Revolutionary alpha particle brachytherapy

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Conflict of interest: L. Arazi is co-inventor of Alpha-DaRT, minor share-holder of Alpha TAU Medical and recipient of a research grant from the company.
The DaRT seed emits from its surface a chain of alpha emitting atoms. The atoms disperse by diffusion, creating a ‘kill region’ over several mm.
The decay chain of $^{224}\text{Ra}$ includes:

- $^{228}\text{Th}$ decays by alpha emission with a half-life of 1.91 years to $^{224}\text{Ra}$.
- $^{224}\text{Ra}$ decays by alpha emission with a half-life of 3.66 days to $^{220}\text{Rn}$.
- $^{220}\text{Rn}$ decays by alpha emission with a half-life of 55.6 seconds to $^{216}\text{Po}$.
- $^{216}\text{Po}$ decays by alpha emission with a half-life of 0.15 seconds to $^{212}\text{Pb}$.
- $^{212}\text{Pb}$ decays by beta emission with a half-life of 10.64 hours to $^{212}\text{Bi}$.
- $^{212}\text{Bi}$ decays by alpha emission with a half-life of 60.6 minutes to $^{212}\text{Po}$.
- $^{212}\text{Po}$ decays by alpha emission with a half-life of 0.3 microseconds to $^{208}\text{Pb}$.

- $^{208}\text{Pb}$ is stable.

$^{224}\text{Ra}$ is a short-lived radionuclide that is short enough for rapid clinical effect and long enough for handling and shipping. Replace generators in factory every ~2 years.
Source preparation: electrostatic collection of $^{224}\text{Ra}$
Quadruple generator
Source preparation: 
$^{224}$Ra embedding on source

Electrostatic collection

Heat treatment
Preclinical studies

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Murine Tumor Cells</th>
<th>Human Tumor Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>in Mice</td>
<td>in Nude Mice</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lung Squamous Cell Carcinoma</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Lung Adenocarcinoma</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pancreas adenocarcinoma</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Prostate Adenocarcinoma</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Breast Carcinoma</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Glioblastoma multiforme</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>B-Cell Lymphoma</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Melanoma</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Colon Carcinoma</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Preclinical outcomes on mice

All tumor types respond to the treatment, from growth retardation to cure

DaRT+ chemotherapy increases tumor growth retardation and prolongs survival

*Ablation of tumors by DaRT renders mice resistant to a second tumor cell injection*
Autoradiography of treated tumors in mice

$^{212}$Pb measurements in histological sections of squamous cell carcinoma (SQ2) tumors
Diffusion can be modeled, with parameters extracted from autoradiography data.
Dose modeling based on data from mice

- Therapeutic alpha dose up to ~2.5 mm from source
- Meaningful beta dose in region already covered by alpha, negligible ~2 mm away from source
- Negligible gamma dose everywhere
DaRT TG43 models

Beta+gamma dose (Gy)

\[ A_{Ra} = 2.5 \, \mu \text{Ci/cm} \]
\[ P_{\text{leak}}(\text{Pb}) = 0.2 \]

X [mm]

Y [mm]

Alpha dose (Gy)

\[ A_{Ra} = 2.5 \, \mu \text{Ci/cm} \]
\[ L_{\text{Pb}} = 0.65 \, \text{mm} \]
\[ P_{\text{leak}}(\text{Pb}) = 0.5 \]

X [mm]

Y [mm]
Alpha model dose contours – hexagonal lattice

\[ L_{Rn} = 0.3 \text{ mm} \]
\[ L_{Pb} = 0.6 \text{ mm} \]
\[ P_{\text{leak}}(Pb) = 0.3 \]

5 mm spacing
3 \( \mu \text{Ci} \) \( ^{224}\text{Ra/cm} \)
> 20 Gy everywhere
Safety – adjacent healthy tissue

Negligible beta and gamma dose; rapid clearance of $^{212}$Pb by ordered vasculature limits the kill region diameter to $\sim 2$ mm.
Safety – distant organs

Distant organs: $^{212}\text{Pb}$ leaving tumor through blood spreads throughout the body. Biokinetic + internal dosimetry calculations show that organ doses in typical treatment are 1-2 orders of magnitude below tolerance levels.
Clinical study: Rabin Medical Center and IRST

On-going trials in Rabin Medical Center and Italy: squamous cell carcinoma of the skin and oral cavity

Trials focus on tumors which failed prior surgery or RT and on non-resectable tumors (or where resection would result in massive disfiguration)

