Recoil-based short lived alpha-emitting devices: a new brachytherapy approach

Antonio Damato, PhD, DABR
Memorial Sloan Kettering Cancer Center
• MSK has received funding by Alpha Tau Medical to conduct research on DaRT. I am the PI on some of this research efforts.

• The devices described in this talk are not FDA approved for standard use and are not commercially available in the US

• There are going to be some equations! The horror!!!

• Watch out for *** throughout the talk!
Alpha radiation?

• High LET radiation:
  • Double-strand break
  • Effective against hypoxic tumors ***

• Short range (~50µm)
  • Need a delivery method to the tumor cells
  • Range doesn’t permit direct implantation of alpha emitting “seeds” into bulky tumors
  • Targeted alpha particle therapy typically a nuclear medicine approach
Alpha DaRT: Overcoming the short range of alpha particles

The DaRT seed emits from its surface by recoil a chain of alpha emitting atoms ***

The atoms disperse by diffusion, creating a ‘kill region’ over several mm
Source preparation: electrostatic collection of $^{224}\text{Ra}$

- $^{228}\text{Th}$ panel
- Needle (source)
- Field lines
- $^{224}\text{Ra}^+ \text{ ions}$
- Ground
Source preparation: $^{224}\text{Ra}$ embedding on source

Electrostatic collection

Heat treatment
DaRT: a brachytherapy device
What is “emitted” at the source???

- $^{220}\text{Rn}$ from backscatter $\alpha$-decay $^{224}\text{Ra}$ (in source)
- $^{212}\text{Pb}$ from backscatter $\alpha$-decay $^{216}\text{Po}$ (in source)

- What about:
  - $\alpha$ from $^{224}\text{Ra}$, $^{220}\text{Rn}$ and $^{216}\text{Po}$ (in source) decay?
    - Range $r \sim 10^1$ um – not very relevant for tumor coverage
  - $^{216}\text{Po}$ from backscatter $\alpha$-decay $^{220}\text{Rn}$ (in source)?
    - $^{216}\text{Po}$ has $T_{1/2}$ of 0.15s and a range $r \sim 10^0$ $\mu$m ($+\alpha$ range) – not very relevant for tumor coverage but relevant as a source of $^{212}\text{Pb}$ from the region by the source surface
  - $^{212}\text{Bi}$/$^{212}\text{Po}$ from $\beta$-decay?
    - $\beta$-decay not energetic enough to contribute significantly to emission out of the source of these elements
What is “emitted” at the source?

- $^{220}\text{Rn}$ from backscatter $\alpha$-decay $^{224}\text{Ra}$ (in source)
- $^{212}\text{Pb}$ from backscatter $\alpha$-decay $^{216}\text{Po}$ (in source and by source surface)

Desorption probability = probability that a daughter element will enter the tumor for each decay of its parent

- ~40% for $^{220}\text{Rn}$
- ~55% for $^{212}\text{Pb}$
To understand dose deposition, we need to understand the transport of $^{220}\text{Rn}$, $^{212}\text{Pb}$ and $^{212}\text{Bi}$
Dose Deposition

• Model for macroscopic alpha dose developed by L. Arazi\textsuperscript{1,2}

• Assumptions:
  • Tissue is homogeneous, isotropic and time-independent
  • Transport can be described as a diffusive process
  • $^{212}$Pb and $^{212}$Bi are removed from tumor when they encounter a blood vessel (sink term)
  • $^{220}$Rn does not interact with vasculature (no sink term)

• Promising initial correlations with preliminary results (expected kill zone compared to observed necrotic zone in slides)

Dose Deposition

• Model for macroscopic alpha dose developed by L. Arazi$^{1,2}$

• Assumptions:
  • Tissue is homogeneous, isotropic and time-independent
  • Transport can be described as a diffusive process
  • $^{212}$Pb and $^{212}$Bi are removed from tumor when they encounter a blood vessel (sink term)
  • $^{220}$Rn does not interact with vasculature (no sink term)

• Promising initial correlations with preliminary results (expected kill zone compared to observed necrotic zone in slides)

Transport

- You did not really think you’ll get away without an equation, did you?

