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Clinical Investigation

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

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Purpose: Our purpose was to report the feasibility and safety of diffusing alpha-emitter radiation therapy (DaRT), which entails the interstitial implantation of a novel alpha-emitting brachytherapy source, for the treatment of locally advanced and recurrent squamous cancers of the skin and head and neck.

Methods and Materials: This prospective first-in-human, multicenter clinical study evaluated 31 lesions in 28 patients. The primary objective was to determine the feasibility and safety of this approach, and the secondary objectives were to evaluate the initial tumor response and local progression-free survival. Eligibility criteria included all patients with biopsy-proven squamous cancers of the skin and head and neck with either primary tumors or recurrent/previously treated disease by either surgery or prior external beam radiation therapy; 13 of 31 lesions (42%) had received prior radiation therapy. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events version 4.03. Tumor response was assessed at 30 to 45 days at a follow-up visit using the Response Evaluation Criteria in Solid Tumors, version 1.1. Median follow-up time was 6.7 months.

Results: Acute toxicity included mostly local pain and erythema at the implantation site followed by swelling and mild skin ulceration. For pain and grade 2 skin ulcerations, 90% of patients had resolution within 3 to 5 weeks. Complete response to the Ra-224 DaRT treatment was observed in 22 lesions (22/28; 78.6%); 6 lesions (6/28, 21.4%) manifested a partial response (>30% tumor reduction). Among the 22 lesions with a complete response, 5 (22%) developed a subsequent local relapse at the site of DaRT implantation at a median time of 4.9 months (range, 2.43-5.52 months). The 1-year local progression-free survival probability at the implanted site was 44% overall (confidence interval [CI], 20.3%-64.3%) and 60% (95% CI,

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28.61%-81.35%) for complete responders. Overall survival rates at 12 months post-DaRT implantation were 75% (95% CI, 46.14%-89.99%) among all patients and 93% (95% CI, 59.08%-98.96%) among complete responders.
Conclusions: Alpha-emitter brachytherapy using DaRT achieved significant tumor responses without grade 3 or higher toxicities observed. Longer follow-up observations and larger studies are underway to validate these findings.

Introduction

Although brachytherapy, along with beta- and gamma-emitting radionuclides, has been used for the treatment of solid tumors for many years, the use of alpha-emitting radioisotopes also presents a promising approach supported by compelling radio-biologic rationale. Alpha-emitting radionuclides possess a high linear energy transfer, which produces a dense track of ionization events within cells and DNA, resulting in complex DNA damage and more effective cytotoxic effects than more sparsely ionizing forms of radiation such as gamma rays or x-rays.[1] In addition, alpha-emitting radionuclides exhibit a higher relative biologic effect compared with gamma or x-rays owing to their relative independence to cancer cellular radio-sensitivity associated with cell cycling. Finally, alpha-emitting radionuclides are relatively insensitive to hypoxia, which is associated with radio-resistance and common as tumors outgrow their vascular blood supply.

Recently, a novel method to deliver alpha particles for solid tumor radiation therapy (RT) has been described.[1,2] This method, called *diffusing alpha-emitters radiation therapy (DaRT)*, includes interstitial intratumoral placement of a radium-224 seed (3.7-day half-life) that releases short-lived (approximately 1-minute half-life) radioisotope radon-220, which results in a subsequent cascade of decay events. Radon-220 migrates in the tumor microenvironment until it decays, which is followed by the decay of its daughter radioisotope, polonium-216. Lead-212, the result of this last decay, gives rise to bismuth-212, which emits yet another alpha particle. The final result of these decay events leads to the release of alpha particles, which kill the tumor cells.[3] The decay products diffuse into the tumor from the seed over a distance of 2 to 3 mm, facilitating their ability to treat tumors when multiple DaRT seeds are deployed within a tumor. Because the radioisotope has a short half-life, nearly the entire radiation absorption occurs within the tumor, rather than elsewhere in the body.

Based on multiple preclinical studies that have demonstrated the capability of DaRT to eliminate cancer cells in vitro and produce tumor responses in vivo, we initiated a feasibility study in 2017 to evaluate this novel approach to treat patients with squamous cell carcinomas (SCC) of the skin and head and neck.[4] In this report, we describe the feasibility, safety profile, and initial tumor control outcomes from this first-in-human clinical trial.

