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Feasibility and safety of endoscopic ultrasound-guided diffusing alpha emitter radiation therapy for advanced pancreatic cancer: Preliminary data

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ABSTRACT

Background and study aims Pancreatic cancer is a devastating disease with limited locoregional treatment options. Diffusing alpha-emitter radiation therapy (Alpha DaRT), a novel cancer treatment using alpha-particle interstitial radiotherapy, may help address this challenge. The aim of this study was to evaluate the feasibility and safety of endoscopic ultrasound (EUS)-guided Alpha DaRT for advanced pancreatic cancer.

Patients and methods Patients with inoperable locally advanced or metastatic pancreatic adenocarcinoma were treated with EUS-guided Alpha DaRT insertion. The Alpha DaRT sources were delivered into pancreatic tumors using a standard EUS needle with a novel proprietary applicator. Adverse events (AEs) were assessed based on the Common Terminology Criteria for Adverse Events version 5.0. Tumor response was evaluated by imaging 4 to 6 weeks post treatment.

Results The first five patients were treated between March and September 2023. The procedure was technically successful in all cases, with Alpha DaRT sources inserted into the target tumor. Estimated gross tumor volume coverage ranged from 8% to 44%. Fourteen AEs were reported among three patients. Four were serious AEs, none of which was associated with the treatment, but rather, with disease progression or medical assistance in dying. Only two AEs (mild) were deemed possibly related to the study device. At the 35-day visit, two patients had progressive disease and three had stable disease, with one of the latter showing partial response 2 months post procedure.

Conclusions Preliminary results from this first-in-human trial indicate that EUS-guided Alpha DaRT treatment for unresectable pancreatic cancer is feasible and safe, with no device-associated serious AEs. Further investigation of this promising novel modality is underway.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related mortality, despite accounting for only 3% of new cancers diagnosed in the United States in 2021 [1]. It is associated with an extremely poor prognosis, reflected by a median survival of 5 to 8 months and a 5-year survival probability of less than 5% when all stages are combined [2, 3, 4]. Only 20% of pancreatic cancers are eligible for curative surgical resection, and of them, up to 85% recur [5]. Locoregional disease burden often causes obstruction of the gastric outlet and bile duct, as well as tumor-related pain, and is a major cause of morbidity and mortality.

Radiation therapy, which plays a pivotal role in treating many cancers, has demonstrated uncertain efficacy in both the neoadjuvant and locally-advanced settings [6]. Furthermore, the ablative dose prescribed to the target tumor is limited by patient dose tolerance and tight dose volume constraints of nearby radiosensitive organs, risking normal tissue toxicity [7]. More encouraging results have been observed in the setting of ablative stereotactic body radiation therapy (SBRT) techniques, allowing for higher doses and more precise delivery of treatment. Studies suggest that SBRT is well tolerated and associated with improved local tumor control compared with conventional radiotherapy, presumably related to higher dose levels overcoming the inherent radiation resistance of pancreatic tumor clones [8].

In recent years, endoscopic ultrasound (EUS) has become a key modality for accessing the pancreas and is considered the gold standard for diagnosing pancreatic cancer [9]; yet EUS-directed targeted therapies have not been adopted as standard clinical practice for treating pancreatic cancer. A few pilot studies have investigated EUS-guided brachytherapy for pancreatic cancer using iodine-125 seeds [10, 11, 12]. Although they reported promising feasibility and safety data over a decade ago, no further studies demonstrating efficacy have been reported. The absence of an accepted standard of care for locoregional treatment of pancreas cancer represents an important unmet need.

