and can, therefore, allow relaxing the seed spacing to some extent. Given the low activity of the seeds, the low-LET dose also drops to negligible levels ∼ 3 mm away from the outermost seeds.

Importantly, the results of the first-in-human DaRT clinical trial on locally advanced and recurrent squamous cell carcinoma of the skin and head and neck,[6] showed that "free-hand" placement of 2 μCi seeds at a nominal spacing of 5 mm led to a 100% positive response (tumor shrinkage by $> 30\%$ in the longest diameter, 28/28), and 79.6% complete response (CR, macroscopic disappearance of the tumor, 22/28), with 77% (17/22) of the tumors displaying CR not relapsing in the follow-up period. Considering placement errors (enhanced because of the lack of grid) and uncertainties in the local diffusion lengths, the high success rate of this trial may indicate that either the diffusion lengths were larger than expected from mice experiments, or that additional effects, not accounted for in the DL model, were in play. Such effects may be of a physical nature—for example, enhanced spread of the diffusing atoms by convective effects—or of a biological origin—for example, damage to the tumor blood supply, activation of an immune response, or bystander effects.[7] The possible role of these mechanisms will be the subject of future studies.

5 | CONCLUSION

This work reports on alpha dose calculations in DaRT seed lattices and their sensitivity to the geometry and model parameters. A parameter scan was performed where the uncertainties related to seed specifications, tissue characteristics, and the seed placement were considered. The required seed spacing was shown to be mostly affected by variations in seed placement and the dominant diffusion length. A therapeutic alpha dose (in the range of $\sim 10-20$ Gy) was shown to be achievable with a nominal seed spacing of $\sim 3.5-4.5$ mm, including compensation for uncertainties in the main model parameters. This spacing can be relaxed by ∼ 0.5 mm by increasing the initial ^{224}Ra seed activity from 3 to 6 μCi/cm. While multiple seed placement at such spacing is challenging, ongoing clinical studies, to be described elsewhere, indicate that they are clinically feasible.

ACKNOWLEDGMENTS

The authors wish to thank Prof. Itzhak Kelson for his thoughtful advice. This work was partly funded by Alpha TAU Medical Ltd (ATM). ATM was not involved in the study design and analysis, the writing of this article or the decision to submit it for publication.

CONFLICT OF INTEREST

L.A. is a minor shareholder of ATM. The scholarships of G.H. and A.R. are partially paid by ATM and that of M.D. is fully paid by ATM through a research agreement with Ben-Gurion University of the Negev. L.A. is co-inventor of several DaRT-related patents. G.H. and M.D. are co-inventors of a pending patent application on DaRT dose calculations.

DATA AVAILABILITY STATEMENT

No experimental data were used in this article. The numerical code, along with all numerical results presented here, are available upon request to the corresponding author.

REFERENCES

1. Arazi L, Cooks T, Schmidt M, Keisari Y, Kelson I. Treatment of solid tumors by interstitial release of recoiling short-lived alpha emitters. *Phys Med Biol*. 2007;52:5025-5042.
2. Arazi L. Diffusing alpha-emitters radiation therapy: approximate modeling of the macroscopic alpha particle dose of a point source. *Phys Med Biol*. 2020;65:015015.
3. Lagrange JL. Recherches d'arithmètique. *Nouveaux M'emoires de l'Acad'emie Royale des Sciences et BellesLettres de Berlin*. 1773;3:693-758. Reprinted in Oeuvres.
4. Rivard MJ, Coursey BM, DeWerd LA, et al. Update of AAPM task group no. 43 report: a revised AAPM protocol for brachytherapy dose calculations. *Med Phys*. 2004;31:633-674.
5. Arazi L, Cooks T, Schmidt M, Keisari Y, Kelson I. The treatment of solid tumors by alpha emitters released from 224 Ra-loaded sources-internal dosimetry analysis. *Phys Med Biol*. 2010;55:1203.
6. Popovtzer A, Rosenfeld E, Mizrachi A, et al. Initial safety and tumor control results from a "First-in-Human" Multicenter prospective trial evaluating a novel alpha-emitting radionuclide for the treatment of locally advanced recurrent squamous cell carcinomas of the skin and head and neck. *Int J Radiat Oncol Biol Phys*. 2019;106:571-578.
7. Pouget JP, Constanzo J. Revisiting the radiobiology of targeted alpha therapy. *Front Med*. 2021;8:692436.

How to cite this article: Heger G, Dumančić M, Roy A, Arazi L. Alpha dose modeling in diffusing alpha-emitters radiation therapy. Part II: Lattice studies. *Med Phys*. 2023;1-12. https://doi.org/10.1002/mp.16155