Methods and Materials

Patient enrollment

Patients with SCC lesions were enrolled in the trial between February 2017 and March 2019 from the Rabin Medical Center Petach in Tikva, Israel and the Instituto Scientifico Romagnolo per Lo Studio e la Cura dei Tumori in Meldola, Italy. Both medical centers received approval from their respective institutional ethical committees and the local ministries of health. All patients received informed consent before initiating protocol therapy.

The primary objective of this study was to serve as a pilot study and evaluate the safety of the Ra-224 DaRT seed treatment, including incidence, severity, and frequency of adverse events as characterized by the Common Terminology Criteria for Adverse Events (version 4.03) classification. The secondary objectives of the study were to evaluate the early tumor responses to the Ra-224 DaRT seed treatment based on clinical and imaging assessments made 30 to 45 days post-DaRT insertion and preliminary evaluation of local progression-free survival (PFS).

Eligibility criteria included all patients with biopsy-proven SCC of the skin and head and neck. Most patients (60.7%) had recurrent and previously treated disease by either surgery, prior external beam RT, or both; 13 of 31 (42%) had received prior RT. The rest (39.3%) had a primary tumor. Additional inclusion criteria included a required tumor size of $\leq$5 centimeters in the longest diameter and lesions without nodal spread. Patients had to be $\geq$18 years old with an Eastern Cooperative Oncology Group (ECOG) Performance Status Scale of $\leq$2 and a life expectancy of more than 6 months.

Three patients had major protocol deviations. In 1 patient, immunosuppressant medications were taken owing to a previous kidney transplant, although this was part of the exclusion criteria. In another case, a patient had a parasitic infection, which developed while the DaRT implant was in place and necessitated its premature removal 10 days postplacement. One additional patient was not evaluable because she expired owing to unrelated pneumonia, which clinically manifested 3 weeks after the DaRT procedure. Although these patients were included in the toxicity analysis, they were not evaluable for tumor response. Therefore, they are not included in all statistics related to response and outcome. As a result, toxicity analysis and baseline measurements are reported for all treated lesions

Table 1 Patient and disease characteristics

Age (years)		Number of patients	28
		Mean (standard deviation)	78.7 ± 11.2
		Median (range)	80.5 (59, 94)
Sex	Male	% (n/N)	71% (20/28)
	Female	% (n/N)	29% (8/28)
1.1.1	1.1.2	1.1.3	1.1.4
1.1.5	1.1.6	1.1.7	1.1.8
Tumor volume (cm^3)		Number of lesions	31
		Mean (±standard deviation)	3.9 (±6.4)
		Median (range)	1.7 (0.2, 33.9)
Primary versus recurrent	Primary	% (n/N)	35.5% (11/31)
	Recurrent	% (n/N)	64.5% (20/31)
Tumor location	Nonhead and neck	% (n/N)	13% (4/31)
	Head and neck	% (n/N)	87% (27/31)
Previous RT	Yes	% (n/N)	42% (13/31)
	No	% (n/N)	58% (18/31)
Previous surgery	Yes	% (n/N)	61.3% (19/31)
	No	% (n/N)	38.7% (12/31)

Abbreviation: RT = radiation therapy.

(31 lesions in 28 patients, Table 1). Twenty-eight lesions in 25 patients were evaluable for response at 30 to 45 days postinsertion and they are reported in the response analysis.

Study design

Initially, 4 patients were enrolled to demonstrate feasibility, which was defined as the ability to implant the tumor without grade 3 toxicity at 3 months. Once feasibility was established, an additional 24 patients were included to further evaluate toxicity and initial efficacy. Patients were screened based on the described protocol eligibility criteria and were enrolled in the trial once written informed consent was obtained. During the screening visit, demographic information and concomitant medications were obtained. The ECOG Performance Status scale was also evaluated at baseline.

Lesions were photographed and measured physically. Additional baseline (preinsertion) examinations included complete blood test, liver and kidney function tests, urinalysis, and radioactivity measurements in blood and urine. After enrollment, eligible patients underwent a computed tomography (CT) scan to obtain pretreatment tumor volume. These values were used to determine the appropriate number of DaRT seeds required to encompass tumor volume. Before treatment, an experienced head and neck surgeon evaluated all patients to assess feasibility for further salvage surgery.

