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Original Investigation | Oncology

Feasibility and Safety of Diffusing Alpha-Emitter Radiation Therapy for Recurrent or Unresectable Skin Cancers

Mark A. D'Andrea, MD; Noam A. VanderWalde, MD, MS; Matthew T. Ballo, MD; Pradeep Patra, PhD; Gil'ad N. Cohen, MS; Antonio L. Damato, PhD; Christopher A. Barker, MD

Abstract

IMPORTANCE Patients with recurrent or unresectable skin cancers have limited treatment options. Diffusing alpha-emitter radiation therapy (DaRT), a novel solid tumor management strategy using alpha-particle interstitial brachytherapy, may address this challenge.

OBJECTIVE To evaluate the feasibility and safety of using DaRT to manage recurrent or unresectable skin cancers.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study of patients who received a 2-week to 3-week treatment course and were followed up for 24 weeks after treatment during 2021 and 2022 at 2 sites in the US. Patients with malignant skin tumors or soft tissue tumors were recruited if they had limited treatment options for tumors recurrent after prior surgery or external beam radiotherapy or unresectable tumors.

INTERVENTION Patients underwent DaRT to deliver a physical dose of 10 Gy (equivalent weighted dose of 200 CGE) to the tumor.

MAIN OUTCOMES AND MEASURES Feasibility of the DaRT procedure was evaluated based on the ability of investigators to successfully deliver radiation to the tumor. Patients were followed up for adverse events (AEs) for 24 weeks and for tumor response by physicians' physical examination and imaging 12 weeks after device removal.

RESULTS This study included 10 participants with recurrent or unresectable skin cancer (median [IQR] age, 72 [68-75] years; 6 males [60%]; 4 females [40%]). Six patients (60%) had recurrent disease, and 4 (40%) had tumors that were deemed unresectable. Tumors were located on the nose, chin, eyelid, scalp, neck, trunk, and extremities. Median (range) tumor volume before treatment was 2.1 cm^3 (0.65-12.65 cm^3). The mean (SD) prescription dose coverage of the gross tumor volume was 91% (2.8%) with all tumors having coverage of 85% or more. No device-related grade 3 AEs were noted. Common AEs were grade 1 to 2 erythema, edema, and pruritus. At 12 weeks following treatment, there was a 100% complete response rate. Nine of 10 complete responses (90%) were confirmed by CT imaging.

CONCLUSIONS AND RELEVANCE This cohort study suggests the feasibility and preliminary safety of DaRT in the management of recurrent or unresectable skin cancers. The favorable safety profile and high response rates are promising. A US trial for marketing approval based on this pilot study is under way.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04377360

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Key Points

Question What is the feasibility and preliminary tolerance of diffusing alpha-emitter radiation therapy (DaRT) for patients with recurrent or unresectable skin cancer?

Findings This cohort study enrolled 10 patients with skin cancers who successfully underwent DaRT. Treatment was well tolerated with adverse events limited to grade 1 to 2 erythema, edema, and pruritus, and all patients achieved a complete response at 12 weeks following treatment.

Meaning These findings suggest that DaRT was safe and feasible for tumors that are often associated with poor outcomes.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Recurrent or unresectable skin cancers present clinical management challenges. In some cases, prior surgery may preclude additional excision due to limitations in reconstruction options and/or unacceptable functional or cosmetic outcomes. In addition, either external beam radiotherapy or reirradiation may not be well tolerated in some situations, given the risk of radiation injury to adjacent organs and tissues.

Compared with traditional beta and gamma radiotherapy, alpha-particle therapy has inherent oncologic advantages, especially in the setting of locally advanced and recurrent tumors, as previously described.[1,2] The mechanism of action has been previously described extensively in preclinical studies.[3,4] To this end, a previous report[5] summarized the results of a first in human pilot study using diffusing alpha-emitter radiation therapy (DaRT; AlphaTau Medical), a novel alpha-particle therapy delivered via interstitial intratumoral placement of radium-224 sources (3.7 days

Figure 1. Study Flow Diagram

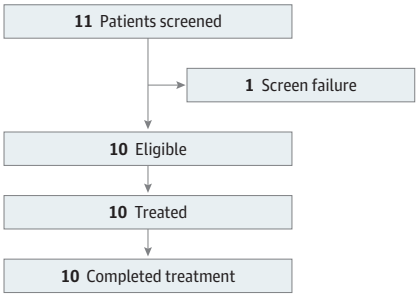


Table 1. Baseline Patient and Disease Characteristics

Characteristics	Patients, No. (%), n = 10
Age, median (range)	72 (57-92)
Sex	
Female	4 (40)
Male	6 (60)
ECOG score	
0	8 (80)
1	1 (10)
2	1 (10)
Tumor location	
Chin	2 (20)
Extremities	2 (20)
Nose	2 (20)
Eyelid	1 (10)
Neck	1 (10)
Scalp	1 (10)
Torso	1 (10)
Histopathology	
Basal cell carcinoma (BCC)	6 (60)
Squamous cell carcinoma (SCC)	4 (40)
Reason for limited treatment options	
Unresectable	4 (40)
Recurrent	6 (60)
Clinical target volume (CTV), cm^3	
Median (range)	2.1 (0.7-12.7)