Patient population 60-102 y, tumor size < 5 cm

Seed activity 2-3 μCi $^{224}$Ra, apply between a few to ~170 seeds (>5 μCi per gram tumor)

Seeds removed 2 weeks after treatment
Clinical study outcomes

First 15 patients which completed follow-up: 100% positive response, of which 73% complete response

No observable local or systemic radiation-induced side effects

Tumors shrink within days

Blood measurements consistent with biokinetic model
Clinical study outcomes

21/3/2017

1/6/2017
Clinical study outcomes
New clinical trials

- Rabin Medical Center: Cutaneous and mucosal tumors. Started
- Memorial Sloan Kettering: Cutaneous and mucosal tumors. Final approval by the FDA
- Istituto Dermatologico San Gallicano (IRCCS) at IFO, Rome: Cutaneous and mucosal tumors. Approved by local IRB, awaiting approval of Italian MoH.
- Azienda Policlinico Umberto I - Roma, Sapienza Università di Roma: SCC in the skin. Approved by local IRB, awaiting approval of Italian MoH.
- Rambam Medical Center: Cutaneous and mucosal tumors. Approved by IRB, will commence shortly.
Clinical targets (protocols exist or under preparation)

- SCC of the Skin and oral cavity
- Cutaneous and Mucosal Neoplasia
- Prostate
- Breast
- GYN (Cervical, Vulvar)
- Pancreas
- Renal
- Liver
- Rectal
- Soft tissue sarcomas
- Lung
Regulatory approvals

- Approval by the Commonwealth of Massachusetts Radiation control program as a sealed source medical device for treatment of patients
- Approval in Japan by the MHLW as a medical device
- Final audit for CE mark as a medical device
- Approval of the Israel Ministry of Health for the treatment of cutaneous tumors
- Approval of the Italian Ministry of Health for the treatment of SCC
Clinical studies in 63 distinguished cancer centers
Summary

**DaRT is the first form of brachytherapy utilizing alpha particles against solid tumors**

Effective against radio-resistant/hypoxic tumors

Procedure is simple and can be done in relatively short time

Tumors shrink within days with **no observable radiation-induced adverse effects**

**So far 100% positive response, 73% complete response**

Partial response can be ‘fixed’ by re-application

Treatment planning is challenging, but simple modeling appears to provide a good starting point

Can be combined with other methods, e.g. boosting EBRT or together with immunotherapy
Backup slides
The diffusion-leakage model

Simplifying assumptions:

• The tumor tissue is homogeneous, isotropic and does not change with time

• Chaotic nature of tumor vasculature allows describing convective spread as effective diffusion

• Only $^{220}\text{Rn}$ and $^{212}\text{Pb}$ diffusion should be modeled, their short-lived daughters are in local secular equilibrium

• $^{220}\text{Rn}$ decays inside the tumor, $^{212}\text{Pb}$ removal by the blood modeled as a uniform “sink” term
The diffusion-leakage model: Space and time behavior of $^{220}$Rn and $^{212}$Pb

\[
\frac{\partial n_{Rn}}{\partial t} - D_{Rn} \nabla^2 n_{Rn} = s_{Rn} - \lambda_{Rn} n_{Rn}
\]

Effective diffusion coefficient
Source term (release from seed surface)
Radioactive decay

\[
\frac{\partial n_{Pb}}{\partial t} - D_{Pb} \nabla^2 n_{Pb} = s_{Pb} - \lambda_{Pb} n_{Pb} - \alpha_{Pb} n_{Pb}
\]

Effective diffusion coefficient
Source term
Radioactive decay
$^{212}$Pb removal by blood
Average removal time $1/\alpha_{Pb}$

\[
s_{Rn}(r, t) = P_{des}(Rn) \Gamma_{Ra}^{src}(0) e^{-\lambda_{Ra} t} \delta(r)
\]

\[
s_{Pb}(r, t) = \lambda_{Rn} n_{Rn} + \left[ P_{des}^{eff}(Pb) - P_{des}(Rn) \right] \Gamma_{Ra}^{src}(0) e^{-\lambda_{Ra} t} \delta(r)
\]
Approximate analytical point-source solution for the alpha particle dose: $^{220}$Rn + $^{216}$Po

$$Dose_{\alpha}^{asy} (^{220}\text{Rn} + ^{216}\text{Po}; r) = \frac{1}{4\pi} \cdot P_{des}(\text{Rn}) \Gamma_{Ra}^{src} (0) \tau_{Ra} \cdot \frac{E_{\alpha}(^{220}\text{Rn} + ^{216}\text{Po})}{\rho L_{Rn}^3} \cdot \frac{e^{-r/L_{Rn}}}{r/L_{Rn}}$$

