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A Comprehensive Review of Diffusing Alpha-Emitters Radiation Therapy (DaRT): From Dosimetry to Its Biological Effectiveness

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ABSTRACT

Diffusing alpha-emitters radiation therapy (DaRT) represents a groundbreaking development in cancer therapy, offering a solution to the limitations of conventional radiation therapy. By deploying ^{224}Ra embedded seeds, DaRT achieves targeted delivery of high-dose alpha particles directly to tumor sites, showing considerable efficacy in tumor control and minimal damage to adjacent healthy tissues. This comprehensive review analyzes the published literature regarding mechanisms, seed production, dose calculation, measurement, and biological experiments related to DaRT. It includes in-depth discussions on mathematical models, Monte Carlo simulations for dose distribution, real-time *in vivo* dosimetry developments, and biological experiments both *in vitro* and *in vivo*. Clinical trial outcomes are also examined to evaluate the therapy's effectiveness in various cancer types. DaRT utilizes ^{224}Ra-labeled seeds, using the decay chain of ^{224}Ra to deliver alpha particles effectively within a tumor. Several asymptotic diffusion-leakage models were developed to calculate the alpha dose distribution of DaRT. *In vivo* dosimetry techniques have been developed for real-time monitoring. Biological experiments demonstrated the cytotoxic effects of DaRT across various cancer cells, with varying radiosensitivity. Additionally, the enhanced effects of combined therapy with chemotherapy and immunotherapy were suggested by many *in vivo* studies. Clinical trials have shown high complete response rate in squamous cell carcinoma, with minimal side effects, suggesting DaRT's feasibility and safety. DaRT emerges as a highly localized cancer treatment method with minimal side effects compared to traditional radiation therapy. It directly ablates tumors and potentially enhances immune responses, indicating a significant advance in cancer therapy. Future research and ongoing clinical trials will further elucidate its efficacy across different cancer types and in combination with other treatments.

Keywords: Diffusing Alpha-Emitters Radiation Therapy, Brachytherapy, Alpha Particle Therapy

Review

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Introduction

Radiation therapy (RT) is a double-edged sword. External beam RT has played a crucial role in the realm of cancer treatment, offering superior local tumor control even without invasive approaches. Patients who received RT exceeded 50% of the total cancer patients, either as monotherapy or combination therapy [1]. However, external radiation beams cause adverse side effects by penetrating normal tissues lying along the trajectory of the beam. This feature detrimentally affects tumor control because the prescription dose to the target should be restricted according to the tolerance of healthy

tissues. Additionally, the extensive dose distribution of traditional RT contributes to the immunosuppressive effect, which impairs the efficacy of combination therapy between RT and immunotherapy [2, 3]. For example, Kim et al. [4] reported a 50% reduction in lymphocyte count 8 days after the initiation of RT.

In recent years, cancer treatment using alpha particles has emerged as a promising avenue in the realm of targeted cancer treatments [5]. Alpha particles, characterized by their high linear energy transfer (LET) of 50–230 keV/μm, form intense and localized dose distribution into adjacent cells within 100 μm [6]. This property of high LET inflicts dense cytotoxic damage through a direct effect, decreasing the dependency on oxygen and the cell cycle compared to X-rays. Hence, alpha particles generate complex strand break patterns, thereby rendering damaged tumor cells unrepairable. However, difficulties exist in delivering sufficient energy to the target due to the multistep decay chain, a physical trait of alpha emitters [7]. The conjunction between the recoiling progeny and ligand is destabilized after alpha decay [8]. Thus, the alpha-emitter is released to the body before it reaches tumor cells, leading to an increase in radiation dose to normal tissues.

Among the novel approaches in the realm of alpha particle therapy, diffusing alpha-emitters radiation therapy (DaRT) has gained substantial attention. DaRT involves a novel strategy that addresses the challenges associated with delivering alpha particles to solid tumors [9]. Many positive reports have demonstrated the feasibility of this treatment as a monotherapy to eradicate tumors [10–12]. For example, D'Andrea et al. [12] reported a 100% complete response rate in skin cancer cases, without long-term toxic effects. As well as the ability to eradicate locally advanced tumor cells, DaRT can increase the efficacy of immunotherapy with immune checkpoint inhibitors by stimulating the generation of antitumor immune cells, called the abscopal effect [10]. In this paper, we aim to provide a comprehensive review of DaRT with respect to its mechanisms and applications.

Introduction to Diffusing Alpha-Emitters Radiation Therapy

1. Mechanisms

The diffusing alpha-emitter RT is a novel brachytherapy using alpha particles (4–9 MeV) from ^{224}Ra-labeled seeds inserted into the tumor [9]. In conventional alpha particle therapy, the excessively short range of the alpha particle restricts the delivery of sufficient energy to the cells further than 100 μm from the source. Such localized dose distribution involves therapeutic limitations especially in solid tumor. To address this, DaRT harnesses the complex decay chain of ^{224}Ra, with daughters diffusing within the target. Once ^{224}Ra labeled to the seed decays, the isotope transformed into ^{220}Rn escapes from the seed due to the energy of the recoil nucleus (100–170 keV). Subsequently, the daughters undergo diffusion and decay, delivering the energy to the relatively distant region.