Diffusing alpha-emitters Radiation Therapy (Alpha DaRT, Alpha Tau Medical, Jerusalem, Israel) is a novel method of delivering alpha radiation to solid tumors, using intratumor placement of wires impregnated with radium-224 sources (3.7-day half-life). Decay of the primary isotope triggers a decay chain of alpha-emitters inside the tumor, with the aim of causing tumor cell death. The mechanism of action has been detailed in preclinical studies [13, 14, 15, 16]. Alpha DaRT combines the advantages of local intratumor irradiation with the destructive power of alpha particles, which are recognized to be significantly more potent than other forms of radiation. In addition, because of the short range of alpha particles in tissue, most of the radiation absorption occurs within the tumor and the surrounding healthy tissue is spared. Pilot studies using Alpha DaRT for treatment of skin and head and neck cancers have demonstrated feasibility, safety, and high response rates [17, 18].

The present pilot study suggests a novel approach for treatment of pancreatic tumors by employing EUS-guided intratumor alpha radiation. We aimed to evaluate the feasibility and safety of EUS-guided intratumor alpha radiation-mediated therapy with Alpha DaRT sources for treatment of advanced pancreatic cancer.

Patients and methods

This was a prospective, single-arm, open-label study with a planned accrual of 37 patients (ClinicalTrials.gov Identifier NCT04002479). The study was approved by the Research Ethics Board (MEO-02–2023–3386) and patients provided written informed consent. Here we report on the first five patients enrolled as per a pre-planned interim analysis. The study population consists of patients with imaging confirmation by computed tomography (CT) scan or EUS of inoperable locally advanced or metastatic, biopsy-proven pancreatic adenocarcinoma or who are medically unfit for surgery. Tumor size was restricted to 4 cm in longest diameter. The required Eastern Cooperative Oncology Group performance status was ≤ 2. Patients could not receive concomitant chemotherapy or immunotherapy, as shown in **Supplementary Table 1**. Baseline CT scan was at most 30 days before screening and a maximum of 65 days prior to the study intervention.

A customized applicator was designed to backload the Alpha DaRT sources into an EUS needle, avoiding the need to directly handle them. Sources were inserted into the pancreatic tumor under EUS guidance, similar to the established technique for inserting fiducial markers into the pancreas for image guidance during radiation therapy delivery [19]. The appropriate number of Alpha DaRT sources required to perform the procedure was determined from volumetric measurements of the pancreatic tumor as seen on baseline CT scan, based on the previously-described diffusion-leakage model to estimate dose distribution of Alpha DaRT sources [20, 21]. Treatment was delivered using a linear echoendoscope (SU-1/EG-580UT, Fujifilm Medical Co., Tokyo, Japan). Alpha DaRT sources were inserted into the tumor using a standard 22-gauge EUS aspiration needle (Expect Slimline, Boston Scientific Co., Natick, Massachusetts, United States) with a novel proprietary applicator developed by Alpha Tau Medical to advance the sources. Standard biohazard gowns and gloves were used as protective equipment for the endoscopist and assisting staff, because alpha particles are generally unable to penetrate even the outer layer of skin. The sources

▶ **Table 1** Summary of baseline characteristics.

Patient	Age (years)	Sex	ECOG score	Tumor stage	Tumor location	Reason that pancreatic cancer is inoperable	Prior treatments
1	78	Male	1	IV	Pancreatic head/uncinate	Metastatic disease	Chemotherapy: Gemcitabine with paclitaxel; gemcitabine
2	68	Female	2	III	Pancreatic head	Unresectability	Chemotherapy: Folforinox (fluorouracil + leucovorin + oxaliplatin); gemcitabine + paclitaxel
3	69	Female	0	II	Pancreatic head/neck	Unresectability	Chemotherapy: Folforinox; abraxane and gemcitabine
4	84	Female	1	IV	Pancreatic head	Metastatic disease	Capecitabine
5	71	Female	0	IV	Pancreatic neck	Metastatic disease	None

ECOG, Eastern Cooperative Oncology Group.

contain 3 µCi of Ra-224 and were implanted at a targeted interval distance of 5 mm and at least 2 mm from major blood vessels and vital organs. A pretreatment plan was used to guide optimal endoscopic source placement; however, because this was a first-in-human trial, investigators chose to take a conservative approach and increase the total activity and sources for successive initial patients to avoid any untoward safety issue. EUS procedures were performed under conscious sedation or monitored anesthesia care at the interventional team's discretion and peri-procedural antibiotics were administered. The position of the Alpha DaRT sources was documented with a post-insertion CT performed immediately after the insertion procedure.