Abbreviations: BCC, basal cell carcinoma; CTV, clinical target volume; SCC, squamous cell carcinoma.

half-life). In a single center clinical trial with a median follow-up time of 6 months, the pilot study of patients with head and neck cancer demonstrated no grade 3 or higher toxic effects. In addition, 78% of the tumors demonstrated a complete response to DaRT, and the remaining lesions manifested a partial response (>30% tumor reduction). Overall survival rates at 12 months post-DaRT implantation were 75% among all patients and 93% among complete responders.[5]

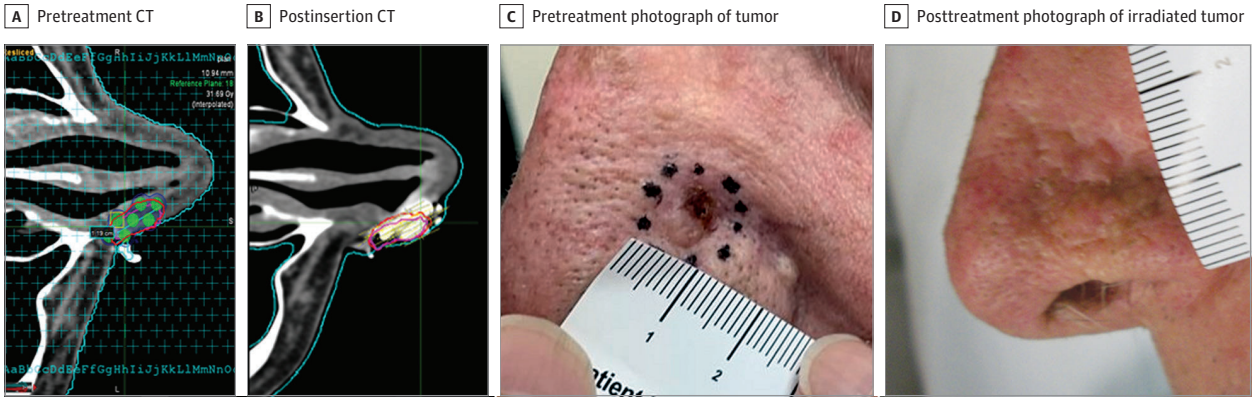
Our current study reports on a prospective multicenter pilot study using DaRT for recurrent and unresectable skin cancers. The purpose of this study was to evaluate the feasibility and safety of using DaRT to manage skin cancers in anticipation of planning a larger pivotal study.

Methods

This cohort study was approved by the Western institutional review board (IRB) and the Memorial Sloan Kettering Cancer Center IRB, and it was conducted using the DaRT device under a United States Food and Drug Administration Investigational Device Exemption. All participants provided written informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The study protocol can be found in Supplement 1.

The primary objective of this pilot study was to explore the feasibility of DaRT and determine the frequency and severity of acute adverse events related to delivering interstitial radiotherapy for malignant skin and superficial soft tissue tumors using DaRT. Feasibility was defined as the successful delivery of radiation to the tumor by DaRT; failure to execute the workflow of pretreatment imaging, brachytherapy planning, device procurement, or technical inability to place the DaRT device constituted feasibility failure. Feasibility was further confirmed by imaging immediately after placement of the DaRT device, to estimate tumor radiation dose delivery (dosimetry). Safety was evaluated using Common Terminology Criteria for Adverse Events (CTCAE) version 5 grading of adverse events as assessed and attributed by the investigator at the time of DaRT removal, and 6, 12, and 24 weeks thereafter. The development of 3 or more treatment-related or device-related serious adverse events (grade ≥3 adverse events by CTCAE) was prespecified as a reason to halt accrual due to safety concerns. A secondary objective was to assess the tumor response based upon the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, using calibrated digital photography, and computed tomographic (CT) imaging performed 12 weeks after DaRT, as assessed by the investigator.

Figure 2. Computed Tomography (CT) Planning and Clinical Imaging Before and After Diffusing Alpha-Emitter Radiation Therapy (DaRT)



A, Pretreatment CT, pink contour indicate gross tumor volume; red contour, clinical target volume; green-filled circles, planned locations of DaRT seeds; orange dotted lines, path and orientation for seed insertion. B, Postinsertion CT showing seeds in tumor interstitium; yellow lines indicate seed location. C, Pretreatment photograph of tumor with dotted outline of clinical target volume. D, Posttreatment photograph of irradiated tumor 12 weeks after DaRT removal.

