Original Article

Bronchoscopic deployment and implantation of Diffusing alpha-emitters Radiation Therapy into the lung and mediastinum for treatment of lung cancer: a pre-clinical safety and feasibility study

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Background: Radiotherapy is a standard treatment modality in cancer therapy, particularly for lung cancer. Diffusing alpha-emitters Radiation Therapy sources (hereafter, "Alpha DaRTs") are fixed with Ra-244 (half-life =3.6 days) that releases alpha-emitting atoms into the tumor tissue to an effective range of a few millimeters.

Methods: The feasibility, usability, and safety of Alpha DaRTs deployment and implantation via bronchoscopy into the lung parenchyma and mediastinum in a big animal model of healthy swine was studied in two phases: (I) inert and (II) active Alpha DaRTs deployment. The Alpha DaRTs were inserted in both individual and cluster patterns based on a predefined plan. Swine health was monitored throughout the study. The usability of bronchoscopic deployment and implantation was evaluated using a user questionnaire. The movement and migration of the Alpha DaRTs were assessed. Necropsy was performed, and lungs were evaluated via gross pathology and histopathology.

Results: A total of 158 Alpha DaRTs were inserted successfully in the lung parenchyma and mediastinum of five swine in two phases. It was possible to deliver and place the Alpha DaRTs in clusters of no more than 4 mm distance between the Alpha DaRTs. No adverse event or change in the health and general condition of animals was observed. Hematologic evaluation did not show any clinically significant abnormality related to the Alpha DaRTs. Histopathology demonstrated local mild inflammatory changes, minimal fibrosis, and dystrophic mineralization with giant cells. Minimal movement and no migration of Alpha DaRTs were observed.

Conclusions: Bronchoscopic deployment of Alpha DaRTs in the lung parenchyma and mediastinum of the porcine animal is feasible, precise, and safe.

Keywords: Bronchoscopy; endobronchial ultrasound (EBUS); Diffusing alpha-emitters Radiation Therapy sources (Alpha DaRT); radiotherapy; lung cancer

Submitted Oct 06, 2023. Accepted for publication Jan 10, 2024. Published online Jan 29, 2024.
doi: 10.21037/tlcr-23-639
View this article at: https://dx.doi.org/10.21037/tlcr-23-639

Introduction

Lung cancer is the leading cause of death from cancer in the United States and Europe, leading to 1.8 million deaths globally per year (1). Lung cancer is often asymptomatic in its early stages, and therefore many patients present with advanced disease (2). Options for local therapy include tumor resection and external beam radiotherapy, and systemic treatment options include cytotoxic chemotherapy, immunotherapy, and targeted biologic agents (3).

In the past two decades, stereotactic ablative body radiotherapy (SABR) has emerged as an effective modality for treating small lung tumors, particularly when surgery is not feasible. However, toxicity concerns limit the use of SABR in patients with severe pulmonary disease (e.g., fibrosis), tumor proximity to vital anatomic structures, or previous radiation treatment (4). This limitation may lead to the use of sub-curative treatment. To address this, local therapies to achieve tumor ablation in lung cancer are being investigated. These include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, pulsed electric field (PEF), photodynamic therapy, thermal vapor ablation, and high-intensity focused ultrasound (5-9). Most of these are administered via a transthoracic approach, with computed tomography (CT) guidance. Transthoracic approaches have inherent complication risks that include pneumothorax, bleeding, and pain. A bronchoscopic treatment approach, if available, could have favorable safety and tolerability profiles (10). Furthermore, bronchoscopy allows mediastinal lymph node staging in the same procedure to help ensure that an appropriate treatment strategy is adopted (11).

Diffusing alpha-emitters Radiation Therapy sources (hereafter, "Alpha DaRTs") is a unique technology to deliver alpha particles using interstitial sources that release alpha emitting atoms into the tumor (12). Alpha DaRTs are several millimeters long stainless-steel thin tubes loaded with Ra-224 (half-life =3.631 days), which is fixed on their surface (12). Following implantation, Rn-220 is released from the source and continues the decay chain inside the tumor tissue, such that alpha emitting atoms spread in the tumor and deposit an alpha radiation dose in a temporal and spatial distribution that was previously described in an effective range of about 4–5 mm (12). Multiple Alpha DaRTs implanted into the tumor allow alpha particles to spread and deposit effective dose within the entire tumor volume (12-15).

Alpha radiation is a type of high linear energy transfer (LET) radiation with high relative biological effectiveness (RBE) due to the creation of hard-to-repair DNA damage in the form of clustered double strand breaks (DSBs) (16). Since Alpha DaRTs are effective over a range of only several millimeters, where it is very efficient, it may provide a focused solution for the delivery of "ablative" particle radiotherapy, with almost no effect on the adjacent tissues. These characteristics position Alpha DaRTs as a promising treatment option in situations where surgery or SABR is not possible.

Implantation of Alpha DaRTs into subcutaneous murine- or human- derived tumors of the lung has been shown to delay tumor growth and extend overall survival in mice (17). Similar results were demonstrated for other indications such as pancreas, breast, prostate, glioblastoma multiforme, and colon (18-20). Unlike the X-rays typically utilized when administering SABR, alpha radiation has proven efficacy that is independent of tumor oxygenation. Alpha DaRTs were shown to stimulate an antitumor immune response as a monotherapy or when combined with various types of immunotherapies in other indications (20-23). Specifically, the treatment synergizes with immune checkpoint blockade (24), which is approved for use in the treatment of lung cancer patients. Alpha DaRTs are currently being tested in clinical trials to treat multiple solid tumors, including pancreas, liver, skin, head and neck, prostate,

Highlight box

Key findings

- A total of 158 inert or active Diffusing alpha-emitters Radiation Therapy sources (Alpha DaRTs) were successfully deployed and implanted in the lung and mediastinum of healthy swine.
- Delivering the Alpha DaRTs in clusters was possible.
- Minimal movement and no migration were observed following Alpha DaRTs implantation.
- No significant adverse clinical events were noted in relation to the deployment and presence of the Alpha DaRTs *in vivo*.
- Local mild inflammatory changes, minimal fibrosis, and dystrophic mineralization with giant cells were observed on histopathology of tissue around the active Alpha DaRTs after 28 days *in vivo*.

What is known and what is new?

- Alpha particles are highly effective in killing cancer cells. However, they are not currently used to treat lung cancer.
- This is the first study to demonstrate the feasibility and safety of local alpha particle delivery to the lung and mediastinum.

What is the implication, and what should change now?

- The study is an important step towards a clinical trial for lung cancer patients.

and breast cancers (NCT05657743, NCT05829291, NCT05323253, NCT05047094, NCT03970967, NCT04543903).

In this study, we assessed the feasibility and safety of the bronchoscopic delivery of Alpha DaRTs for the treatment of lung and mediastinal tumors. Given the normal movement of lung tissue during breathing cycles, our aim was to investigate the stability of Alpha DaRTs after their placement. In addition, we investigated the feasibility of placing clusters of Alpha DaRTs with 4 mm spacing. Finally, we evaluated animals' overall general health and safety using blood and urine samples and performed pathologic analysis. We present this article in accordance with the ARRIVE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-639/rc).

Methods

Animals

All procedures were conducted in accordance with all Federal and State animal welfare laws, regulations, policies, and guidelines, and with approval by the Montefiore Medical Center Institutional Animal Care and Use Committee (IACUC) (study protocols #20-11-100 and 09-100-22) and Radiation Safety, Environmental Health and Safety. A protocol was prepared before the study without registration. Five female Yorkshire swine 4–5 months old and weighing 65–75 kg were purchased from a commercial swine vendor with a closed herd (Animal Biotech Industries, Inc., ABI, Doylestown, PA, USA).