Feasibility was determined by confirmation of Alpha DaRT source placement directly within the pancreatic tumor or in the surrounding tissue, as noted on the post-procedure CT scan. Early tolerance was based on patient evaluations made at scheduled visits through 4 weeks post-procedure. Adverse events (AEs) were assessed as per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Tumor response was evaluated by imaging 4 to 6 weeks post treatment (RECIST V1.1, longest diameter of the target tumor). The need for biliary stent placement to address biliary obstruction was assessed over the course of Alpha DaRT treatment and follow-up as an indirect assessment of local tumor progression.

Results

The first five patients were treated between March and September 2023 at the Jewish General Hospital, Montreal, Canada. Baseline demographic and disease characteristics are shown in ▶ **Table 1**. Patients ranged in age from 68 to 84 years old and four of the five were female. Cancer stage varied, with three patients having stage IV cancer according to UICC classification, 8th edition [22]. Tumor location varied, but four involved the pancreas head.

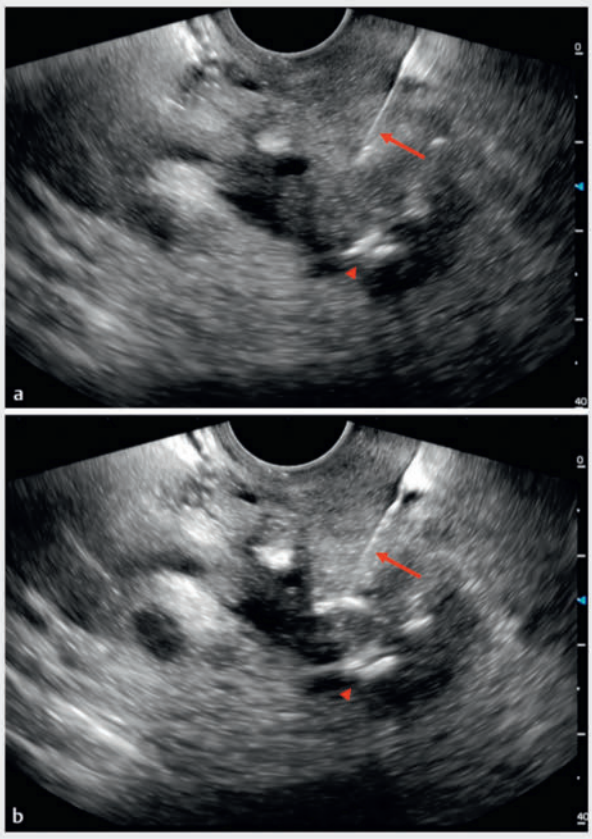
Feasibility of Alpha DaRT source placement

The Alpha DaRT procedure was deemed technically successful in all five cases included in this report, with Alpha DaRT sources inserted in or surrounding the pancreatic tumor (▶ **Fig. 1**, ▶ **Fig. 2**). ▶ **Table 2** lists details of the procedures, including number of sources inserted, percent dose coverage, and number of needle applicators used. With one source per needle deployed, the number of passes made ranged between 3 and 21. As noted, the total number of Alpha DaRT sources increased with each successive procedure.