The initial decay of ^{224}Ra in the source seeds results in the release of daughter nuclei, which have sufficient kinetic energy to reach the adjacent cells around the source. However, there is a 40% probability that recoil nuclei will bounce back into the seed during decay, preventing the subsequent diffusion of ^{220}Rn after the initial decay [13]. The atoms that remain inside the seed either escape through subsequent alpha decay or continue to stay within, with a desorption probability of 55% for ^{212}Pb [13]. Among the diffusing elements, ^{212}Pb (with a half-life of 10.64 hours) and ^{212}Bi (with a half-life of 60.6 minutes) should be primarily considered due to their relatively long half-lives. It is assumed that the daughter nuclei, excluding these, deposit all their energy at the site where ^{212}Pb and ^{212}Bi decay.

2. Seed Production

In study of Arazi et al. [9], the DaRT seed production commences with a thin layer generator coated with ^{228}Th which emits positive ions of ^{224}Ra via recoil. These ions are collected on a negatively charged DaRT wire, positioned near the generator. This process spends a few days collecting sufficient ions due to the half-life of ^{224}Ra (3.7 days). The wire then undergoes heating, allowing radium atoms to diffuse into deeper surface. This method prevents the prompt emission of alpha particles, when implanted in tumors, effectively delivering localized RT.

Dosimetry

1. Mathematical Models

Measurements of DaRT dose distribution is restricted due to the short range of alpha particle. Thus, mathematical models provide a practical alternative that allows for estimating dose distribution without the need for complex devices.

The study of Arazi et al. [9, 13], discussed a simplified ap-

proach to model the transport of alpha-emitting isotopes in tumor tissues for DaRT. The diffusion-leakage model was employed to estimate the density of predominant diffusive migration of isotopes (^{220}Rn, ^{212}Pb, and ^{212}Bi) at a specific time. The cumulative behavior of the isotopes was provided by integrating the diffusion-leakage models. To compute macroscopic dose of alpha particles, the respective concentration of atoms calculated using the diffusion-leakage model is multiplied by the kinetic energies of the emitted alpha particles, mass density, and decay constant. The macroscopic alpha particle dose was divided into two components: ^{220}Rn/^{216}Po and ^{212}Bi/^{212}Po. For ^{220}Rn/^{216}Po, the dose calculations are straightforward due to the short half-life of ^{220}Rn. An approximate formula was derived for the dose, which quickly approaches its asymptotic value within about 1 to 2 weeks. On the other hand, the ^{212}Bi/^{212}Po dose is more complex due to the chemical and physical traits of ^{212}Pb. Isotope ^{212}Pb is effectively eliminated through its conjunction with proteins or blood components. Additionally, the relatively long half-life of ^{212}Pb travels an extended distance from the source. For these reasons, the additional equation for ^{212}Bi/^{212}Po dose considered aspects such as the effective desorption probability of ^{212}Pb. According to the model, seed containing a few μCi of ^{224}Ra has the potential to generate therapeutic region within a range of 4 to 7 mm.

In two series of publications by Heger et al. [14, 15], in-depth analysis of alpha dose modeling in DaRT for solid tumors. Part 1 presents a model with one- and two-dimensional numerical schemes for time-dependent solutions, emphasizing that the one-dimensional solution is accurate within about 2 mm from the seed edge. It is suitable for parametric studies of DaRT seed lattices, whereas the more complex two-dimensional solution is recommended for dose lookup tables. Part 2 extends these findings to lattice structures, showing that a hexagonal lattice with 3.5–4.5 mm spacing using seeds of a few μCi/cm of ^{224}Ra is effective. The study highlights the significant impact of uncertainties in seed placement and diffusion lengths on lattice spacing, with crucial implications for practical applications and treatment planning, despite certain limitations like not accounting for tumor nonuniformities.

Zhang et al. [16] developed a two-dimensional finite element solution for the alpha dose diffusion-leakage model in DaRT, implemented using the FEniCS software library (www.fenicsproject.org). This approach allows for modeling more complex geometries and heterogeneous matters. The study validates the solutions against the one- and two-dimensional DaRT models, showing minimal discrepancies.

2. Monte Carlo Simulation

Fedorchenko and Alani [17] conducted the first Monte Carlo (MC) study for DaRT. This study did not provide the entire dose distribution but investigated the desorption probabilities of atoms, their distribution inside the seed, and the contribution of alpha emitters inside the seed to surrounding tissue. As a result, at a 40% desorption probability of ^{220}Rn, the impregnated layer thickness on the seed was 3.5 nm. After decay, average depths inside the seed were 6.4, 11.2, and 13.8 nm, respectively for ^{220}Rn, ^{212}Pb, and ^{208}Pb. The calculated dose to tissue from decay inside the seed was found to exceed 2.9 Gy for an initial ^{224}Ra activity of 3 Ci. The desorption probability of ^{220}Rn showed 39.8%, followed by the desorption probabilities of ^{216}Po (15%) and ^{212}Pb (12%). Additionally, it reported that recoil atoms travel 100–200 nm in tissue, with average radial distances around 30 nm, except for ^{208}Pb of 39.2 nm.