Treatment technique and dosing

Initially, CT simulation was performed, and the clinical tumor volume was delineated based on clinical examination and baseline CT or magnetic resonance imaging evaluation. The planning target volume was defined as a 5-mm extension beyond the clinical tumor volume, a geometric loading pattern and technique. For placement of the Alpha DaRT, strands were used at 5-mm interval spacing and DaRT seeds were placed 5 mm beyond the tumor edge for adequate dosimetric coverage. For larger tumors >5 mm in depth, bi- or multiplanar needle geometry was employed. Treatment was delivered through radioactive seeds containing 2 μCi ^{224}Ra per seed inserted into the tumor under local anesthesia in an outpatient setting.

In contrast to gamma and beta sources for which the dose at any point is determined by the source geometric arrangement, DaRT source dose depends both on geometric position and on the diffusion characteristics of the alpha emitters in the tumor. However, preclinical study of SCC tumors implanted in mice provided quantitative information on the diffusion parameters and on the dose required to achieve tumor cell elimination.[1] A direct comparison was made between the actual distribution of radioactive atoms (from which the dose and the dose rate could be measured) and the observed region of cell death in the tumor. A minimal total dose of approximately 10 gray was required and the resultant kill region around the source had a diameter of 5 mm. The treatment plan was based on these preclinical findings.

DaRT seeds were inserted according to the preplan with the calculated number of applicators and DaRT seeds per applicator. After placement of the DaRT seeds, a standard postprocedure brachytherapy CT was obtained to assess final seed positions within the tumor for quality assurance (QA) evaluation. This QA check corroborated that 95% of the tumor volume was consistently covered with DaRT seeds. If undercoverage was detected based on this QA check (n = 3), seeds were added before completing implantation.

DaRT seeds were implanted at a distance of 10 mm from major blood vessels (eg, the carotid artery). A radiation

Geiger monitor with a collimator was used to check emission of radioactivity from the seeds immediately after insertion. Seeds were removed 15 to 30 days after implantation with or without local anesthesia, depending on the anatomic location of the implanted site.

Radionuclide and applicators

The DaRT seeds were administered using an applicator produced by Alpha Tau Medical, Limited (Tel Aviv, Israel). Each seed consists of a 10-mm long and 0.7-mm diameter 316LVM stainless steel hollow wire with radium-224 fixed on its surface. The seeds were linearly threaded on a single monofilament suture. The seeds are contained within the applicator needle and encapsulated with glycerin; each applicator holds 1 to 6 seeds.

The DaRT applicator consists of 2 major components that are commonly part of interstitial brachytherapy applicators as follows: a needle (with attached hub) used to place the DaRT percutaneously into the tumor and a stylet (with attached hub) used to deploy the DaRT encapsulated seed(s) in the appropriate location within the tumor (Fig. 1). In addition, the device (applicator and seeds) is provided with a protective cap that is kept over the tip of the needle to prevent damage to the needle, and a safety pin is provided to prevent inadvertent detachment of the needle and stylet. The DaRT seeds within the DaRT applicator comprise the Alpha DaRT device.

Follow-up

Study follow-up examinations included repeat blood tests and urinalysis, additional blood and urine radiation measurements, and assessment of ECOG Performance Status scale at 4, 9, and 30 days post-DaRT insertion. Any changes in concomitant medications were recorded during the study. Adverse events were assessed at each study visit and recorded on case report forms. Tumor size was measured again at 30 to 45 days post Ra-224 DaRT seed insertion. Change in tumor size was defined by physical examination, when obvious, and in most cases, imaging, including positron emission tomography-CT scans or CT scans, was also used to assess response.

Tumor response was assessed at a 30 to 45 days follow-up visit using the Response Evaluation Criteria in Solid Tumors (version 1.1). Only the irradiated tumor was considered a target lesion assessed for response. For this report, 28 of the 31 lesions were evaluable for response, as noted in the patient enrollment section discussed previously.

Response criteria were defined as follows: complete response (CR), disappearance of the irradiated tumor; partial response (PR), at least a 30% decrease in the longest dimension of the irradiated tumor; progressive disease, at least a 20% increase in the longest dimension of the irradiated tumor, taking as reference the smallest longest dimension recorded since RT; stable disease, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum since the treatment started.

Four to 6 weeks post-Ra-224 DaRT seed insertion, a biopsy was obtained ($n = 5$) if there was clinical suspicion of residual disease. In cases of histopathologically confirmed residual disease, surgery or systemic therapy was carried out. Patients were subsequently evaluated every 2 months for continued follow-up observation.