Animals were evaluated upon arrival and given Draxxin tulathromycin (10%) 2.5 mg/kg subcutaneous (SQ) prophylactically to prevent swine respiratory disease (SRD) due to transport stress. They were acclimated to the facility for at least 5 days before any procedures were conducted. Throughout the study, the swine were individually housed in adjacent pens with visual, olfactory, auditory and snout tip contact to provide animal to animal social contact. The swine were provided with environmental enrichment. The bedding was wood chips/shavings. They were fed standard swine chow twice a day and had access to water ad libitum. Housing and husbandry conformed to the standards of the Guide for the Care and Use of Laboratory Animals [2011]. Draxxin was repeated immediately prior to the Alpha DaRTs implantation procedure. Animals were monitored daily for their appetite, water consumption, general body condition, attitude, and mobility. Signs of respiratory illness, nasal discharge, abnormal respiratory rate, if any, were documented.

Anesthesia and analgesia

The swine were not fed the night and morning before anesthesia; water was available at all times. Prior to the anesthesia for implantation, premedication with the anticholinergic atropine intramuscular (IM) at 0.05 mg/kg was given to reduce salivary secretions that may obscure the tracheal opening during orotracheal intubation. After a minimum of 15 minutes, telazol (tiletamine-zolazepam) IM at 4.4 mg/kg and ketamine IM at 2.2 mg/kg were given in their home cage to create recumbent immobilization for ease of transport to the surgical prep room, where the swine was placed on a warm water circulating blanket to prevent hypothermia during anesthesia. A rectal temperature probe was placed. A pulse oximeter was placed to monitor SPO_2 and baseline heart rate. Vital signs were continuously monitored and recorded every 15 minutes. Ophthalmic ointment was applied to both eyes to prevent corneal drying. The swine was placed on 2–4% isoflurane with oxygen by facemask to preoxygenate the swine and further sedate for placement of intravenous access via marginal ear vein for anesthesia induction via a slow IV bolus of propofol at 1–3 mg/kg IV. Following anesthetic induction, the larynx was sprayed with approximately 0.2–0.5 mL of a local analgesic, cetacaine, to reduce the risk of laryngeal spasm. An endotracheal tube (ETT) was passed under direct visualization into the larynx past the buccal pouch into the trachea. The ETT was connected to a closed circle anesthesia unit with an isoflurane vaporizer, ventilator, gas inhalant scavenging system, $ETCO_2$ and respiratory rate monitoring. Anesthetic depth and hemodynamic stabilization were confirmed prior to transport to the survival surgery suite.

Maintenance anesthesia consisted of isoflurane (2–2.5%) mixed with 100% oxygen (1.5–2 L/min) and mechanical ventilation (10–15 mL/kg, 10–15 respirations/minute, inspiratory time <1.5 s, inspiratory/expiratory ratio 1:3, peak inspiratory pressure 20–25 cm H_2O, and the MCO_2 range of 30–46 mmHg). A constant intravenous infusion of Lactated Ringers solution or Normosol was given at a rate of 2–5 mL/kg/h. Non-invasive blood pressure was monitored when needed. Continuous vital signs monitoring during anesthesia included heart and respiratory rates, electrocardiography, MCO_2, and body temperature, recorded every 15 minutes.

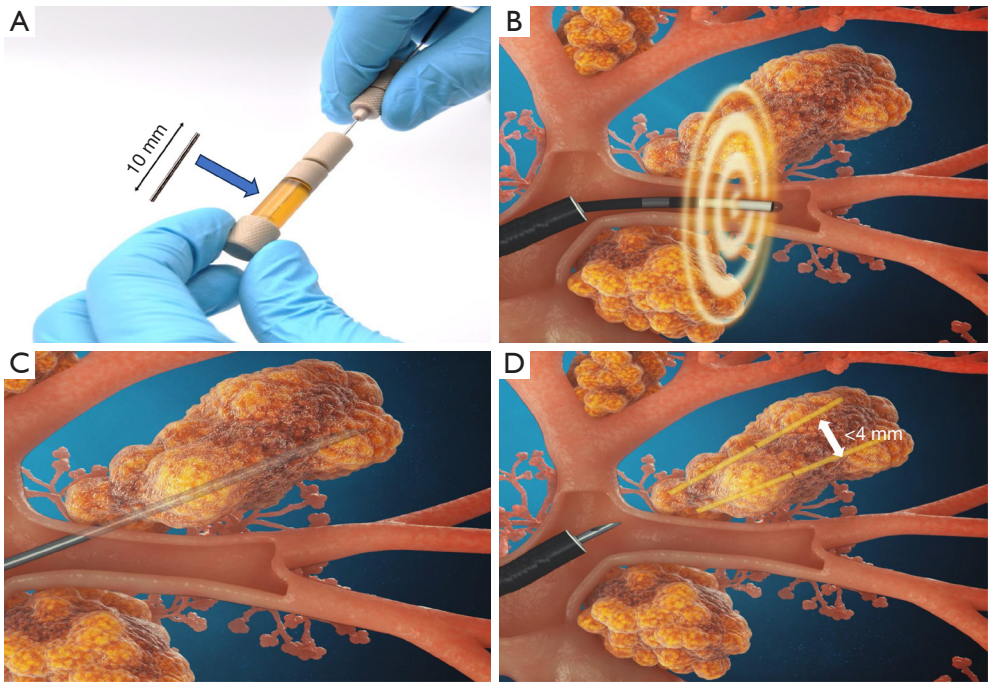


Figure 1 Alpha DaRTs insertion. (A) Stainless-steel tube with a diameter of 0.37 mm and the length of 10 mm, loaded with 2 µCi Ra-224 atoms that are fixed on its surface, is loaded into an FNA needle from a designated loading device. The needle is withdrawn back into the sheath and secured. The blue arrow points out to the Alpha-DaRTs inside the loading device. (B) A rEBUS probe is inserted via working channel of a bronchoscope and examine the lung parenchyma until the target tissue is identified. (C) The rEBUS probe is withdrawn and the loaded FNA needle is inserted via the working channel of the bronchoscope until it reaches the target tissue. (D) Alpha DaRT is released to the tissue by using the FNA needle as introducer and its stylet as a pusher. The needle is then withdrawn, and the Alpha DaRT remains in the tissue. A new loaded needle can be inserted into the bronchoscope and the procedure can be repeated. Several Alpha DaRTs can be placed in the tissue until a cluster of sources is reached according to a predefined configuration (white arrow), minimizing the dose coverage loss. Alpha DaRTs, Diffusing alpha-emitters Radiation Therapy sources; FNA, fine needle aspiration; rEBUS, radial endobronchial ultrasound.

Analgesia was given using standard buprenorphine HCl (short acting) 0.02 mg/kg SQ at the time of anesthesia induction. At the conclusion of the anesthesia and prior to recovery, buprenorphine sustained-release (SR) long-acting 0.2 mg/kg SQ was given which provided 72–96 hours of analgesia.

Alpha DaRTs

Alpha DaRTs (*Figure 1A*), contained inside a designated loading device, were made of 316LVM stainless steel with a diameter of 0.37 mm and the length of 10 mm. The Alpha DaRTs were either inert (non-active) or loaded with Ra-224 atoms (activity of 2 µCi) following an electrostatic collection process similar to that previously described (12). Ra-224 atoms were embedded a few atomic layers into the Alpha DaRTs surface and were fixed to the surface through thermal treatment. Alpha DaRTs are supplied inside a designated loading device (*Figure 1A*). During the study, several Alpha DaRTs were inserted into the lung parenchyma and mediastinum in clusters in a spatial configuration of a hexagonal grid (15), such that the Alpha DaRTs are no more than 4 mm away from each other that minimizes the dose coverage loss (*Figure 1*), according to a predetermined treatment plan and the IACUC approved study design.