In contrast to previous studies on alpha dose calculation, Epstein et al. [18] focused on the low-LET dose from electrons and photons using the MC tools; EGSnrc [19] and FLUKA [20]. The source geometry was modeled on the basis of the isotope positions defined by the concentration map of each isotope calculated using the diffusion-leakage model. There was a 6%–11% difference between the two MC tools, which was caused by the energy cutoff values. The source contributed to the formation of 60%–80% low-LET dose, depending on the ^{212}Pb and ^{224}Ra activities. In a hexagonal lattice with 4 mm spacing, the minimal low-LET dose between three adjacent 3 μCi/cm ^{224}Ra sources was approximately 30 Gy. The low-LET dose drops below 5 Gy approximately 3 mm away from the outermost source in the lattice. This study also investigated the effect of low-LET dose on cell survival using a stochastic linear-quadratic model. Regarding tumor control probability, a cell survival from 0.007 to 0.6 was achieved corresponding to a clinical α value range of 0.02–0.2 Gy^{-1}. Enhancing source activity and reducing the desorption probabilities of ^{224}Ra are crucial for increasing the dose from electrons and photons for tumor ablation without insertion of additional DaRT seeds.

3. Dose Measurement

Su et al. [21] focused on the development of real-time *in vivo* dosimetry in DaRT, alpha-RAD, based on metal-oxide-

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semiconductor technology. The study involved investigating the alpha-RAD's sensitivity and dose-response to alpha particles of 5.49 MeV energy emitted by ^{241}Am. Alpha-RAD showed good linearity with dose and an increase in sensitivity with higher external bias voltages, peaking at 60 V. The device's compactness allowed a brachytherapy needle to be placed next to ^{224}Ra seed implants in tumors. The study confirmed alpha-RAD's suitability for real-time *in vivo* dosimetry in DaRT, with a linear dose-response relationship and good sensitivity to alpha particles. The limitation was the irradiated dose range, which was narrower compared to the broader range in DaRT.

Tepper et al. [22] employed thermography to monitor tumor growth in mice, comparing those treated with DaRT and inert wires. Thermal images of three mice were used to estimate tumor size and track temperature variations. DaRT-treated tumors exhibited lower metabolic activity and heat production than those with inert wires. Tumor area increased by 78% in DaRT-treated mice versus 165% in those with inert wires. DaRT tumors were cooler and showed greater temperature reduction rates than inert wire tumors. The study suggested two key factors for accurate tumor size estimation using thermal imaging: tumor morphology's impact on size estimation and the inverse relationship between tumor size and temperature difference from healthy skin.

Biological Experiments

1. *In Vitro* Experiments

The radiosensitivity of various tumor cells against DaRT has been investigated through cell survival analysis [23–29]. The studies reported the mean lethal dose (D_0) to indicate the radiosensitivity of cells. D_0 was derived fitting on the following exponential function $f(D) = e^{-D/D_0}$, where D and $f(D)$ indicate dose and survival fraction at D, respectively. In the study of Milrot et al. [28], the inhibitory dose at 50% survival (ID50) was used to quantify the radiosensitivity of tumor cells. Table 1 included the radiosensitivity parameters, including D_0 and ID50, of each tumor cell according to previous studies.

Cooks et al. [23] focused on squamous cell carcinoma (SCC) cells, SQ2, exposed to alpha particles. A significant inhibition of cell proliferation was observed, with a lower surviving fraction at 2 Gy. The survival curve indicated that direct hits by alpha particles effectively killed SCC tumor cells, with calculated D_0 values between 1.3 Gy and 1.6 Gy.

Cooks et al. [24] evaluated the antiproliferative effects of alpha particles on lung carcinoma cells using the XTT assay. Higher activity levels and longer exposure durations led to increased cell toxicity. DaRT effectively inhibited cell proliferation and colony formation ability in LL2, NCI-H520, and A427 cells, specifically D_0 values at 0.8 Gy for LL2 and 1.5 Gy for NCI-H520 cells.