Statistical methods

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Study results were tabulated, and continuous measures are summarized as mean, standard deviation, minimum, median, and maximum values; binary variables are presented as a count and percentage. Serious adverse event (SAE) incidence rates are presented with 2-sided 95% score confidence intervals (CI). Kaplan-Meier estimates for the overall survival probability and of local PFS probability were calculated. Two survival curves were

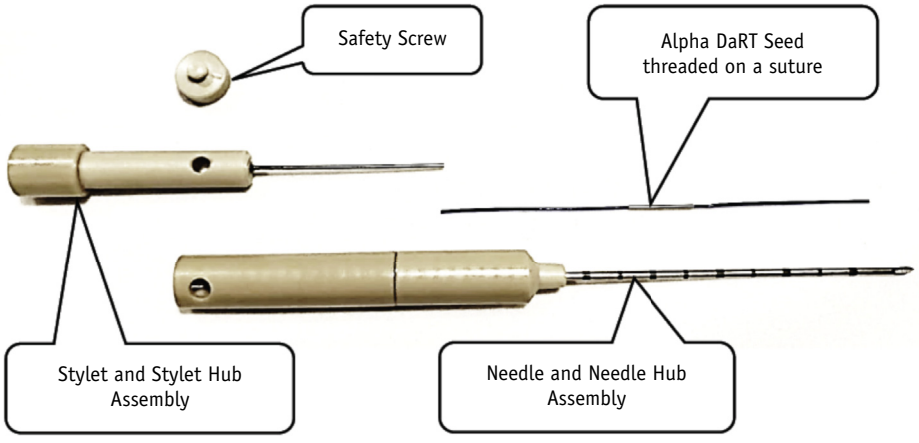


Fig. 1. DaRT applicator and components (18 gauge needle, 140 mm in length).

compared using a log-rank test. Overall survival was measured from the DaRT insertion procedure date. Local PFS was stratified based on the recorded initial response date. The median follow-up was 6.7 months (range, 1.45-23.36 months).

Results

Thirty-one lesions in 28 patients were evaluated in this study between February 2017 and March 2019, including 22 patients from Rabin Medical Center Petach, Israel, and 6 from Instituto Scientifico Romagnolo per Lo Studio e la Cura dei Tumori, Italy. Of these 28 patients, 3 were treated twice for 2 separate tumors, for a total of 31 lesions. Baseline demographics, disease characteristics, and tumor location of these 28 treated patients are summarized in Table 1. Specific sites treated included skin (n = 12, 4 of which were in the extremities), ear (n = 7), lip (n = 5), tongue (n = 3), nose (n = 2), and parotid (n = 2). All tumors were SCC.

The average number of Ra-224 DaRT seeds inserted into the tumors was 27.72 seeds (range, 3-169 seeds), with an average treatment duration of 16.3 ± 4.3 days. The average activity of the seeds on the day of insertion was 55.42 ± 61.46 μCi.

Biosafety evaluation

Radioactivity measurements (at insertion site, at different body areas, and in blood and urine samples), vital signs, and general assessments of the patients' medical condition were recorded at baseline and at follow-up visits. Among patients undergoing the procedure, the average radioactivity in the blood and urine approximately 4 days after treatment was 41.2 ± 34.4 and 6.1 ± 5.3 kBq/L, respectively. The average radioactivity in the blood and urine decreased to 12.7 ± 10.2 kBq/L and 2.5 ± 2.9 kBq/L, respectively, approximately 9 days after treatment. There was no measurable radioactivity in the blood and urine 30 days after treatment, except in 1 patient who was treated with DaRT seeds in 2 SCC lesions in 2 separate sessions 15 days apart; because of this overlap, radioactivity was still detectable at day 30 after the first insertion procedure. By day 30 after the second procedure, there was no measurable radioactivity in the blood and urine in this patient.