Bronchoscopic implantation procedures

Once intubated, anesthetized, and relocated from the surgical prep room to the survival surgery suite, the animal was placed in ventral recumbency and positioned for bronchoscopy. An ETT adapter (swivel-three way) was applied at the tip of the ETT. The Olympus bronchoscope

BF-P-190 and BF-MP190 (Redmond, WA, USA) were used. Initial airway inspection was performed to assure there was no unexpected abnormality. The bronchoscope was advanced into the lung lobes. The bronchoscope was positioned at the peripheral airways with diameters of about 3–4 mm, and more distal airways as small as 1 mm in diameter were visualized. An Olympus radial endobronchial ultrasound (EBUS) probe UM-S20-17S was inserted via the bronchoscopic working channel.

Lung tumors are expected to invade the lung parenchyma and mediastinal areas and we developed the mechanism to be able to place the sources in both areas. Since we do not have a live large animal model for lung cancer, sources were placed in the normal mediastinum and lung parenchyma. We carefully selected the areas of the lung and mediastinum that had minimal soft tissue to give enough space for placement of the source without any injury to the surrounding normal structures.

Under radial EBUS and fluoroscopy (Mobile C-arm, BV Pulsera, Phillips, Eindhoven, Netherlands) imaging, the lung parenchyma was examined to locate lung tissue at least 1–2 cm from the pleural surface and without an adjacent blood vessel. The radial EBUS probe was then retracted and an Olympus Peri-view Flex 21-gauge needle NA-403D-2021 preloaded with radioactive Alpha DaRTs or inert Alpha DaRTs passed via the working channel of the bronchoscope (*Figure 1B-1D*).

The needle was visualized at the tip of the bronchoscope with direct bronchoscopic view, fluoroscopy image, or both. Alpha DaRT was placed in the tissue by using the fine needle aspiration (FNA) needle as introducer and its stylet as a pusher. The Alpha DaRT remained in the tissue while the needle was withdrawn through the bronchoscope (*Figure 1B-1D*). For mediastinal insertions, an Olympus BF-UC180F or BF-UC190 EBUS scope was passed via the ETT, and the mediastinum around the paratracheal and subcarinal areas was examined using a linear array EBUS. After finding a desired location with adequate soft tissue depth, a ViziShot EBUS-TBNA Needle (21 gauge) (Redmond, WA, USA) preloaded with Alpha DaRTs (either active or inert, as specified below) were passed via the working channel of the bronchoscope. The needle was visualized at the tip of the bronchoscope with direct bronchoscopic view, EBUS or fluoroscopy image or a combination of all three. The Alpha DaRTs were inserted in the desired position in the mediastinum (*Figure 1B-1D*).

For both locations, in case the position of the Alpha DaRTs needed to be adjusted, a 1.5 mm forceps was passed via the working channel to move the Alpha DaRTs into optimum position. If the Alpha DaRTs could not be optimally adjusted, it was removed by the forceps. An Olympus BF-1TH190 therapeutic bronchoscope was available in case of any excessive airway bleeding to clear the airways and maintain ventilation, however it was not needed during any of the implantation procedures.

CT

After the implantation procedure and at the specified timepoints, CT lung scans were conducted on each swine. On the scanning table, the animal was positioned headfirst in ventral recumbency and secured to the table in a straight position. CT scans (LightSpeed VCT, GE, Boston, MA, USA equipped with a 64-slice scanner, data acquisition system HDAS64, GE, Boston, MA, USA) were performed during brief hypopnea (apnea was not feasible) following hyper inspiratory ventilation. Scan slice thickness did not exceed 1 mm.

Animal housing and monitoring

After each procedure, animals were housed in a limited-access animal facility in pre-disinfected pens and were fed commercial swine diet, with free access to drinking water. Animals were examined daily by the animal care staff for any changes in gait, posture, appetite, feces, urination, temperature, presence of nasal or ocular discharge, and any abnormalities in breathing.

Blood and urine samples

Samples for complete blood count (CBC), and serum biochemistry profile were collected at specified time points: days 1, 7 and 28 in phase II. For blood collection, venipuncture of the auricular vein was conducted while subjects were under general anesthesia. Five ml blood was drawn from each subject and was divided into two tubes: one red-topped Becton Dickinson Vacutainer tube (BD, Franklin Lakes, NJ, USA) for serum chemistry and one ethylenediaminetetraacetic acid (EDTA) purple-topped Becton Dickinson Vacutainer tube for complete cell blood count. The red-topped tube was allowed to clot for 30 min at room temperature before the serum was separated from the clot by centrifugation for 10 min at 1,500 g. The sera and blood were stored at 4 ℃ until assay by using the Beckman Coulter AU5800 automated chemistry analyzer

(Antech Diagnostics, New Hyde Park, NY, USA) for serum chemistry and Siemens Advia 2120 automated hematology analyzer (Siemens, Munich, Germany) for the CBC.

Urine specimens for urinalysis (UA) were collected from each subject by clean-catch during spontaneous micturition the day after the bronchoscopy and Alpha DaRTs implantation procedure. The samples were submitted the same day to Antech Diagnostics for analysis by Siemens Novus Automated Urine Analyzer.

Euthanasia

Animals were euthanized in the animal facility while under anesthesia using an IV injection of intravenous potassium chloride (1–2 meq/mL) or 100 mg/kg Euthasol (Virbac, Westlake, TX , USA) (pentobarbital sodium 390 mg/mL and phenytoin 50 mg/mL). Death was confirmed by thoracic auscultation for cessation of heartbeat. The method used is consistent with the current American Veterinary Medical Association (AVMA) guidelines.

Pathology

On termination day of phase II, necropsy and gross pathology were conducted, and Alpha DaRTs placement sites were collected and processed for histopathological evaluation. Immediately after euthanasia, necropsy was performed by a veterinarian pathologist for gross pathology examination of the thoracic cavity. Major mediastinal organs (pericardium, myocardium, aortic arch, cranial and caudal vena cava, esophagus, untreated lymph nodes) were assessed for pathological changes.

Heart, lungs, trachea, esophagus, and parts of the adjacent mediastinal adipose tissue were eviscerated. All implanted sites were identified with fluoroscopy. Tissue specimens in a diameter of at least 2–5 cm around the Alpha DaRTs were sampled, and specimens were put into 10% formaldehyde. After fixation, specimens were prepared for histopathology: multiple parallel cross sections were made in equal gaps/spaces of 3–5 mm. In order to identify all Alpha DaRTs, Alpha DaRTs were removed, and tissue biopsies were cut precisely around each Alpha DaRTs individual or cluster location. The total Alpha DaRTs number was compared to the procedure documentation, to ensure all have been collected. Specimens were embedded in paraffin. Histological sections (5 or 10 µm) were prepared, stained with hematoxylin-eosin (H&E), and analyzed by a histopathologist.

Experimental design

The study was performed in two phases: non active (inert Alpha DaRTs) phase and active (radium-loaded Alpha DaRTs) phase (see *Figure 2*). In the first phase of the study (hereafter, "phase I") we aimed at establishing the delivery method, gaining experience in deploying the inert sources in the lung, determining the best method to investigate source migration and movement, and performing basic safety evaluations. In the second phase (hereafter, "phase II"), we added CT scans for stability analysis and elongated the follow-up period, as well as additional safety tests, such as blood and urine tests and pathological evaluation.