Table 1. Radiosensitivity Parameters of Tumor Cells Irradiated by Alpha Radiation ^{224}Ra

Cell line	Parameter, unit	Value	Reference
SQ2	D_0, Gy	1.44±0.12	[23]
LL2	D_0, Gy	0.8	[24]
NCI-H520	D_0, Gy	1.5	[24]
C32	D_0, Gy	1.17±0.09	[25]
FaDu	D_0, Gy	0.64±0.06	[25]
HCT15	D_0, Gy	1.12±0.1	[25]
PC3	D_0, Gy	0.86±0.11	[25]
U87	D_0, Gy	Not reported	[25]
Panc02	D_0, Gy	1.1±0.1	[26]
CT26	D_0, Gy	1.25±0.34	[27]
FaDu	D_0, Gy	0.69±0.09	[27]
Panc1	D_0, Gy	0.95±0.06	[27]
Panc02	D_0, Gy	1.09±0.04	[27]
NCI-H520	D_0, Gy	1.5±0.14	[27]
SQ2	D_0, Gy	0.85±0.02	[27]
U87	D_0, Gy	1.2±0.2	[29]
C33A	ID50, Gy	0.24	[28]
CaSki	ID50, Gy	0.12	[28]
HeLa	ID50, Gy	0.2	[28]
SiHa	ID50, Gy	0.4	[28]

Values are presented as mean±standard deviation unless otherwise indicated.
D_0, the mean lethal dose; ID50, the radiation dose required to inhibit cell survival by 50%.

Cooks et al. [25] assessed the survival fraction of various cancer cell lines, including C32, HCT15, PC3, and FaDu, based on colony formation assays. The sensitivity of these cells to alpha particles varied, with C32 showing relative resistance and FaDu being more sensitive than other type of cells. The different D_0 values implicated that the DaRT efficacy may depend on the radiosensitivity of tumor cells to alpha particles.

Horev-Drori et al. [26] investigated the combined effect of alpha particles and chemotherapy on pancreatic cancer cells. It found that alpha particles, specifically when combined with gemcitabine or 5-fluorouracil (5-FU), were more effective in cell killing. The D_0 values for Panc02 cells were around 1.2 Gy, and the study highlighted the efficacy of alpha particles in causing irreparable DNA damage.

The radiosensitivity of different cell lines to the alpha particle was investigated in the study of Lazarov et al. [27]. The

mean lethal dose (D_0) and microdosimetric parameter (Z_0, specific energy) were determined through *in vitro* irradiation to cell lines (CT26, FaDu, NCI-H520, Panc1, Panc02, and SQ2). The radiosensitivity among cell lines was highest in order of FaDu, SQ2, Panc1, Panc02, CT26, and NCI-H520. D_0 values ranged from 0.69 Gy (most sensitive) to 1.50 Gy (least sensitive) and Z_0 varied from 0.56 Gy to 1.32 Gy across cell lines.

Milrot et al. [28] explored the effectiveness of DaRT in combination with methyl jasmonate (MJ) on cervical cancer cells. Cell survival was assessed by the proliferation and clonogenicity assays using the XTT. The combination showed potent cytotoxic effects, suggesting the need for further *in vivo* studies.

Nishri et al. [29] combined alpha particle irradiation with temozolomide (TMZ) on U87 cells, revealing enhanced cytotoxic effects compared to mono-treatments. The D_0 value for alpha particles was about 1.2 Gy, and the combination with TMZ significantly reduced the surviving fraction. The study supported the superiority of combining DaRT with standard-of-care drugs for improved tumor control.

These studies demonstrated that the DaRT effectively inhibits tumor growth in various cancer types. The effectiveness varies depending on the intrinsic sensitivity of cell lines to alpha particles. Combining DaRT with chemotherapy agents shows synergistic effects, enhancing tumor control.

2. *In Vivo* Experiments

Numerous *in vivo* studies have demonstrated the feasibility of DaRT in ablating various solid tumors (breast, colon, glioblastoma, lung, melanoma, myeloma, pancreatic adenocarcinoma, prostatic adenocarcinoma, and SCC). Table 2 presents a comparison of tumor volume development following DaRT treatment versus control groups using inert wire. These studies reported the capability of DaRT not only as a standalone therapy in eradicating tumor cells but also its promising role in combined therapy with chemotherapy and immunotherapy.

1) Breast cancer

In the study by Domankevich et al. [30], the synergistic effects of intratumoral polyinosinic-polycytidylic acid polyethyleneimine (polyIC(PEI)) and DaRT were investigated in human-derived breast cancer cells (4T1). Retardation in tumor growth and reduction in lung metastases was reported after combined treatment with the DaRT and polyIC(PEI). Quantitatively, there was an 82% decrease in tumor size and a decrease in lung metastase incidence, down to 23% compared to 75% in the control group. The combination treatments with low-dose cyclophosphamide and systemic low-dose decitabine also showed notable effects in reducing tumor volume and preventing metastases-related death.

2) Colon cancer

In colon cancer, human-derived cells (HCT15) and mice-derived cells (CT26) were used to investigate the effect of DaRT on tumor development [25, 31–34]. The study by Cooks et al. [25] focused on the effects of DaRT on tumor development, specifically examining HCT15. Thirty-eight days after the initiation of the treatment, the average volume of the tumors treated with the DaRT wires was 4.7 times smaller than those in the inert wire-treated group.