Tolerance of Alpha DaRT placement

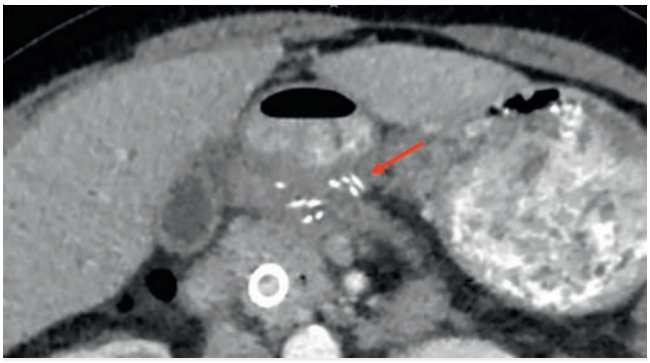
A total of 15 AEs were reported among 3 patients. Four of the AEs were considered serious (SAEs), all of which were either not related to treatment or probably not related to treatment, but rather due to disease progression or medical assistance in dying. Of the two deaths, one was from a medically assisted death and the other due to gastrointestinal bleeding thought to be related to tumor progression. The latter occurred over 80 days after Alpha DaRT insertion, in the context of progressive duodenal tumor invasion on therapeutic anticoagulation, and the nearest Alpha DaRT source was estimated to have been more than 5 mm from the focus of bleeding. All other AEs were of mild (7) or moderate (3) severity and only two AEs (mild) were deemed possibly related to the study device. ▶ **Table 3** lists details about all AEs.

Regarding biliary stent placement, two patients had a previous metal stent, one of whom underwent endoscopic retrograde cholangiopancreatography with coaxial stent placement due to suspected tumor ingrowth about 1 month after Alpha DaRT insertion. A third patient, who had no previous biliary stent, had a stent inserted 41 days after Alpha DaRT insertion. Notably, this patient had partial biliary obstruction prior to the study intervention, with biliary dilation noted on pre-procedural CT scan. The remaining two subjects had no stent intervention reported at the time of this report.



▶ **Fig. 1** **a** EUS image of pancreatic tumor with FNA needle (arrow) within and **b** with the Alpha DaRT seed (arrow) deployed. Note the previously placed Alpha DaRT sources (arrowheads).

Blood and urine radioactivity laboratory tests were performed at baseline and on Days 6 and 35. ▶ **Fig. 3** shows the clear increase and subsequent return to baseline levels of radioactivity in blood and urine by Day 35. Each line in the figures represents a single subject's levels of radioactivity over time.



▶ **Fig. 2** CT image of pancreatic tumor with Alpha DaRT sources in situ (arrow).

Tumor response

Tumor measurements for each patient as well as the response assessment according to modified RECIST criteria are listed in ▶ **Table 4**. At the Day 35 visit, three patients showed stable disease and two had progressive disease. One patient with stable disease at Day 35 showed partial response of the tumor on scan 2 months post procedure. Another patient with stable disease at Day 35 remained stable on scan more than 3 months after intervention. Of note, evaluation of RECIST was performed using CT scans from several days prior to the treatment (as many as 57 days prior). Baseline scans performed on the day of treatment were done without contrast and, as such, were not reliable for evaluating tumor size. At the time of this report, the surviving patients had documented survival through 9, 8, and 6 months post procedure.

Discussion

Advanced pancreatic cancer represents one of the most formidable disease management challenges. Many patients present with bulky local disease with attendant morbidity associated with biliary obstruction, gastric outlet obstruction and pain, and ultimately disease-related mortality. The availability of alpha particle treatment may help address the significant unmet need for effective and safe locoregional pancreatic cancer therapy due to its enhanced biologic potency coupled with its short

▶ **Table 2** Alpha DaRT insertion parameters.