- Total number of $^{220}$Rn atoms released into the tumor
- Typical dose contributed by $^{220}$Rn + $^{216}$Po decay
- Spatial distribution factor

$$Dose_{\alpha}^{asy} (^{212}\text{Bi} / ^{212}\text{Po}; r) \approx \frac{1}{4\pi} \cdot [1 - P_{\text{leak}}(\text{Pb})] \cdot P_{des}^{eff} (\text{Pb}) \Gamma_{Ra}^{src} (0) \tau_{Ra} \cdot \frac{E_{\alpha}(^{212}\text{Bi} / ^{212}\text{Po})}{\rho L_{Pb}^3} \cdot \frac{e^{-r/L_{Pb}}}{r/L_{Pb}}$$

- Fraction of $^{212}$Pb atoms remaining in tumor
- Total number of $^{212}$Pb atoms released into the tumor
- Typical dose contributed by $^{212}$Bi or $^{212}$Po decay
- Spatial distribution factor
Diffusion lengths of $^{220}\text{Rn}$ and $^{212}\text{Pb}$

The diffusion lengths determine the spatial extent of the treatment

- $^{220}\text{Rn}$ diffusion length:
  \[ L_{\text{Rn}} = \sqrt{D_{\text{Rn}} \tau_{\text{Rn}}} \]
  where $\tau_{\text{Rn}} = 1/\lambda_{\text{Rn}}$ is the mean radioactive decay lifetime of $^{220}\text{Rn}$

- $^{212}\text{Pb}$ diffusion length:
  \[ L_{\text{Pb}} = \sqrt{D_{\text{Pb}} \tau_{\text{Pb}}^{\text{eff}}} \]
  where $(\tau_{\text{Pb}}^{\text{eff}})^{-1} = \lambda_{\text{Pb}} + \alpha_{\text{Pb}}$ is the effective mean lifetime of $^{212}\text{Pb}$ including radioactive decay and removal by blood

Reasonable values: $L_{\text{Rn}} \sim 0.2 - 0.4$ mm, $L_{\text{Pb}} \sim 0.4 - 0.8$ mm
Estimated dose correlates with tissue necrosis → 10 Gy is a good number!

1. Estimated necrotic area: 12.7 mm²
   Corresponding dose: 5-11 Gy
   \( S_{Rn}(0) = 0.40 \, \mu\text{Ci} \)

2. Estimated necrotic area: 18.4 mm²
   Corresponding dose: 6-15 Gy
   \( S_{Rn}(0) = 0.52 \, \mu\text{Ci} \)
**Organ dose example**

4 cm diameter spherical tumor, 30% $^{212}$Pb leakage, 10 $\mu$Ci $^{224}$Ra per gram of tumor tissue (*conservative estimates*)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Alpha Dose (Gy)</th>
<th>Treatment dose/tolerance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>0.35</td>
<td>&lt; 0.09</td>
</tr>
<tr>
<td>Red bone marrow</td>
<td>0.06</td>
<td>&lt; 0.08</td>
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<tr>
<td>Ovaries</td>
<td>0.02</td>
<td>&lt; 0.04</td>
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<tr>
<td>Liver</td>
<td>0.09</td>
<td>&lt; 0.013</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>0.09</td>
<td>&lt; 0.011</td>
</tr>
<tr>
<td>Testes</td>
<td>0.01</td>
<td>&lt; 0.009</td>
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<tr>
<td>Lungs</td>
<td>0.08</td>
<td>&lt; 0.008</td>
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Clinical trials - RMC

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Tumor Location</th>
<th>Previous RT</th>
<th>Response</th>
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<tbody>
<tr>
<td>1</td>
<td>87</td>
<td>Sub-Mandibular + Mandible</td>
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<td>Partial</td>
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<tr>
<td>2</td>
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<td>Ear</td>
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<td>Complete</td>
</tr>
<tr>
<td>3</td>
<td>94</td>
<td>Tongue</td>
<td>Yes (x2)</td>
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<td>Yes</td>
<td>Partial</td>
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<tr>
<td>6</td>
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<tr>
<td>14</td>
<td>88</td>
<td>Parotid</td>
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