In a series of studies, different treatments were evaluated for their efficacy in removing CT26 tumors, yielding promising results. Keisari et al. [31] reported a 67% complete response rate in post-treatment, with enhanced resistance to tumor rechallenge. An activated immune response, reduced lung metastatic load, and prolonged survival were supported by the results [31]. Confino et al. [32] observed increased survival and slower tumor growth in DaRT-treated mice compared to controls, with 63%–77% of these mice resisting re-inoculated tumor growth. This suggested a strong antitumor immune response and a reduction in lung metastases, indicating DaRT's efficacy in controlling metastatic spread. Reitkopf-Brodutch et al. [33] showed that combining DaRT with various immunomodulators significantly retarded tumor growth and increased cure rates compared to individual treatments. This combination therapy also led to delayed tumor development upon rechallenge, indicating a tumor-specific immune response. Additionally, Domankevich et al. [30] demonstrated that inserting one or two ^{224}Ra-loaded wires into tumors significantly inhibited tumor growth. specifically, the tumor volume of mice treated with two DaRT wires decreased threefold. This effect was further enhanced when combined with 5-FU chemotherapy, leading to substantial tumor growth retardation and higher rates of complete response.

3) Glioblastoma

Cooks et al. [25] investigated the tumor volume development of the human-derived glioblastoma cells (U87) against DaRT. The study reported that after 24 days, the average tumor volume in the DaRT-treated group was 10 times smaller

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Table 2. Mice Experiments for Investigating Tumor Volume Development in Diffusing Alpha-Emitters Radiation Therapy with ^{224}Ra

Activity (kBq)	Adjuvant	Cell line	Time (d)	Volume ratio[a)]	Reference
11–12		CT26	29	0.63	[33]
22–24		CT26	29	0.34	[33]
22–24	5-FU	CT26	28	0.21	[33]
11.5–29.7		SQ2	30	0.50	[36]
23–59.4		SQ2	33	0.21	[36]
17 – 22		SQ2 (3–4 mm)	36	0.05	[23]
17 – 22		SQ2 (6–7 mm)	20	0.13	[23]
17 – 22		CAL27	15	0.72–0.80	[23]
17–43		Panc02	27	0.52	[26]
17–43	Gemzar	Panc02	27	0.48	[26]
20–24		C32	15	Insignificant	[25]
20–24		HCT15	38	0.21	[25]
20–24		PC3	29	0.33	[25]
20–24		U87	24	0.10	[25]
21.3–35.7		A427	7	0.60	[24]
21.3–35.7		LL2	21	0.39	[24]
21.3–35.7		NCI-H520	27	0.40	[24]
27–39		DA3	24	0.18	[35]
27–39	Sildenafil	DA3	24	0.33	[35]
35–42	PBS	DA3	51	0.63	[35]
35–42	Cyclophosphamide	DA3	51	0.63	[35]
40	PBS	CT26	13	0.39	[34]
40	polyIC	CT26	13	0.22	[34]
40–50		DA3	14	0.69	[32]
40–50	CpG	DA3	14	0.62	[32]
40–50		CT26	14	0.38	[32]
70–75	PBS	4T1	29	0.65	[30]
70–75	polyIC(PEI)	4T1	29	0.24	[30]
85		4T1	18	0.40	[30]
85	polyIC(PEI)+CP	4T1	18	0.46	[30]
75	IgG	SQ2	18	0.21	[37]
75	aPD-1	SQ2	18	0.16	[37]
75–110		U87	20	0.46	[29]
75–110	TMZ	U87	20	0.17	[29]
75–110	BEV	U87	23	0.23	[29]
75–110	IgG	U87	23	0.19	[29]
Unknown, but 10 Gy delivered		CT26	35	0.26	[31]
Unknown, but 10 Gy delivered	CpG	DA3	Not reported	0.20	[31]

The table is sorted in ascending order by activity.
5-FU, 5-fluorouracil; PBS, phosphate buffered saline; polyIC, polyinosinic-polycytidylic acid; CpG, CpG oligodeoxynucleotide; polyIC(PEI), polyinosinic-polycytidylic acid polyethyleneimine; CP, cyclophosphamide; IgG, immunoglobulin G; aPD-1, anti-programmed death-1; TMZ, temozolomide; BEV, bevacizumab.
[a)]In this review, volume ratio was defined as the volume of tumor treated by diffusing alpha-emitters radiation therapy (DaRT)/the volume of tumor treated by inert wire. A volume ratio less than 1 indicates the superiority of DaRT, while a ratio greater than 1 suggests the opposite.

compared to that in the inert wire-treated group. Interestingly, there was one case of complete regression of the tumor in the DaRT-treated group and one in the inert wire-treated group. This suggested that even inert wire insertion can influence tumor behavior, due to mechanical disruption or other factors not related to radiation.