The estimated average alpha doses to the lungs, kidneys, and bone marrow from the radioactive decay product of DaRT (Pb-212) were calculated from blood and urine radioactivity results using the model described by Arazi et al.[5] The Pb-212 leakage probability (fraction of Pb-212 leaving the tumor through the blood) was 0.40 ± 0.15 (40%). The mean ± standard deviation alpha dose levels to the lungs, kidneys, and bone marrow were as follows: 0.03.2 ± 0.02, 0.02.8 ± 0.017, and 0.012 ± 0.007 cGy, respectively. These values are well within the maximum tolerable doses of radiation for the lungs, kidneys, and bone marrow at 1500, 500, and 100 cGy, respectively.[5]

Toxicity

Table 2 summarizes the incidence of acute toxicity events observed up to 3 months after the DaRT insertion procedure.

Acute toxicity of Ra-224 DaRT seed treatment (considered to be possibly or most probably related to protocol therapy) included mostly local pain (n = 11) and erythema (n = 10) at the implant site, followed by swelling (n = 8) and mild skin ulceration (n = 4). For pain and grade 2 skin ulcerations, 90% of patients had resolution within 3 to 5 weeks. In general, these acute toxicities were resolved within a median time of 15 days (range, 4-183 days). In 8 patients the DaRT seeds were inserted adjacent (less than 5 mm) to bone and teeth; none developed osteoradionecrosis.

Two SAEs were reported, both of which were determined to be unrelated to the protocol therapy. One patient developed pneumonia after therapy and subsequently expired owing to their underlying poor performance status and multiple comorbidities. In a second patient treated with DaRT for a SCC confined to the nose, cerebral edema was attributed to a prior course of RT to the base of skull and posterior orbit. No device-related SAEs were observed during the course of treatment or follow-up. The incidence rate of device-related SAEs was 0% over time (95% CI, 0-12.06%) and the incidence rate of unrelated SAEs was 7.14% (95% CI, 1.98-22.65%). To date, no late toxicities have been observed.

Initial tumor response

Of the 28 patients treated, 28 out of 31 treated lesions were evaluable to determine tumor response. This evaluation was limited to patients who met the study eligibility criteria, received the planned DaRT therapy protocol, and completed the minimum follow-up at 6 weeks after treatment.

CR to the Ra-224 DaRT seed treatment (reduction in tumor dimensions of 100%) was achieved in 22 lesions (78.6%) and 6 lesions (21.4%) manifested a PR (tumor reduction between 30%-100%). Therefore, all patients

Table 2 Incidence of acute local toxicity (all treated lesions, n = 31)

	Incidence (%)		
	Severity grade		
Acute local toxicity	1	2	3
Erythema	11 (35%)	9 (29%)	0 (0%)
Swelling	6 (19%)	8 (26%)	0 (0%)
Pain	9 (29%)	11 (35%)	0 (0%)
Discharge	2 (6%)	6 (19%)	0 (0%)
Ulcer	4 (13%)	3 (10%)	0 (0%)
Paresthesia	3 (10%)	0 (0%)	0 (0%)
Pruritus	3 (10%)	0 (0%)	0 (0%)
Scarring	0 (0%)	1 (3%)	0 (0%)

exhibited some level of response to treatment. An example of a complete response is shown in Figure 2. Among patients who did not receive prior RT, 15 of 16 patients (94%) demonstrated a CR and, among those who were previously treated with RT, 7 of 12 (58%) had a CR.

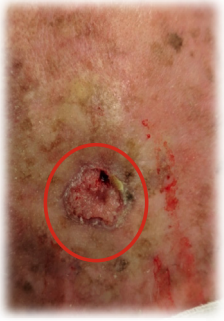
Among the 22 lesions that achieved a CR, 5 developed a local relapse at the site of DaRT implantation at a median of 4.9 months (range, 2.43-5.52 months) after treatment. The Kaplan-Meier estimated local PFS rate for all patients at 1 year was 44% (CI, 20.3-64.3%). Among patients with an initial CR to treatment, the Kaplan-Meier estimated local PFS rate at 1 year was 60%. Only 32% of the patients had a full year follow-up. Patients who achieved an initial CR had significantly higher local PFS and overall survival rates at 1 year compared with those who achieved a PR (60.1% and 93% compared with 0% and 0%, respectively) (Fig. 3). Overall survival rates to 12 months post-DaRT implantation were 75% (95% CI, 46.14-89.99%) among all patients and 93% (95% CI, 59.08-98.96%) among complete responders. The median follow-up was 6.7 months (range, 1.45-23.36 months).

One patient who was treated twice for skin SCC exhibited a unique response, as each time 1 lesion was treated, a second unrelated lesion responded as well, manifesting as CR to the treatment.