In each phase, two sessions of Alpha DaRTs insertions were performed at different time points, as described in *Figure 2* and in *Table 1*. In phase I, inert Alpha DaRTs were inserted into the lung and mediastinum of three swine (swine #1, 2, 3). In phase I, session 1, five inert Alpha DaRTs were implanted in each cranial, middle/accessory and caudal lobes (15 Alpha DaRTs in all lobes per swine) of the right lung and 3–4 inert Alpha DaRTs in the mediastinum for each swine. Fluoroscopy on day 7 was found not to be sensitive enough to detect slight movement of the Alpha DaRTs. Therefore, CT scans were performed on day 17 to identify Alpha DaRTs' location and to validate no migration from the lung to external organs during the experiment. In phase I, session 2, on day 33, 15 additional inert Alpha DaRTs were placed in the cranial and caudal lobes of the left lung in each swine and a CT scan was performed on the same day. The third CT scan was done on day 38 (before euthanasia). The animals' condition was monitored from day 0 until day 38. The Alpha DaRTs that were placed in phase I, session 2 served for the movement analysis, and their position was checked to calculate the movement between phase I, session 2, day 33 and phase I study end on day 38.

In phase II, 51 Alpha DaRTs were inserted into the lung parenchyma and mediastinum of two swine. In phase II, session 1 (day 0) 44 active Alpha DaRTs were placed in the bilateral lung parenchyma of the two swine (swine #4, 5) and 7 in the mediastinum of only swine #5). In phase II, session 2, day 28 prior to euthanasia, 6 inert Alpha DaRTs were inserted into the mediastinum of swine #4 for completeness of feasibility testing. These inert Alpha DaRTs were not included in the stability (movement) analysis in phase II. In phase II, the usability of the procedure was assessed by a user questionnaire completed by the surgeon, rating the ease of performing the procedure on a 5-point Likert scale

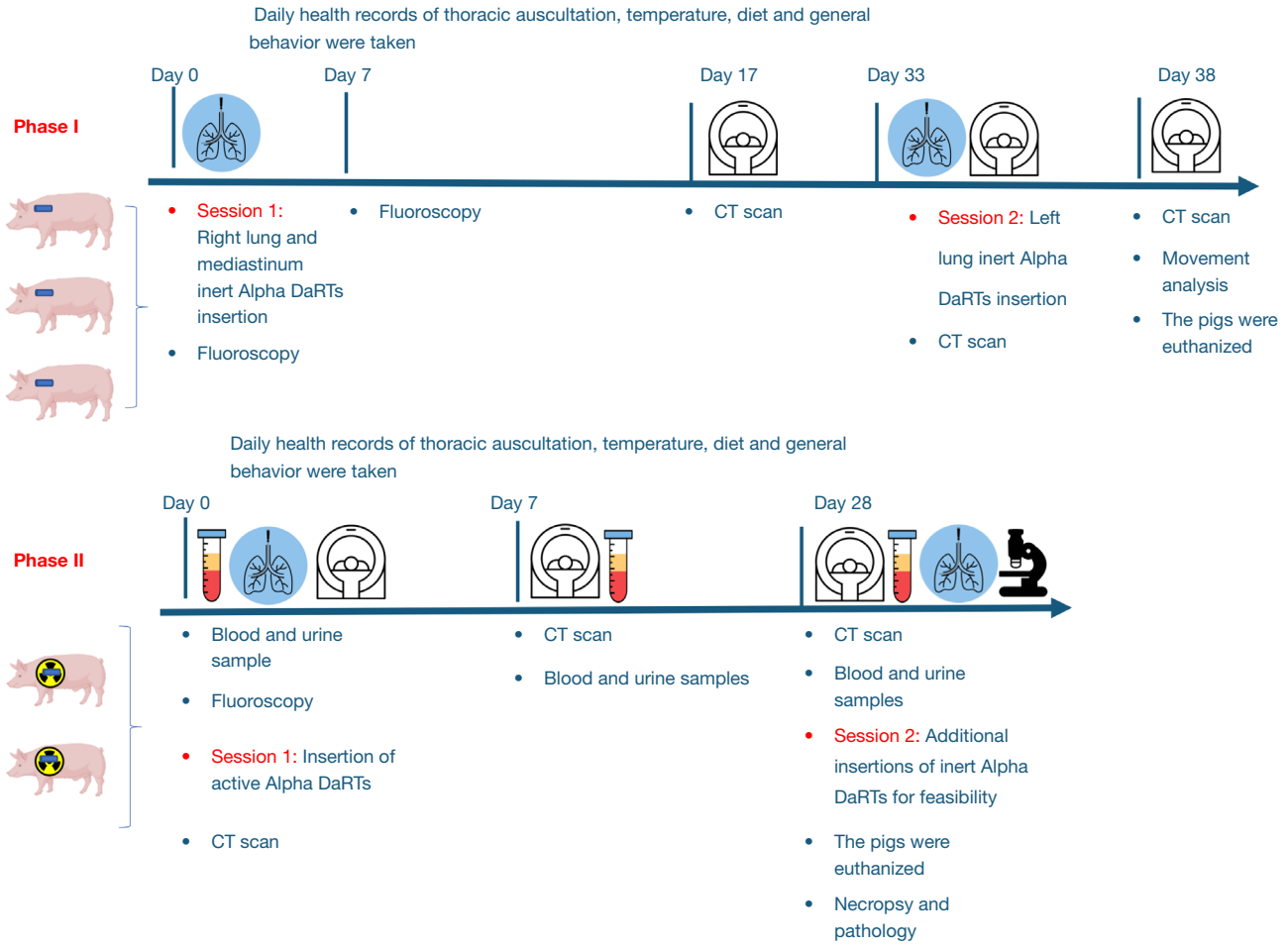


Figure 2 Experimental design. The study was conducted in two phases, evaluating the deployment of: (I) inert Alpha DaRTs; (II) active Alpha DaRTs. Computed tomography scans were used for movement and migration analysis, daily health records, blood, urine and pathology tests were used to evaluate the animal condition. Alpha DaRTs, Diffusing alpha-emitters Radiation Therapy sources; CT, computed tomography.

(*Table 2*). CT scans and blood and urine samples were taken on days 0, 7, and 28. Following euthanasia, necropsy and pathology were performed. Out of all 158 Alpha DaRTs inserted in all phases, 94 were used for stability analysis (*Table 3*).

Migration and movements calculations

CT scans were visualized using MIM software, V7.25. The Alpha DaRTs' location was manually identified, and a virtual Alpha DaRT was created and located in the exact position. The process of matching between two coordinate systems of two sequenced CT scans ("registration") was performed using an in-house contour-based [Coherent Point Drift (CPD) method] (25) or CT-based (Affine and BSpline method) (26) python script developed at Alpha Tau Medical (Jerusalem, Israel). The script was based on the deformable registration method CPD algorithm and used the python library "Probreg" V0.1.6 (Kenta-Tanaka *et al.*, https://probreg.readthedocs.io/en/latest/), with some adjustments.

The contours of the lungs were created using the MIM "region grow" tool. The contours were used as the initial contours for the registrations. The registration was performed such that one CT scan was constant and the other was adjusted to it in a semimanual iterative process. The identification of Alpha DaRTs pairs between two sequenced CT scans was performed using an in-house python script developed at Alpha Tau Medical. The script

Table 1 Alpha DaRTs deployment according to study design

Study	Session	Insertion day	Active/inert	Swine #	Alpha DaRTs implant location	Alpha DaRTs #
Phase I	1	0	Inert	1	Right lung lobe	15*
Phase I	1	0	Inert	2	Right lung lobe	15*
Phase I	1	0	Inert	3	Right lung lobe	15*
Phase I	1	0	Inert	1	Mediastinum	3
Phase I	1	0	Inert	2	Mediastinum	4
Phase I	1	0	Inert	3	Mediastinum	4
Phase I	2	33	Inert	1	Left lung lobe	15#
Phase I	2	33	Inert	2	Left lung lobe	15#
Phase I	2	33	Inert	3	Left lung lobe	15
Phase II	1	0	Active	5	Mediastinum	7
Phase II	1	0	Active	4	Right & left lung lobes	20***
Phase II	1	0	Active	5	Right & left lung lobes	24##
Phase II	2	28	Inert	4	Mediastinum	6**

A total of 158 Alpha DaRTs were deployed in two phases. In phase one session one, 45 inert Alpha DaRTs were placed in the right lung of three animals, and 11 inert Alpha DaRTs were placed in their mediastinum. In phase one session two, 45 inert Alpha DaRTs were placed in the left lung of three animals. In phase two session one 44 active Alpha DaRTs were placed in both lungs of two animals and 7 active Alpha DaRTs in the mediastinum of one animal. In Phase two session two, 6 inert Alpha DaRTs were placed in mediastinum of one animal. Several Alpha DaRTs were not included in the stability analysis as: *, their location was not CT scanned on day 0; **, they were inserted on the last day of the follow up; #, two Alpha DaRTs were outliers. ***, two Alpha DaRTs were used to test an experimental accessory that was not included in the study and three Alpha DaRTs were outliers; ##, four Alpha DaRTs were outliers. Alpha DaRTs, Diffusing alpha-emitters Radiation Therapy sources.

