Alpha-Particle Brachytherapy: Translation of Pre-Clinical Data to the Initiation of First Trials in Patients with Squamous Cell Carcinoma

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INTRODUCTION

A unique intra-tumoral alpha radiation based tumor ablation treatment termed ***Diffusing Alpha emitters Radiation Therapy*** **(DaRT)** was developed in our laboratories. DaRT provides, for the first time, an efficient method for treatment of the entire volume of solid tumors by alpha radiation. We summarize our preclinical results and describe the initiation of the first clinical trial in humans with skin squamous cell carcinoma in order to evaluate their response to Alpha DaRT Seeds containing Radium-224.

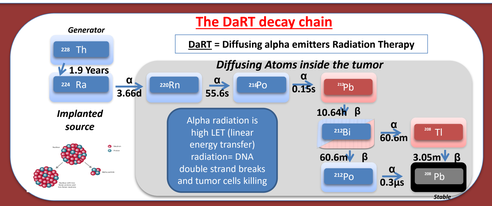
AIMS

A. Examine the ability of alpha radiation emitting seeds to destroy malignant tumors in mice.
B. Examine the induction of anti-tumor immunity following ablation of the tumor by alpha radiation emitting wires.
C. Initiate a clinical trial to test the effect of Alpha DaRT seeds in SCC cancer patients.

MATERIALS AND METHODS

Radium-224 loaded seeds (stainless steel) are inserted into solid tumors and release by recoil short-lived alpha-emitting atoms (Rn-220, Po-216. Pb-212, Bi-212, Po-212, Tl-208). These atoms disperse in the tumor and spray it with highly destructive alpha radiation. The decay products diffuse in the tumor mass to a distance of at least 5 mm.

The DaRT decay chain



The distribution of radioactive atoms inside the tumor in comparison with the necrotic areas they cause

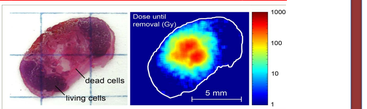


Figure 1. (Left) Hematoxylin-eosin (H&E) stained section taken from a SCC tumor treated with a ^{224}Ra DaRT source. Darker (purple) regions in (A) are composed of viable cells, lighter (pink) regions are necrotic. (Right) The radiation pattern of the same section.

Alpha DaRT seeds destroy mouse and human derived SCC tumors

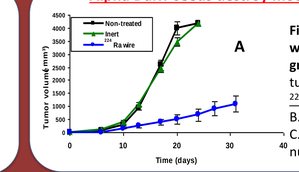
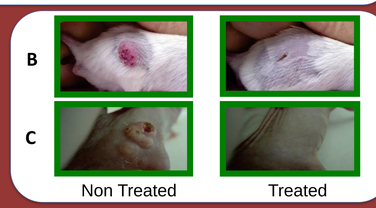


Figure 2: BALB/c mice bearing SCC tumors, treated with a single DaRT seed and monitored for tumor growth and survival. Non-Treated – Non-treated tumor bearing mice . Inert – Non radioactive wires . ^{224}Ra wire – Ra-224 loaded DaRT wires (*n* = 22).
B. Tumor development of murine SQ2 cells.
C. Tumor development of human CAL27 cells in nude mice.



Dose measurements of intra-tumoral radioactivity reveals differences in the distribution pattern between tumors of different histotypes

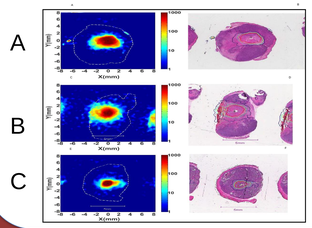


Table-1: Average radioactive values measured at all tested models are presented as effective **(>10 Gy)** *dose average area (mm2).*

Tumor	*n*	[b]Absorbed 10 Gy area (mm^2)
C32	4	9.45 ± 2.43
PC3	2	12.23 ± 0.12
HCT15	5	14.96 ± 3.69
U87	4	20.09 ± 10.82
FaDu	4	21.60 ± 1.70

Figure 3: Normalized effective dose formed by interstitial ^{224}Ra wires in different human solid tumors.