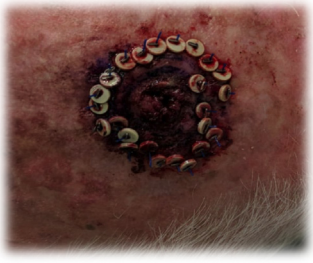
There was no statistically significant difference in local PFS between primary (newly diagnosed) and recurrent lesions at 1 year ($P = .9$). Median local PFS among patients with recurrent tumors was 5.5 months and was 5.09 months for those with primary tumors. There was no statistically significant difference in local PFS between recurrent or primary lesions ($P = .59$) either. There was no significant difference in initial response rates and toxicity outcomes between patients who received prior RT (n = 12) and those who did not (n = 16) ($P = .59$). Median local PFS among patients with prior radiation was 5.2 months and was 5.1 months for those without previous radiation.

Discussion

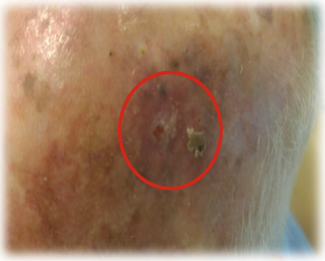
Here, we report the first-in-human clinical results of a feasibility and safety prospective study evaluating the early toxicity and tumor response of an alpha-emitting brachytherapy source for the treatment of locally advanced and recurrent SCCs of the head and neck. As the primary focus of this trial was a feasibility study, the treated population was heterogeneous, with different sites of the head and neck and skin treated. The cohort in this report represented a very unfavorable prognostic risk group, many elderly patients unfit for surgery (median age = 80.5). Furthermore, the majority of this study population was previously treated with surgery or prior chemotherapy/RT. Based on pretreatment evaluation by the head and neck surgeon of all patients, further surgery instead of the DART brachytherapy treatment was presumed to increase risk of morbidity.



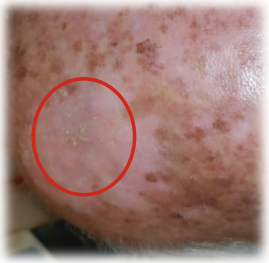
Pre - Treatment



DaRT Insertion



Day 30 After DaRT Insertion



5.5 Months After DaRT Insertion

Fig. 2. Deeply infiltrating SCC of the scalp with complete response noted at day 30.

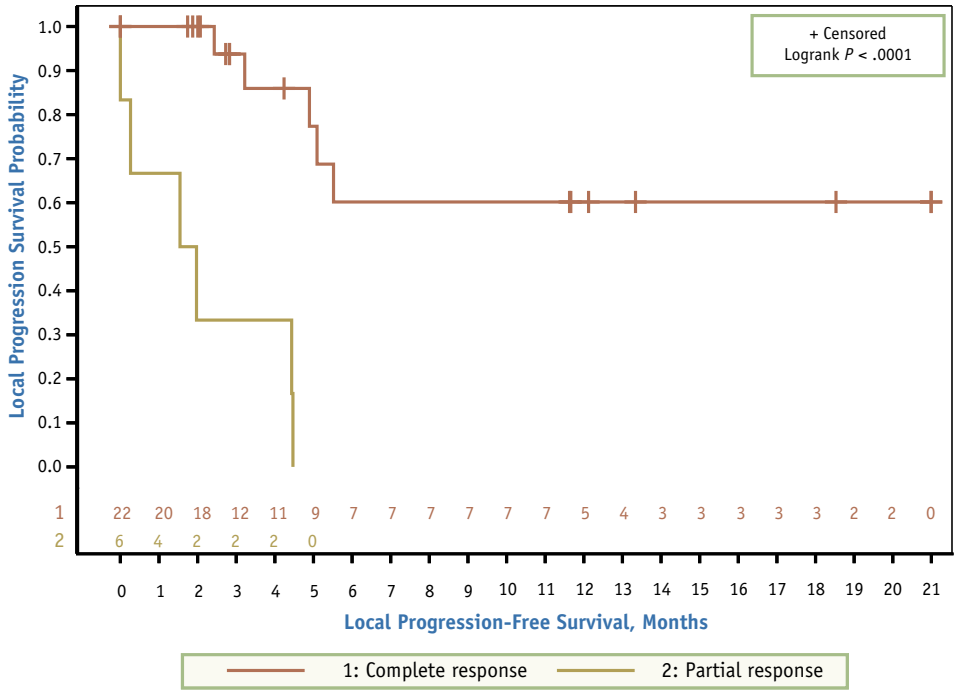


Fig. 3. Local progression-free survival stratified by response status.