Table 2 Questionnaire used for operator assessment of the usability & feasibility of the deployment methods

Usability & feasibility rank*	Mediastinum	Parenchyma
How difficult was it to deploy the Alpha DaRTs properly from the applicator?	1	2
How difficult was it to place the Alpha DaRTs where the user intended them to be placed?	1	1
How difficult was it to place a cluster of 4 Alpha DaRTs in a spacing of 4 mm?	1	2
How difficult was it to navigate to each designated target for each insertion?	1	1
How difficult was it to place Alpha DaRTs in proximity to blood vessels/the heart without causing damage to the blood vessel during the placement?	1	1
How difficult was it to have a clear visualization of the lung and mediastinal tissue with the EBUS before starting the insertions, using endobronchial ultrasound, bronchoscopy video and fluoroscopy surveillance?	1	1
How difficult was the visualization of the Alpha DaRTs in the CT scan?	1	2
Did any Alpha DaRTs fall out during the procedure?	1	1

*, 1–5 scale: 1, very easy; 5, very difficult. DaRTs, Diffusing alpha-emitters Radiation Therapy sources; CT, computed tomography; EBUS, endobronchial ultrasound.

Table 3 Stability analysis

Phase	Session [movement between days #]	Duration of follow-up (days)	Swine #	Source type	Location	N	Alpha DaRTs mean movement (mm)*	SD	Total error (mm)**
Phase I	Session 2 [33–38]	5	1	Inert	Mediastinum	3	1.7	0.8	2.3
Phase I	Session 2 [33–38]	5	2	Inert	Mediastinum	4	1.0	0.3	2.9
Phase I	Session 2 [33–38]	5	3	Inert	Mediastinum	4	1.3	0.5	2.6
Phase II	Session 1 [0–28]	28	5	Active	Mediastinum	7	3.1	1.3	1.7
Phase I	Session 2 [33–38]	5	1	Inert	Parenchyma	13	2.7	1.4	2.6
Phase I	Session 2 [33–38]	5	2	Inert	Parenchyma	13	3.3	1.1	2.5
Phase I	Session 2 [33–38]	5	3	Inert	Parenchyma	15	3.6	2.0	3.1
Phase II	Session 1 [0–28]	28	5	Active	Parenchyma	20	6.9	4.7	2.8
Phase II	Session 1 [0–28]	28	4	Active	Parenchyma	15	4.7	2.7	2.5

The stability analysis is based on a comparison of CT images on two different timepoints. *, the mean of a set of "N" Alpha DaRTs per condition (animal, location, active/inert), excluding outliers. For each source Alpha DaRT mean movement (mm) was calculated by averaging the distances the locations of the edges or the center of the same source on different days (33 and 38 on phase I; 0 and 28 on phase II). **, the total error including registration error and intra-observer errors. #, "number". DaRTs, Diffusing alpha-emitters Radiation Therapy sources; SD, standard deviation; CT, computed tomography.

employed the Munkres global assignment method (27). This method allows to globally minimize the sum of distances between every Alpha DaRTs pair, such that all Alpha DaRTs optimally fit between two scans.

The distance between two Alpha DaRTs within a single pair was calculated using an in-house python script as follows. For each Alpha DaRTs, 3 points were marked: two edges and one center of mass. Thus, for each pair of Alpha DaRTs, three types of distances were calculated: (I) the distance between the two top edges; (II) the distance between the two bottom edges and (III) the distance between the two centers of mass. The distance between two Alpha DaRTs in a pair was calculated by averaging over all three distances mentioned above.

Statistical analysis

For the movement analysis, the following parameters were calculated using the Python script mentioned above. The average movement for each swine was obtained by averaging the distance between two Alpha DaRTs within a pair for all pairs of Alpha DaRTs. Associated standard deviation (SD) for each swine were calculated as well.

The root mean square error (RMSE) was calculated as the average distance between the vertices of the two contours of the lungs of both CT scans. This number expresses the registration error stemming from either the accuracy of the registration or the actual average movement of the lungs as a whole organ. In addition, an intra-observer error was calculated to express the error of Alpha DaRTs detection in MIM software, due to the manual manner of its performance. Finally, a total error was calculated as the root mean square of both the registration error and the intra-observer error. An outlier test for multiple outliers was performed using the "ROUT" procedure with default parameter Q=1% on the movement data of all Alpha DaRTs for each location (mediastinum/parenchyma) in each swine separately.

Results

Feasibility and usability of Alpha DaRTs deployment

A total of 158 Alpha DaRTs were delivered in two phases (see study design in the methods section and *Table 1*). Fifty-one (32%) were active Alpha DaRTs. The Alpha DaRTs were delivered either in clusters (up to 4 mm hexagonal spacing between Alpha DaRTs) or as individuals (minimum 1 cm spacing between Alpha DaRTs). Twenty-four Alpha DaRTs were deployed successfully in the mediastinum and 134 into the lung parenchyma. In phase I, a total of 101 Alpha DaRTs were inserted into 3 swine, 11 in mediastinum and 90 in the lung parenchyma (*Figure 3A*). In session 1, 5 inert Alpha DaRTs were implanted in the right lung (3 clustered Alpha DaRTs and 2–3 additional individual or clustered