Nishri et al. [29] investigated the combination of DaRT and chemotherapy agents, including TMZ and bevacizumab (BEV). The DaRT with TMZ notably decreases tumor growth and extends the duration before tumors reach a quintuple increase in volume. Additionally, integrating DaRT with BEV was particularly effective in larger tumors, leading to the eradication of up to 29% of tumors and no recurrence over 3 months. This enhanced efficacy of the combined therapy could be due to the increased distribution of alpha particles within the tumor and a diminished blood supply to the tumor, maximizing the

exposure of tumor cells to alpha radiation.

4) Lung cancer

Cooks et al. [24] reported promising results in treating lung carcinoma with DaRT, particularly for LL2, A427, and NCI-H520 cell lines. For LL2 murine lung carcinoma, DaRT resulted in a 49% decrease in tumor growth and improved life expectancy by 48%, with a 39% reduction in tumor volume and an increase in mean survival of 31%–44% compared to control groups. In human lung carcinoma (A427), over 80% of A427 tumors treated with DaRT were reduced, including complete eradication in 57% of cases. Additionally, a significant survival benefit was observed, with 65% of mice treated with DaRT compared to the inert wire-treated group. On the other hand, NCI-H520 tumors exhibited a lower response, with a 42% inhibition in tumor growth. These results not only demonstrate the potential of alpha particles in treating lung cancer but also indicate varying responses among different cell lines.

5) Melanoma

In the study by Cooks et al. [25], the C32, a human-derived melanoma cell line, was utilized to evaluate the effectiveness and dose distribution of DaRT. Among the various cell lines, the C32 tumors had the smallest average area corresponding to a 10 Gy dose of alpha particles, meaning restricted diffusion of alpha particles. C32 tumors implanted in mice showed an insignificant decrease in tumor growth compared to an inert wire-treated group, but there was an improvement in survival rates.

6) Myeloma

In the study conducted by Confino et al. [32], mice treated with DaRT exhibited a notable decrease in the size of their myeloid (DA3) tumors. The average volume of tumors in the group treated with DaRT was approximately 2 to 2.6 times smaller than that of the group treated with inert wires. Additionally, a robust antitumor immune response was observed in the mice receiving DaRT treatment. The average survival of mice treated with a combination of DaRT and CpG oligodeoxynucleotide (CpG) was significantly improved, at 99 days, in contrast to those receiving only DaRT treatment (83 days), only CpG (88 days), or no treatment at all (64 days). This enhanced immune response was further demonstrated by the slower growth of tumors re-inoculated into the DaRT-treated mice and decreased lung metastases compared to the control group.

In the study by Confino et al. [35], DaRT therapy was improved when combined with inhibitors of immunosuppressive cells, including myeloid-derived suppressor cell (MDSC) and Treg inhibitors, as well as CpG. This combined therapy led to the complete elimination of primary tumors in 15% of the mice (three out of 20), while substantially reducing tumor size and the spread of lung metastases in the rest of the group [35]. In the group of 20 mice receiving DaRT+immunomodulators, six achieved total tumor regression. The remaining 14 exhibited inhibited tumor growth, with the mean tumor size being 67.6 ± 61.3 mm^3 at 26 days post-treatment, in contrast to the 177.7 ± 56.4 mm^3 observed in the control group. Even without the addition of CpG, DaRT in conjunction with Treg or MDSC inhibitors diminished tumor volumes, lung metastatic spread, and mortality rates compared to the control group. The combined treatment of DaRT with these immunomodulators led to a significant decrease in metastatic occurrence, with only about a third of the treated mice developing lung metastases, compared to over half in the group treated with inert wire and the same set of drugs.

Keisari et al. [31] investigated the enhanced effect of DaRT on antitumor immunity, demonstrating its effectiveness in both suppressing primary tumor growth and stimulating the immune system to resist subsequent tumor cell inoculation. DaRT combined with CpG, an immune stimulant, showed enhanced performance in the DA3 tumor model known for its lower immunogenicity. In evaluations of tumor volume and immune response, it was observed that tumors treated with combined therapy exhibited a substantial size reduction, averaging 35 ± 8 mm^3, as opposed to 206 ± 64 mm^3 with DaRT alone, and 174 ± 90 mm^3 with inert wires and CpG. Furthermore, DaRT induced a targeted antitumor immune response against DA3 tumor cells, leading to decreased metastasis and the activation of tumor-targeting immune cells. In DA3 cell lines, 67% of the mice treated with DaRT showed no tumor growth, a significant improvement over the 33% observed in mice treated with inert wires.

7) Pancreatic adenocarcinoma

Horev-Drori et al. [26] investigated the efficacy of combining gemcitabine and 5-FU with DaRT in pancreatic cancer treatment. The study reported that DaRT inhibited the proliferation of Panc02 and significantly reduced tumor growth, especially when combined with chemotherapy agents like 5-FU and gemcitabine. This combination therapy demon-

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strated a pronounced synergistic effect, resulting in tumor sizes that were up to four times smaller compared to those treated with inert wire after 25 days. The most significant reduction in tumor size was noted during the first 12 days following the treatment.