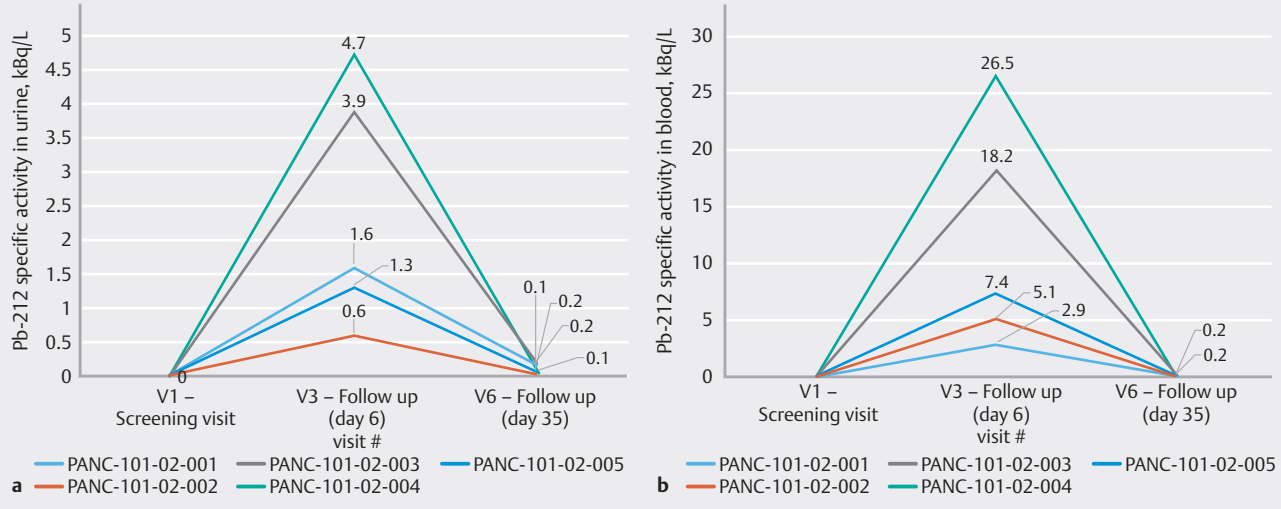
Patient	Number of 1-cm sources inserted	Number of 2-cm sources inserted	Total sources inserted	Equivalent number of 1-cm sources	Percent coverage GTV* (%)
1	3	0	3	3	8
2	11	0	11	11	13
3	21	0	21	21	44
4	10	6	16	22	12.5
5	4	10	14	24	29.5

GTV, gross tumor volume.
*Percent coverage GTV is corrected for overall dose of 16 Gy Alpha.

▶ **Table 3** Adverse events.

Patient	Adverse event description	Relationship to study device*	Severity grade
1	Fatigue	Probably unrelated	Mild
	Loss of appetite	Possibly related	Mild
	Abdominal pain	Possibly related	Mild
	Medical assistance in dying	Not related	Death
2	Urinary tract infection	Not related	Mild
	Abdominal pain	Not related	Moderate
	Gastrointestinal bleed	Probably unrelated	Severe
	Cholangitis	Probably unrelated	Severe
	Loss of appetite	Not related	Mild
	Gastrointestinal bleeding†	Probably unrelated	Death
3	Allergic reaction	Not related	Mild
	Constipation	Probably unrelated	Moderate
	Dizziness	Not related	Mild
	Biliary obstruction	Probably unrelated	Moderate

*An adverse event was considered associated with the use of the Alpha DaRT if the attribution was possible, probable, or very likely.
†This occurred in an area removed from the Alpha DaRT insertion and was thought to be due to disease progression with duodenal invasion. Patient was on anticoagulant and also had external beam radiation after the first bleeding episode.



▶ **Fig. 3** Plot per patient of Pb-212-Specific Activity Measured in **a** urine and **b** blood.

range of activity, limiting radiation dose to adjacent heathy tissue.

Alpha DaRT therapy is a novel method for delivering alpha particles for solid tumor radiation therapy. Results from the first clinical study of Alpha DaRT for treatment of squamous cell carcinoma of the skin and oral cavity were promising and demonstrated the safety of Alpha DaRT with no device-related SAEs [18]. In a follow-up pilot study in the United States, treatment with Alpha DaRT resulted in few AEs, and no device- or procedure-related SAEs [17].