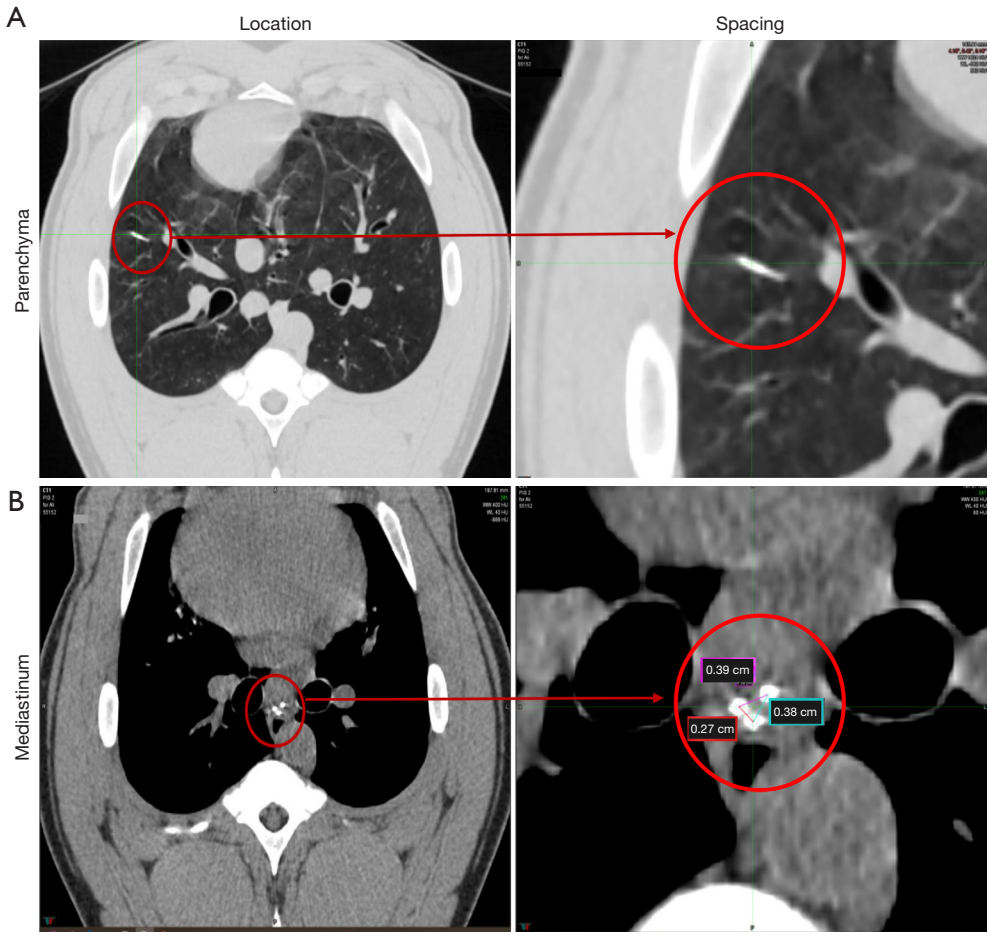


Figure 3 Inert Alpha DaRTs placement. Axial Computed tomography of porcine animal demonstrating inert Alpha DaRTs placement. (A) Individual source in lung parenchyma. (B) Cluster of 3 sources in mediastinum with a maximum gap of 4 mm between Alpha DaRTs. Alpha DaRTs, Diffusing alpha-emitters Radiation Therapy sources.

Alpha DaRTs in each lobe) of each swine. In total, 45 Alpha DaRTs were inserted in the right lung parenchyma in all swine. In addition, 3–4 inert Alpha DaRTs were implanted in mediastinum for each swine (total 11 for all 3 swine). Moreover, the required maximal gap of 4 mm between Alpha DaRTs in any cluster was obtained (*Figure 3B*). In session 2, 15 additional inert Alpha DaRTs were placed in the left lung lobe of each swine (3 clusters, 5 Alpha DaRTs in each cluster). The total number of Alpha DaRTs placed in this session was 45.

In phase II a total of 57 Alpha DaRTs were inserted. In session 1, active Alpha DaRTs were placed in the parenchyma of both left and right lung lobes of the two swine (*Figure 4A*). In one swine (swine #4), 8 individual Alpha DaRTs and 3 clusters (4 Alpha DaRTs per each cluster) were placed (a total of 20 Alpha DaRTs). No Alpha DaRTs were placed in the mediastinum of swine #4 due to animal temporal distress during the prolonged procedure, (~3 hours). The situation was resolved within an hour. In the second swine (swine #5) 12 individual Alpha DaRTs and 3 clusters (4 Alpha DaRTs per cluster) were placed in the lung parenchyma (a total of 24 Alpha DaRTs). A total of 7 Alpha DaRTs were delivered to mediastinum in one cluster (4 Alpha DaRTs per cluster), and 3 individual Alpha DaRTs. In session 2, a total of 6 inert Alpha DaRTs were inserted to the first swine (swine #4) mediastinum in one cluster (4 Alpha DaRTs per cluster) and 2 individual Alpha DaRTs.

Alpha DaRTs were placed in the lung parenchyma and mediastinum using basic bronchoscopic techniques described in the method section. Alpha DaRTs deployed

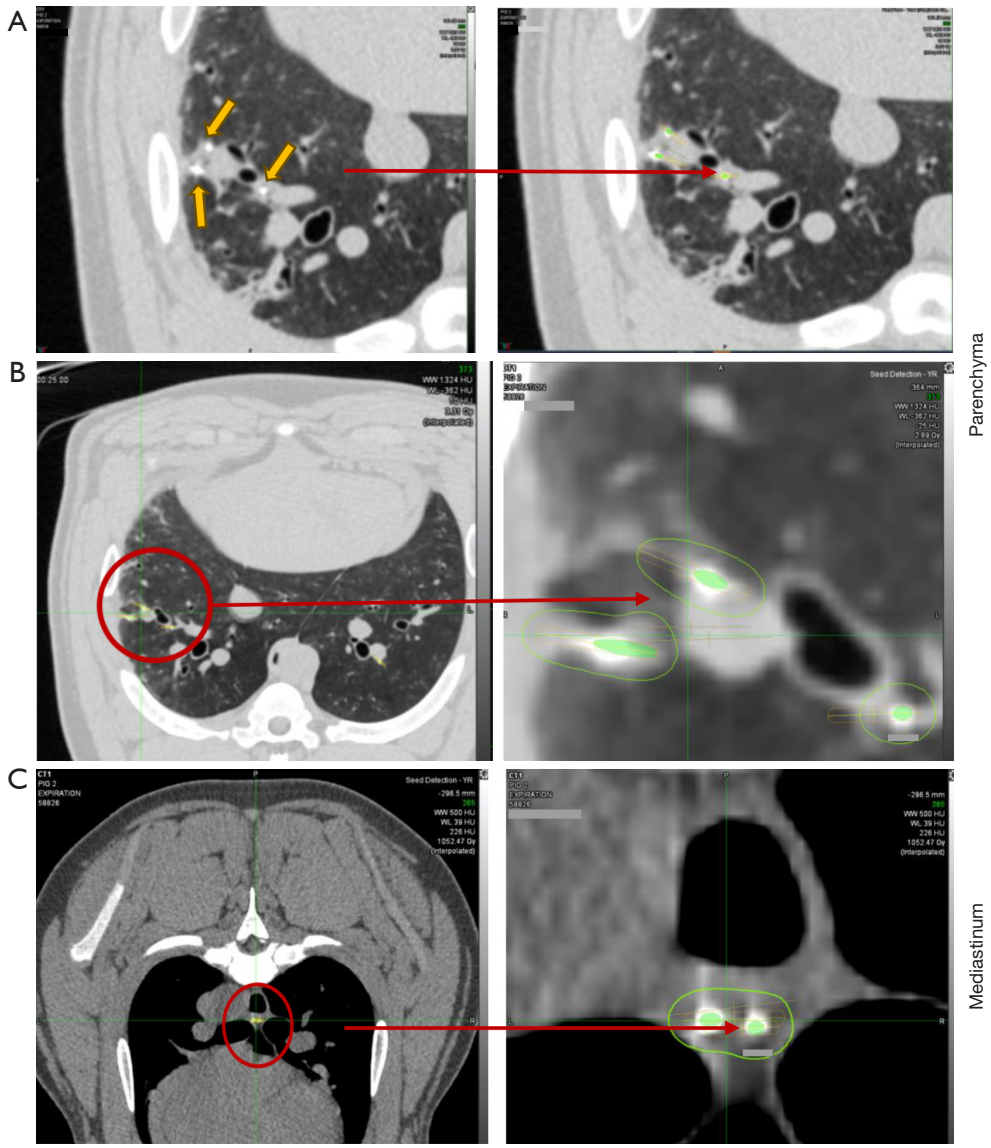
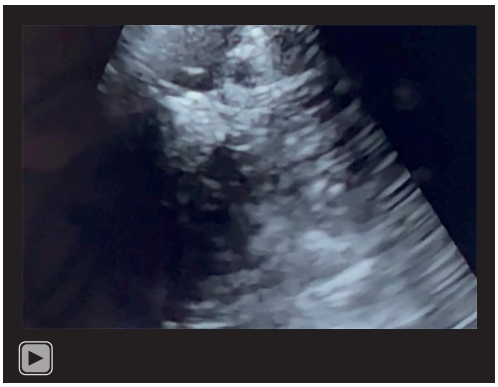