Despite the heavily pretreated nature of these patients, observed toxicity to date has been limited, with 48% with acute grade 2 toxicity; no patients developed grade 3 or higher toxicity. Furthermore, in all cases the toxicity resolved within a month.

The favorable tolerance results may be related to the highly conformal dose distribution achieved with the DaRT method. This novel approach takes advantage of the decay of radium–224 that releases short-lived radon-220, into which its daughter atoms disperse in the tumor microenvironment, creating a dose cloud that does not diffuse much beyond 5 mm.[1] With proper seed placement geometry, a tight dose distribution is achieved, limiting exposure to surrounding organs. Although our reported results are encouraging, longer follow-up is necessary to confirm these observations.

Our report also highlights impressive early tumor responses observed despite the recurrent and relatively radioresistant tumors that characterized this patient cohort. Dramatic tumor reduction after DaRT placement was relatively rapid, often noted with the first 2 weeks postplacement; so far, the response has been durable in the majority of cases. The initial local response, with 60% manifesting complete resolution of disease, seems superior compared with outcomes previously reported using standard reirradiation with external beam or traditional brachytherapy approaches in which the response rates are lower than 40%.[6,7] CRs were noted in 58% of patients with radio-recurrence and in 94% of those who never previously received RT. These findings may in part be attributed to the enhanced radio-biologic attributes associated with alpha particle therapy, which could potentially overcome radio-resistant clones and achieve greater efficacy compared with traditional brachytherapy gamma sources.

The current study represents an excellent example of successful recapitulation and validation of preclinical studies that demonstrated impressive tumor responses.[1-4,8-12] The innovative development of a brachytherapy dose delivery that takes advantage of short-range diffusion of alpha particles is unique and could potentially be paradigm changing. Brachytherapy has relied on radioactive beta and gamma sources for many years, and new, radio-biologically more potent sources could provide great benefit for patients with other solid tumors whose prognosis is poor. Other feasibility and safety trials are underway that evaluate the role of DaRT therapy for other solid tumors such as pancreatic tumors and recurrent breast, prostate, and vulvar cancers (personal communication Y.K.).

Preclinical studies have suggested that DaRT therapy may be employed to harness the immune response when used in conjunction with immunotherapy.[12,13] One patient in this report experienced an immune repose with reduced disease at other tumor sites concomitant with treatment of 1 of the symptomatic lesions with DaRT therapy in the absence of any other therapy. In selected tumors with oligometastases, the use of DaRT targeted to a lesion in conjunction with immunotherapy could further augment the immune response compared with immunotherapy alone; trials are currently in development to test this hypothesis. Systemic alpha RT using radium-223 showed a significant survival advantage in castrate-resistant prostate cancer, which could possibly be related in part to an immunologic mechanism that could affect further metastatic progression of disease.

Based on the current pilot study, we certainly cannot make any definitive conclusions regarding response rates; nevertheless, these data are reported as part of our preliminary observations for this small pilot study. Our early results are promising and suggest that alpha particle brachytherapy may represent a new opportunity and fertile area for continued research exploration with tumors heretofore considered radio-resistant and nonresponsive. These findings also indicate that DaRT therapy is a feasible approach and should be considered under the category of reirradiation, which has promise for potentially less morbidity for patients compared with stereotactic body RT or other external beam techniques.

Phase I/II prospective studies are currently being initiated in more homogeneous patient populations among those with recurrent and persistent local disease, where surgery and external beam RT have already been exhausted. In these studies, there will be better assessment of late toxicity, and secondary endpoints will include tumor control outcomes. Opportunities to harness the immune system with targeted DaRT therapy to a lesion could have value as well and will need to be tested in prospective trials. Although standard modes of treatment planning methods were used for these patients, it appears that radio-biologic-based treatment planning and new methods will be helpful and, in fact, critical when integrating alpha source brachytherapy with other established therapies. These new paradigms in treatment planning coupled with novel approaches integrating this therapy with other established therapeutic strategies must be accomplished through larger well-designed prospective trials.

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