Patient Enrollment

Eligible patients harbored a primary malignant tumor of the skin, such as keratinocytic carcinomas (basal cell carcinoma or squamous cell carcinoma), melanocytic tumors (melanoma), soft tissue tumors (cutaneous angiosarcoma or leiomyosarcoma), or neural tumors (Merkel cell carcinoma). Patients with metastatic lesions of the skin and superficial soft tissues were eligible, such as metastases from breast cancer, lung cancer, melanoma, kidney cancer, and others. Patients were also eligible if they had recurrent tumors that failed at least 1 standard therapy, such as previous radiotherapy or surgery. Tumors deemed inappropriate for surgical resection were defined for this study as scenarios where complete resection would not be technically possible due to location or size or where resection would lead to a cosmetically compromising outcome such as requiring amputation of a digit, lip, eyelid, or ear. Patients were excluded from the study if they had ever received radiotherapy to the target tumor with doses more than 60 Gy (equivalent dose in 2 Gy fractions using α/β of 8.5) or any radiotherapy in the previous 6 months.

Treatment Intervention

Eligible patients underwent a volumetric assessment of the tumor via a CT radiotherapy planning scan. The volumetric images were used to generate the optimal plan to deliver DaRT by defining the optimal number, size, and location for DaRT source placement. Using these planning parameters, the DaRT sources were inserted by investigators. Immediately after placement, a standard radiotherapy planning CT was performed to assess source positions within the tumor and estimate doses delivered to the tumor. A physical dose of 10 Gy was prescribed, which was equivalent to a weighted radiation dose of 200 Cobalt Gray Equivalent (CGE).

Approximately 2 to 3 weeks after placement of the DaRT sources, the sources were removed. Tumor response to DaRT was then reevaluated at 12 weeks after removal of the device by physical examination and documented using digital photography and CT imaging.

Statistical Analysis

Given the exploratory nature of this pilot study, a sample of 10 patients was chosen to descriptively evaluate feasibility and safety. Summary statistics are presented with 95% CIs calculated using Wilson Score; statistical analyses were performed using SAS version 9.4 (SAS Institute) (Supplement 2). Statistical analysis was performed in April 2022.

Results

Patient Characteristics

In this study, 10 patients (median [IQR] age, 72 [68-75] years; 6 [60% male; 4 [40%] female) were treated and accrued between July and October 2021 at the University Cancer and Diagnostics Centers in Houston, Texas, and the West Cancer Center and Research Institute in Germantown, Tennessee, by 3 different investigators (MAD, NAV, MTB). One patient was excluded during eligibility screening due to the concomitant use of another therapy for skin cancer (**Figure 1**). Baseline patient and disease characteristics are summarized in **Table 1**. Histopathologic results at baseline indicated that 6 patients (60%)[6] presented with basal cell carcinoma (BCC) and 4 patients (40%)[4] with squamous cell carcinoma (SCC).

DaRT Feasibility

All 10 patients (100%; 95% CI, 72.3%-100.0%) enrolled were successfully treated with DaRT, with the device placed in the target tumor as planned. An example of the planned and actual placement of the DaRT device in the tumor is presented in **Figure 2**. The median (range) tumor volume before treatment was 2.1 cm^3 (0.65-12.65 cm^3). The mean (SD) radiation dose delivery of the gross tumor volume was 91% (2.8%) in all 10 patients, with all tumors having coverage of 85% or more. A summary of radiation dose delivery estimates is shown in **Table 2**.

Table 2. Dosimetric Assessment After DaRT Placement

Assessment	Treated patients (n = 10)
No. of seeds	
Mean (SD)	42.3 (21.2)
Median (range)	33.5 (20-79)
% Coverage GTV, %	
Mean (SD)	90.8 (2.8)
Median (range)	90.8 (86-94)
% Coverage CTV, %	
Mean (SD)	86.4 (7.7)
Median (range)	89.0 (71-94)
DaRT treatment duration, d	
Mean (SD)	17.2 (2.9)
Median (range)	15 (15-21)

Abbreviations: CTV, clinical target volume; DaRT, diffusing alpha-emitting radiation therapy; GTV, gross tumor volume.

Toxicity Outcomes

Overall, patients tolerated DaRT well, with 22 adverse events (AEs) reported across 7 patients (70%); 13 AEs were considered unrelated to procedure or treatment. There were only 2 serious adverse events (SAE) reported in a single patient (syncope and hypotension), but both events were unrelated to the procedure or treatment. As shown in **Table 3**, 20 (91%) of the procedure or treatment-related AEs were of mild or moderate severity and no grade 3 or higher toxic effects were noted. The most common toxic effects were dermatitis and pruritus over the implanted area, which subsequently resolved when treated with conservative measures. No device-related SAEs were reported, and no long-term toxic effects were observed.