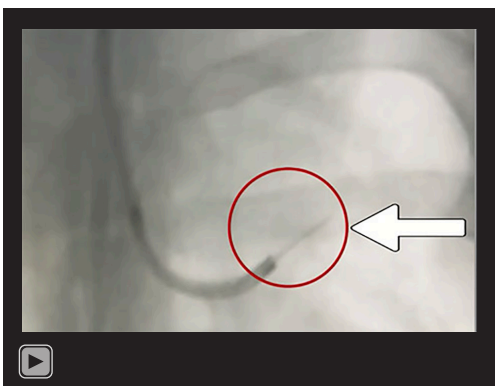
Figure 4 Active Alpha DaRTs placement. (A) Alpha DaRTs placed in the lung parenchyma (marked in yellow arrows). Images in the right side show the outlined active Alpha DaRTs in green. (B) Active Alpha DaRTs in parenchyma. In the right enlarged image including isodose of the Alpha DaRTs outlined in green line that represents the border area in which dose >10 Gy. (C) Active cluster of Alpha DaRTs in mediastinum. In the right enlarged image including isodose of active Alpha DaRTs cluster is outlined in green line, representing the border area in which dose >10 Gy. Alpha DaRTs, Diffusing alpha-emitters Radiation Therapy sources.

safely and avoided blood vessels even when placed in clusters. *Figure 3A,3B* demonstrates the isodose of individual or clustered sources. Two video files representing the placement of the Alpha DaRTs in mediastinum and lung parenchyma are provided (*Videos 1,2*).

A semi quantitative assessment of the physician's comfort using the Alpha DaRT deployment technique was performed. EBUS visualization of the mediastinal area and bronchoscopic view during Alpha DaRTs deployment in the parenchymal tissue was rated by the surgeon as "Very Easy". Navigation to each designated target and implant the Alpha DaRTs with 4 mm hexagonal spacing between them was "Very Easy", with a slight challenge in the deeper areas of the lung parenchyma. The Alpha DaRTs did not fall off



Video 1 Diffusing alpha-emitters Radiation Therapy sources (Alpha DaRTs) placement in the mediastinum via bronchoscopy with real time endobronchial ultrasound guidance.



Video 2 Diffusing alpha-emitters Radiation Therapy sources (Alpha DaRTs) placement in the lung parenchyma under fluoroscopy surveillance. The site of deployment was assessed by radial array endobronchial ultrasound immediately before deployment to confirm it was away from vasculature or other vital organs.

the applicator during the navigation.

Stability of Alpha DaRTs placement: migration and movement assessment

The stability of Alpha DaRTs in the lung and mediastinum was assessed (*Table 3*). In phase I, session 1, inert Alpha DaRTs were placed in the right lung lobe and mediastinum. Fluoroscopy used during a period of 30 days showed no migration of Alpha DaRTs outside the lung to external organs, yet it was not sensitive enough to detect slight movement of the Alpha DaRTs. Therefore, CT scans were added in session 2, in which additional placement of inert Alpha DaRTs was performed in the left lung lobe (without mediastinum). The placement of these Alpha DaRTs and of the Alpha DaRTs placed in the mediastinum in the previous session, were surveyed by fluoroscopy and serial CT scans (day 33, day 38), which showed minimal movement of Alpha DaRTs and no migration (*Table 3*). The mean movement ± total error was 1.33±2.6 mm in the mediastinum and 3.2±2.73 mm in parenchyma.

In phase II, active Alpha DaRTs were placed in the first session. The Alpha DaRTs were placed in mediastinum and parenchyma (both right and left lung lobes), and CT scans were taken and compared between days 0 and 28 to follow-up Alpha DaRTs migration and movement and effect of radioactive treatment on the surrounding lung tissue. The mean movement in the mediastinum was 3.1±1.7 mm and ranged in the parenchyma between 5.8±2.7 mm.

Animal health and behavior during the follow-up periods

The only clinically significant alteration in the serum chemistry, CBC and UA results was a rise in serum creatine phosphokinase (CPK) above the reference range on days 1 and 7 for swine #4 and on days 1, 7, and 28 for swine #5. These alterations were related to the result of intramuscular injections of three preanesthetic medications for each of the procedures and the duration of the anesthesia. The only clinical abnormality noted during the 28-day study was mild intermittent coughing of two days duration by swine #4 after recovery from the Alpha DaRTs implantation procedure. The coughing resolved without treatment. Consistent with the final pathology report below, CT scans showed lung opacities with variable degrees around the inserted sources, representing inflammatory changes, and possibly focal minor bleeding and atelectasis (*Figure 4*, next to the yellow arrows).

Pathology following active Alpha DaRTs implantation

Necropsy and gross pathology were performed in phase II, swine #4 and #5. In swine #4 multifocal lung adhesions to the rib cage pleura and in the mediastinum, lung hyperemia, and areas of consolidation were observed. In addition, mild quantity of serosanguineous pericardial effusion (10–15 mL) was observed. No lesions were observed in the myocardium.

Histopathological findings of the same swine (#4) showed similar changes in all sections. In most sections of the right lung lobes, mild to moderate interstitial pneumonitis was

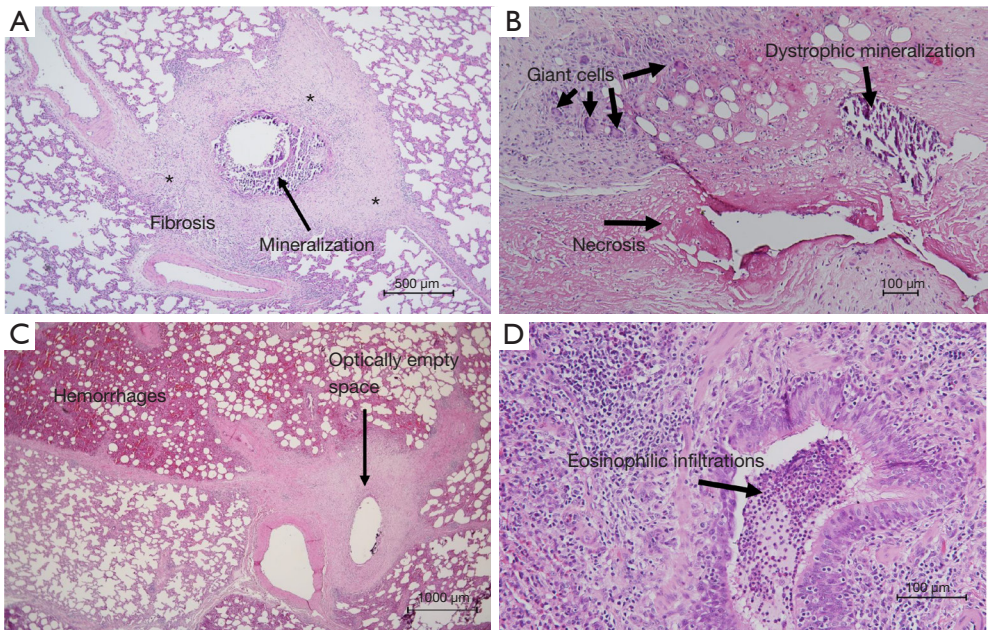


Figure 5 Histopathology from necropsy 28 days after Alpha DaRTs placement in lung parenchyma and mediastinum using hematoxylin eosin staining. (A) Focal optically empty space made by Alpha DaRTs surrounded by moderate fibrosis with mineralization (×4). The star (*) denotes fibrosis in several locations. The histopathology image was of swine #4. (B) Hemorrhages in the parenchyma are seen in different severities (×2). (C) Focal optically empty space made by an Alpha DaRTs in the mediastinal connective tissue surrounded by necrosis and dystrophic mineralization and few Giant cells (×10). (D) Eosinophilic infiltrations are evident in bronchioles and parenchyma (×20). The histopathology images of (B-D) were of swine #5. Alpha DaRTs, Diffusing alpha-emitters Radiation Therapy sources.

observed, with a focal optically empty space (*Figure 5A*) made by Alpha DaRTs, surrounded by moderate fibrosis, mild inflammatory infiltration (lymphohistiocytic and eosinophilic infiltrates), and focal dystrophic mineralization with Giant cells and neovascularization present and hemosiderin-laden macrophages demonstrated locally. In addition, focal thickening of the pleura by mild fibrosis and mesothelial hyperplasia ("papillary") was observed. In the left lung lobes, marked local atelectasis with mild interstitial pneumonitis, smooth muscle hyperplasia, and suspected bronchus-associated lymphoid tissue (BALT) hyperplasia were observed.