Representative radioactivity distributions and H&E stained slides to correlate with necrotic domains are presented from HCT15 (colon) (A), U87-GM (glioblastoma) (B), and C32 (melanoma) (C) models. The mean effective area for the FaDu (SCC) and U87 cells is two fold bigger than for the melanoma C-32 cells

Combined treatment of tumors with DaRT, inhibitors of MDSCs and regulatory T cells and the immunostimulant, CpG, abolished primary tumors and extended survival

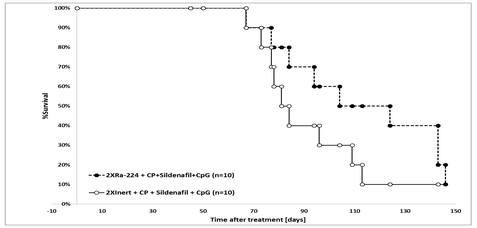


Figure 4: Survival of Mice bearing breast carcinoma (DA3) tumors treated with either two Ra-224 loaded or inert wires in combination with low dose CP, Sildenafil and CpG. *Presented is the Kaplan-Meir curve of 2XRa-224 + CP + Sildenafil + CpG (n = 10), or 2XInert wire+ CP + Sildenafil + CpG (n = 10)*

Treatment	Elimination of Primary tumor[a]	PR[b]	NR[c]
2 X Ra-224 loaded wires + CP+ Sildenafil + CpG	3	16	1
2XInert + CP + Sildenafil + CpG	1	8	11

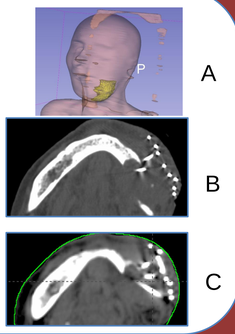
Table 2: Effect of combined treatment of DaRT, MDSC inhibitor (Sildenafil) , Tregs inhibitor (low dose CP) and immunostimulant (CpG) on tumor response
[a] Elimination of Primary tumor
[b] PR (Partial response) - Number of mice in which the tumor shrunk or did not grew after treatment.
[c] NR (No response) - Number of mice in which progressive tumor growth was scored.

CLINICAL TRIAL

A) Feasibility and safety clinical study started for 35 patients with skin or head and neck squamous cell carcinoma. Tumor size ≤ 5 centimeters in the longest diameter. Ra-224 loaded Alpha DaRT Seeds, each carrying a low dose of 2 μCi, will be placed to achieve ^{224}Ra activity of about 5 μCi per gram of tumor. CT will be used to check the position of the radioactive seeds. Four weeks after treatment the seeds will be removed.

B) Three patients ages 78-94 were treated by DaRT seeds. Seeds were implanted under local anesthesia.
- A patient with skin SCC was implanted with 37 seeds for 4 weeks. Tumor shrinkage was evident with no side effects.
- A patient with SCC in the ear received 5 seeds for 21 days. Considerable tumor shrinkage was evident with no adverse effects.
- A patient with SCC of the tongue, 2 cm longest diameter, was treated with 8 seeds for 5 days. No adverse effects were observed.

C) CT scan (axial cut) of DaRT seeds implanted in a patient with skin SCC on the face (A) on day of treatment (B) and after 5 days (C).



SUMMARY

- DaRT seeds were able to destroy mouse and human Tumors of different histological origin.
- DaRT relies on alpha particles and thus, may be effective against hypoxic tumors.
- DaRT seeds can be produced with various intensities, sizes and shapes and enable custom designed seeds for individual patients to deliver a more effective and conformal treatment to non-resectable tumors and metastatic lesions.
- DaRT is characterized by negligible gamma radiation and is thus safer for physicians during intervention and to patient post treatment.
- DaRT can be combined with other treatment modalities such as external beam radiation, surgery, chemotherapy and immunotherapy.