In the present first-in-human study for pancreatic cancer, Alpha DaRT is applied to the target tumor under EUS guidance. The current report of the first five patients treated indicates the feasibility of this novel approach. Only two mild device-associated AEs and no serious device-associated AEs were observed. Based on this analysis, use of Alpha DaRT under EUS guidance in pancreatic cancer appears to be feasible and safe.

▶ **Table 4** Tumor measurements and response.

Patient	Visit	Timing of CT (days from procedure)	Longest diameter (cm)	Response	Metastases
1	Screening	–57	2.3		Yes
	Response evaluation	40	3.1	Progressive disease	Yes
2	Screening	–29	3.9		No
	Response evaluation	31	5.6	Progressive disease	Yes
3	Screening	–7	2.4		No
	Response evaluation	28	2.4	Stable disease	No
	Follow-up visit	69	1.6	Partial response	Yes
4	Screening	–3	3.9		Yes
	Response evaluation	28	3.7	Stable disease	Yes
	Follow-up visit	98	4.3	Stable disease	Yes
5	Screening	–25	3.9		Yes
	Response evaluation	28	4.3	Stable disease	Yes

CT, computed tomography.

The initial efficacy results from this interim analysis are promising, with three of the five patients having stable disease at 1-month follow up and one of them showing partial response 2 months post procedure. Importantly, the baseline size measurement evaluation was performed prior to the date of the procedure. Given the relatively fast pace of growth of pancreatic tumors, it can be assumed that the tumors were larger at the time of the Alpha DaRT procedure than at the screening scan, thus potentially resulting in an underreporting of the true benefit of Alpha DaRT based on modified RECIST evaluation. At this early stage, these observations are hypothesis-generating only.

A few limitations should be mentioned. The present analysis includes few patients treated at a single tertiary care center by one endoscopist (CSM). The full study is currently underway, which includes a larger sample size and patients treated at an additional center. However, results from the pre-planned interim analysis are important for dissemination given the novelty of the experimental treatment modality and its potentially major impact. The reported follow-up duration, while suitable for the primary outcomes of feasibility and safety assessment, is inadequate for drawing meaningful conclusions about tumor response.

Should feasibility and safety be confirmed with the results of the full study, efficacy of Alpha DaRT for pancreatic cancer can then be further studied in select patient populations and in conjunction with different therapies. In addition to the potential for improved outcomes related to locoregional tumor symptoms, improved tumor control with EUS-guided Alpha DaRT could ultimately translate into higher conversion rates for patients with borderline unresectable disease into resectable disease or higher R0 resection rates. Further, combination therapies with chemotherapy or immunotherapy might yield an increased therapeutic benefit for patients. Concomitant checkpoint inhibitor therapy, for which emerging data are demonstrating enhanced tumor responses with the synergistic effects of such combined therapy approaches, may be explored. Indeed, a potent synergistic antitumor effect when Alpha DaRT is used in combination with immune check point inhibitors for various solid tumors has been previously demonstrated in animal models [23]. Future studies comparing Alpha DaRT to proposed locoregional EUS-guided therapies such as radiofrequency ablation will also help elucidate the role this novel modality has in the treatment of pancreatic cancer.

Conclusions

In conclusion, preliminary results from this pilot study indicate that EUS-guided Alpha DaRT treatment for unresectable pancreatic cancer is feasible and safe. Further investigation of this promising novel modality is underway.

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Conflict of Interest

Corey S. Miller is a consultant for Alpha Tau Medical and Boston Scientific. Anand Sahai is a consultant for Boston Scientific. All other authors have no relevant conflicts.

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MEDTEQ + consortium and Alpha Tau Medical

Clinical trial

ClinicalTrials.gov (http://www.clinicaltrials.gov/)
Registration number (trial ID): NCT04002479
Type of Study: Prospective

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