8) Prostatic adenocarcinoma

Cooks et al. [25] showed the effectiveness of DaRT in inhibiting the growth of the human-derived prostate adenocarcinoma cell line (PC-3). Athymic mice implanted with PC-3 tumors received either DaRT or inert wire treatment. After 29 days of DaRT, tumors were on average three times smaller in volume compared to those treated with inert wires.

9) Squamous cell carcinoma

Cooks et al. [23] conducted a study on the effectiveness of DaRT in damaging SCC cells. In their experiments with SQ2 cell lines, the application of a single DaRT source to 6–7 mm SCC tumors in mice resulted in varied responses in over 45% of the cases, ranging from temporary shrinkage to complete elimination of the tumors. In smaller tumors measuring 3–4 mm in diameter, the volume of tumors treated with DaRT was found to be 19 times smaller than that of the control group after 5 weeks. The survival rate for mice treated with DaRT exceeded 90% 35 days after the tumor inoculation, a significant improvement compared to the survival rate of the control group (< 10%). Regarding the treatment of human-derived CAL27 cells, there was an 80% reduction in tumor size within the first 2 weeks, with 30% of these cases showing either a temporary or a permanent disappearance of the tumor in that period. The study determined that DaRT is effective in inflicting severe damage to primary SCC tumors, with a strong possibility of a decrease in metastatic progression.

Cooks et al. [36] explored the effects of using DaRT with the chemotherapy drug cisplatin on SCC tumors. This combination not only inhibited the growth of SQ2 cells but also triggered increased cell apoptosis. Tumors treated with two DaRT wires+cisplatin setup were 14 times smaller, while those with a single DaRT wire+cisplatin were three times smaller compared to the control group. The average overall survival of mice receiving only cisplatin was 51.4 days, while those treated with DaRT wires alone lived for an average of 66.5 days. The group that received the combined treatment showed a notable enhancement in survival. Additionally, this combined therapy also effectively reduced local tumor growth and prevented metastatic lung cancer.

Mare et al. [37] investigated the gene expression patterns triggered by DaRT and its ability to improve the effectiveness of immune checkpoint inhibitors targeting programmed death-1 (PD-1). The combination of DaRT and anti-PD-1 treatment was more successful in inhibiting tumor progression than DaRT alone. The most significant reduction in tumor growth was observed approximately 30 days after the insertion of DaRT seeds. The combined therapy was more effective in decreasing the number of MDSCs in the spleen compared to either anti-PD-1 treatment or the control group. Furthermore, DaRT activated dendritic cells within the tumor, caused shifts in the distribution of MDSCs, and enhanced the expression of genes associated with apoptosis, interferon signaling, and myeloid cell functions.

3. Clinical Trials

The first clinical trial involved 28 patients with 31 SCC tumors, size < 5 cm, and no nodal spread [11]. The study initially enrolled four patients to demonstrate feasibility and then included an additional 24 patients to evaluate toxicity and efficacy. Treatment was delivered through radioactive seeds containing 2 μCi ^{224}Ra per seed inserted into the tumor under local anesthesia. DaRT seeds were implanted at a distance of 10 mm from major blood vessels and were removed 15–30 days after implantation. Patients were treated using ^{224}Ra DaRT seeds, averaging 27.72 seeds per lesion over about 16 days. After treatment, blood and urine radioactivity significantly reduced, with no traces after 30 days. The treatment was considered safe for organs at risk. Common side effects like pain and skin redness resolved within 15 days and no serious adverse events linked to the treatment were reported. The therapy achieved a 78.6% complete response rate, with a 44% 1-year local progression-free survival rate. Overall survival after 12 months was 75% for all patients and 93% for those with complete response. The survival rates did not significantly differ between new and recurrent tumors or based on previous radiotherapy. This positive clinical trial demonstrated the feasibility of DaRT in SCC.

Bellia et al. [10] reported the first case of the abscopal effect in DaRT. A 65-year-old female patient was treated with DaRT to eradicate synchronous cutaneous squamous cell carcinoma (cSCC). DaRT seed with an average of 100 kBq was inserted into the two of three lesions. Although precise dose planning was not conducted, it was assumed that a total of 15 DaRT seeds would cover a dose of 10 Gy into each target.

After removing seeds with 15 days from insertion, the histological examination was performed. As a result, there were no residual malignant cells, indicating complete tumor remission of DaRT. In addition, the study reported the first case of abscopal effect in a patient with multiple cSCC lesions. The size of the untreated lesion decreased naturally, suggesting the potential effect of DaRT on the immune system.

In D'Andrea et al.'s [12] clinical trial, 10 patients with various skin cancers, including primary, metastatic, and recurrent tumors, were treated using DaRT. On average, 42 seeds were prescribed to deliver a 10 Gy dose over 17 days. Patients, with a median age of 72, experienced minimal side effects from this well-tolerated treatment. Mild side effects such as grade 1–2 of erythema and edema were observed, but no significant adverse effects were reported. The average tumor size was 2.1 cm^3, with effective radiation coverage over 85%. The study demonstrated the feasibility and safety of DaRT, achieving a 100% response rate without recurrence at 24 weeks post-treatment.