In the second swine (#5), at necropsy no lesions were seen in the thoracic cavity. Histopathological findings of most sections showed moderate interstitial pneumonitis, focal optically empty space made by an Alpha DaRT surrounded by moderate fibrosis and mild inflammatory infiltration (lymphohistiocytic and eosinophilic infiltrates), focal dystrophic mineralization with giant cells and neovascularization. The left lung lobes included local hemorrhages in the parenchyma in different severities (*Figure 5B*), including severe diffuse broncho-alveolar hemorrhages. In the mediastinum several focal optically empty spaces made by an Alpha DaRT, as described above, were observed in the capsule of lymph node, esophageal serosa, and connective tissue (*Figure 5C*). In the right lung lobes, eosinophilic infiltrates in bronchioles (*Figure 5D*) and BALT hyperplasia were evident.

Discussion

In this study, we demonstrated the feasibility and safety of Alpha DaRTs placement in the lung and mediastinum using basic bronchoscopy techniques guided with EBUS and fluoroscopy. Serial CT imaging was used to assess the placement and stability of the Alpha DaRTs which confirmed insignificant local movement and no migration to other organs. There was no serious adverse reaction or complication during the insertion or the follow-up evaluation (38 days for inert Alpha DaRTs and 28 days for radioactive loaded Alpha DaRTs).

We studied the deployment of the Alpha DaRTs in two

patterns, individually and in clusters. Cluster placement is required for treatment plans with Alpha DaRTs, and we confirmed the feasibility of Alpha DaRTs placement in clusters, separated from each other by approximately 4 mm. Large tumors may require a larger number of Alpha DaRTs placed in a cluster. The Alpha DaRTs were placed away from large vessels, pleural surface, or other vital organs in the parenchyma as was planned.

Since DaRT is a local alpha radiation-based treatment no direct effect is expected at distant organs due to the extremely short range of the radiation in the tissue. A minimal non-clinically significant leakage of ^{212}Pb to the blood is expected, according to the biokinetic model of Alpha DaRT that was confirmed in measurements performed in squamous cell carcinoma patients (skin and head and neck) (12-15).

In addition, Alpha DaRT does not lead to a sizable cavity or extra damage to tissue outside its effective area, it is expected that the placement of the source inside the soft tissue will hold the source in place even after tumor ablation. Therefore, our approach was to place the source into the lung soft tissue using direct visualization in the exact target area. Radial EBUS plus thin or ultrathin bronchoscope visualization confirmed that the source was placed into a soft tissue (that was expected to hold the source) and not in the vasculature. EBUS was used to detect any sizeable vessel in the area of source placement, and none of the sources were seen in a vessel either immediately after placement or in the follow up imaging.

Our approach indeed led to negligible sources movement seen in serial CT scans. The minimal movement of the Alpha DaRTs detected in serial CT imaging (*Table 3*) is likely related to the imaging difference due to respiratory cycle movement, and not true movement of the Alpha DaRTs. There was no migration of the Alpha DaRTs to other organs. Similar results were shown in phase II (active Alpha DaRTs). In the case of active Alpha DaRTs, formation of fibrotic tissue around the Alpha DaRTs (*Figure 5*) might be helpful in movement prevention. The results above support the translation of our approach in the future in patients.

There are several limitations in our study. First, this was performed by a single investigator, thus we were not able to assess the inter-surgeon differences in the use of the delivery method should be further explored. We did not directly assess the impact of misplacement of DaRT in adjacent organs or vasculature to determine safety impact. We also only assessed one configuration of DaRT sources (i.e., one geometry of seed), and thus could not assess the impact of movement with different shapes.

The results of histopathology indicated that Alpha DaRTs cause minimal to mild damage to the surrounding tissues and only mild inflammatory reaction (lymphohistiocytic and eosinophilic infiltrates). This is a favorable response confirming the capability of Alpha DaRTs to safely deliver the desired radiation treatment locally and precisely, without causing injury to adjacent organs. The inflammatory reaction may support the potential activation of an antitumor immune response following tumor ablation by Alpha DaRTs. The effect of the Alpha DaRTs on tumor microenvironment and host immune system could improve outcomes not just through local effects but also by stimulating a systemic antitumor immune response. The synergy of Alpha DaRTs with immunotherapy in the treatment of lung cancer is of great interest and deserves further investigation.

The preservation of the tissue structure, with no obvious necrosis or damage to surrounding organs, as was seen in our histopathology reports in day 28 post Alpha DaRTs placement and the wellbeing of the subjects in the post-implantation time period indicate a good safety profile. Alpha DaRTs could deliver an ablative radiation dose to targeted tumor, with minimal risk of collateral damage. Further investigations to assess the effect of Alpha DaRTs over a longer period are warranted.

Conclusions

Bronchoscopic deployment of Alpha DaRTs in the lung parenchyma and mediastinum of the swine model is feasible, precise, and safe. Further studies to advance this technology to fulfill unmet needs in the treatment of lung cancer are warranted.

Acknowledgments

We would like to thank Alpha Tau Medical team for their support: Yona Keisari, Itzhak Kelson, Noy Haykin-Hoffman, Elad Flaisher, Ofer Magen, Niv Dana, Sraya Makovsky, Yadin Cohen, Almog Hagag, Ilay Kamai, Yoav Raz, Robert B. Den and Vered Domankevich-Bachar. We are also thankful to the following team at Montefiore Medical Center, for providing technical support for the study: radiation safety officer Man Yu Chen, C.A.R.E. personnel Daniel Rivera, Madeline Quinones, Andrew Carbo and Christian D'Agostino, bronchoscopy technicians

Jerry Felicies, Eric Pierson and Rhonda Mata, radiology technicians Edward Altagracia and Felix Moore and admin team Daniel Ceusters, Lillian Murtha and Samuel Green.
Funding: The study was funded by Alpha Tau Medical.

Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-639/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-639/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-639/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-639/coif). All authors report that this study was funded by Alpha Tau Medical. A.S. (Ali Sadoughi) has been compensated for the expenses of educational and training events by Merit Medical, Olympus, Siemens, AcuityMD and Boston Scientific, served on advisory board for Mauna Kea, received consulting fee from Alpha Tau Medical and Olympus, and has stock option at Alpha Tau. N.O. received research funds from AstraZeneca and Merck and received consulting fees from AstraZeneca, Genentech and Merck. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures were conducted in accordance with all Federal and State animal welfare laws, regulations, policies, and guidelines, and with approval by the Montefiore Medical Center Institutional Animal Care and Use Committee (IACUC) (study protocols#20-11-100 and 09-100-22) and Radiation Safety, Environmental Health and Safety.

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Cite this article as: Sadoughi A, Sarkar A, Novotney C, Chan C, Moreno G, Oren S, Moss L, Aharoni K, Bari SE, Edery N, Ohri N. Bronchoscopic deployment and implantation of Diffusing alpha-emitters Radiation Therapy into the lung and mediastinum for treatment of lung cancer: a pre-clinical safety and feasibility study. Transl Lung Cancer Res 2024;13(1):60-75. doi: 10.21037/tlcr-23-639