Clinical Response Outcome

A 100% (95% CI, 72.3%-100.0%) complete response rate at 12 weeks posttreatment was observed at the site of the implant in these 10 patients. An example of the clinical response to treatment is depicted in Figure 2. CT scans obtained at 24 weeks posttreatment showed no evidence of recurrent disease in any of the 10 patients.

Discussion

The findings of this cohort study suggest the feasibility of planning, procuring, and delivering interstitial brachytherapy using the DaRT device and supports previous observations.[5] These findings are important because the only prior clinical trial of this device was carried out at a single center outside the United States, and the present study suggests that DaRT is amenable to study in a larger, multicenter, international clinical trial, which is currently under way. Looking forward, if the trial under way demonstrates favorable outcomes, this new method of skin cancer radiotherapy may become part of clinical practice.

The safety of the DaRT intervention for patients with recurrent and unresectable skin cancers is noteworthy, given the recurrent and unresectable nature of the tumors managed. No grade 3 adverse events related to the treatment or device were observed in this pilot study or in the previously published study. In comparison, a prior study of a molecularly targeted drug therapy for locally advanced, unresectable basal cell carcinoma not amenable to conventional radiotherapy demonstrated a grade 3 or higher adverse event rate of 43%.[6] Likewise, prior studies of immunotherapy for locally advanced, unresectable cutaneous squamous cell carcinoma not amenable to conventional radiotherapy have demonstrated a grade 3 or higher adverse event rate of 44%.[7] Although the patients included in this study did not necessarily have locally advanced tumors, in many cases, the regions of treatment had in many cases previously received significant therapy, including surgery and high-dose external beam radiotherapy, and in some instances would be considered for drug therapy. However, high-grade AEs related to retreatment were not observed despite this further treatment with high doses of alpha radiation. This is likely a result of DaRT depositing a limited, highly conformal, targeted, tumoricidal dose of biologically potent ionizing radiation to the tumor.

Table 3. Summary of Management-Related Adverse Events According to Common Terminology Criteria for Adverse Events, Version 5

	Grade, No.				
Adverse event	1	2	3	4	5
Dermatitis radiation	2	1	0	0	0
Localized edema	1	0	0	0	0
Joint range of motion decreased	0	1	0	0	0
Pain	0	1	0	0	0
Pruritus	2	0	0	0	0
Wound infection	0	1	0	0	0

The preliminary clinical response outcome (100% complete response rate) is also noteworthy, as it exceeds the 78% complete response rate observed in the prior clinical trial of patients with head and neck cancer. This complete response rate is also higher than the 21% and 13% complete response rates noted in studies of molecularly targeted drug or immunotherapy, respectively, in patients with locally advanced, unresectable skin cancers not amenable to conventional radiotherapy.[6,7] While cross study comparisons are potentially hazardous, the current data suggests that the primary skin tumors (keratinocyte carcinomas) managed in this study may be more sensitive to the effects of alpha-particle radiotherapy than head and neck cancers. Alternatively, the ability to place the DaRT device into a skin tumor may be simpler than other anatomic areas, thus lending itself to certain applications based on anatomic considerations. In addition, it suggests that in some situations, keratinocyte carcinomas may be more effectively managed (or remanaged) with alpha-particle therapy than currently available drug therapies.

Limitations

The observations described herein are of a small cohort, with limited follow-up. However, this study was designed to be a pilot assessment of feasibility and safety, and larger, multicenter clinical trials are ongoing to further examine these observations.

Conclusions

In conclusion, this pilot study further suggests the feasibility and the favorable safety profile of using alpha-particle targeted therapy for tumors generally associated with poor outcomes. Based on this pilot study, a multicenter US trial for marketing approval is under way.

ARTICLE INFORMATION

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Corresponding Author: Christopher A. Barker, MD, Memorial Sloan Kettering Cancer Center, 1275 York Ave, Box 22, New York, NY 10065 (barkerc@mskcc.org).

Author Affiliations: University Cancer Centers, Houston, Texas (D'Andrea); West Cancer Center, Germantown, Tennessee (VanderWalde, Ballo, Patra); Memorial Sloan Kettering Cancer Center, New York, New York (Cohen, Damato, Barker).

Author Contributions: Dr Barker had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Cohen, Damato, Barker.

Acquisition, analysis, or interpretation of data: D'Andrea, VanderWalde, Ballo, Patra, Barker.

Drafting of the manuscript: Ballo, Patra, Barker.

Critical revision of the manuscript for important intellectual content: D'Andrea, VanderWalde, Ballo, Cohen, Damato, Barker.

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SUPPLEMENT 1.
Study Protocol

SUPPLEMENT 2.
Statistical Analysis Plan

SUPPLEMENT 3.
Data Sharing Statement