On top of that, additional clinical trials are currently being conducted by multiple centers with respect to four cancer types: skin, oral cavity, prostate, and pancreatic cancer.

Summary & Discussion

DaRT represents a significant advancement in targeted cancer treatment, addressing the limitations of conventional RT. The benefits of DaRT stem from the nature of alpha particles with high LET, which cause concentrated and localized DNA damage within the tumor microenvironment. Upon irradiation, alpha particles traverse cellular membranes and interact with intracellular components, inducing complex double-strand breaks [38]. Although every cell possesses DNA repair pathways, the complex DNA damage inflicted by alpha particles incapacitates its repair. This direct interaction between radiation and DNA reduces the dependency on oxygen concentration within the tumor. Additionally, the localized release of alpha particles may modulate the tumor microenvironment by stimulating the recruitment and activation of immune cells and enhancing the antitumor immune response [39]. These cellular and molecular mechanisms contribute to the biological effectiveness of DaRT, inhibiting tumor growth.

The development of mathematical models and MC simulations has been pivotal in DaRT dose calculation, enabling precise treatment planning despite the short range of alpha particles. These models will play a crucial role in optimizing seed placement and determining the effective dose distribution within tumor tissues. The integration of diffusion-leakage models and finite element solutions, as demonstrated in studies by Zhang et al. [16] and Heger et al. [14, 15], has improved our understanding of alpha particle transport and dose distribution. These advancements are crucial in addressing the complexity of tumor geometries and heterogeneity, ensuring that DaRT can be effectively tailored to individual patient needs. The models also facilitate the exploration of different seed configurations and densities, further refining treatment efficacy and safety.

Innovations in DaRT, such as the use of external radiopaque templates, have further improved the precision and safety of the technique, particularly in cutaneous cancers. This advancement facilitates better visualization of lesions and ensures accurate seed implantation. It allows clinicians to predict the correct number of sources for tumor coverage, including subcutaneous invasion, and aids in the alignment and distribution of seeds, leading to more effective treatment outcomes. These enhancements underscore DaRT's adaptability and potential in treating a wide range of cancer types with increased accuracy and safety.

In the clinical trials referenced in this review, the treatment planning methodology for DaRT is rudimentary, primarily relying on mathematical models to administer a standardized 10 Gy dose to the tumor. While the reported local toxicities, encompassing pain, erythema, swelling, and mild skin ulceration, are generally tolerable, they have the potential to impair patients' quality of life and adversely impact the efficacy of combination therapies [10–12]. Particularly concerning are safety considerations regarding the proximity of implanted seeds to critical anatomical structures such as bone and teeth, which require attentive seed placement. Given the potential risks associated with radiation exposure, a more sophisticated planning approach is imperative to proactively anticipate and address potential side effects. Moreover, comprehensive observation of adverse side effects through multicenter cohorts with long-term follow-up should be performed to accurately assess the toxicity profile of DaRT. In this regard, image-based dose calculations can offer a promising avenue for providing quantitative guidance, facilitating the optimization of dose distribution to enhance therapeutic outcomes while minimizing adverse effects.

Extending beyond direct tumor cell eradication caused by deoxyribonucleic acid strand break, the efficacy of DaRT

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elicits antitumor immune reaction, such as the abscopal effect. This highlights its potential in combination therapies with immunotherapy. DaRT's mechanism of creating dense and localized radiation damage appears to not only destroy tumor cells but also to potentially modify the tumor microenvironment. The alteration may enhance the recruitment and activation of immune cells, leading to systemic antitumor effects, a factor that could significantly boost the effectiveness of immunotherapies. These observations suggest that DaRT could play a crucial role in comprehensive cancer treatment strategies, particularly in cases where traditional therapies alone are insufficient.

Overall, DaRT offers a promising approach for treating various solid tumors, with ongoing clinical trials exploring its application in different cancer types. The continuous refinement of dosimetry models and clinical protocols is essential to fully realize the potential of this innovative therapy in cancer treatment. As research progresses, the expanding scope of clinical trials and the integration of DaRT with other therapeutic modalities, especially immunotherapy, will likely enhance its efficacy and broaden its applicability across a spectrum of oncological conditions. This multidisciplinary approach could lead to more personalized and effective cancer treatments, further solidifying DaRT's role in modern oncology.

Conflict of Interest

Seohan Kim declares no potential conflicts of interest. Wonmo Sung has research collaborations with OncoMed (Seoul, Republic of Korea).

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Author Contribution

Conceptualization: Kim S. Methodology: Kim S. Writing - original draft: Kim S. Writing - review & editing: Sung W. Approval of final manuscript: all authors.

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