- Goal is to find the distribution of the alpha-emitting atoms in tissue at a given distance \( r \) from the source, at a given time.

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

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

\[
\frac{\partial n_{\text{Bi}}}{\partial t} = D_{\text{Bi}} \nabla^2 n_{\text{Bi}} + \lambda_{\text{Pb}} n_{\text{Pb}} - \lambda_{\text{Bi}} n_{\text{Bi}} - \alpha_{\text{Bi}} n_{\text{Bi}}.
\]

$^{220}\text{Rn}$

$$\frac{\partial n_{\text{Rn}}}{\partial t} = D_{\text{Rn}} \nabla^2 n_{\text{Rn}} + s_{\text{Rn}} - \lambda_{\text{Rn}} n_{\text{Rn}}$$
Change in time of the number density of $^{220}$Rn at a given position
$^{220}\text{Rn}$

$$\frac{\partial n_{\text{Rn}}}{\partial t} = D_{\text{Rn}} \nabla^2 n_{\text{Rn}} + s_{\text{Rn}} - \lambda_{\text{Rn}} n_{\text{Rn}}$$

Diffusion of $^{220}\text{Rn}$, where $D_{\text{Rn}}$ is the local effective diffusion coefficient
$^{220}\text{Rn}$ generated (at DaRT surface only) given by desorption probability multiplied by decayed $^{224}\text{Ra}$ activity.
$^{220}\text{Rn}$ decay.
$^{212}\text{Pb}$ and $^{212}\text{Bi}$

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

\[
\frac{\partial n_{\text{Bi}}}{\partial t} = D_{\text{Bi}} \nabla^2 n_{\text{Bi}} + \lambda_{\text{Pb}} n_{\text{Pb}} - \lambda_{\text{Bi}} n_{\text{Bi}} - \alpha_{\text{Bi}} n_{\text{Bi}}.
\]
$^{212}$Pb and $^{212}$Bi

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

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

Generation term is different:

$^{212}$Pb is generated both at DaRT surface and as a decay of transported $^{220}$Rn $\rightarrow$ $^{216}$Po

$^{212}$Bi is generated as a decay of transported $^{212}$Pb
$^{212}\text{Pb}$ and $^{212}\text{Bi}$

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

\[
\frac{\partial n_{\text{Bi}}}{\partial t} = D_{\text{Bi}} \nabla^2 n_{\text{Bi}} + \lambda_{\text{Pb}} n_{\text{Pb}} - \lambda_{\text{Bi}} n_{\text{Bi}} - \alpha_{\text{Bi}} n_{\text{Bi}}.
\]

Additional sink term – elimination due to vasculature
From transport to $\alpha$ macroscopic dose

$$Dose_\alpha (\text{RnPo}; \mathbf{r}, t) = \frac{E_\alpha (\text{RnPo})}{\rho} \int_0^t \lambda_{\text{Rn}} n_{\text{Rn}} (\mathbf{r}, t') dt'$$

$$Dose_\alpha (\text{BiPo}; \mathbf{r}, t) = \frac{E_\alpha (\text{BiPo})}{\rho} \int_0^t \lambda_{\text{Bi}} n_{\text{Bi}} (\mathbf{r}, t') dt'$$
From transport to $\alpha$ macroscopic dose

$$Dose_\alpha(\text{RnPo}; \mathbf{r}, t) = \frac{E_\alpha(\text{RnPo})}{\rho} \int_0^t \lambda_{\text{Rn}} n_{\text{Rn}}(\mathbf{r}, t') dt'$$

$$Dose_\alpha(\text{BiPo}; \mathbf{r}, t) = \frac{E_\alpha(\text{BiPo})}{\rho} \int_0^t \lambda_{\text{Bi}} n_{\text{Bi}}(\mathbf{r}, t') dt'$$

Energy deposition from $\alpha$-decay in tissue per decay
From transport to $\alpha$ macroscopic dose

\[
Dose_\alpha(\text{RnPo}; \mathbf{r}, t) = \frac{E_\alpha(\text{RnPo})}{\rho} \int_0^t \lambda_{\text{Rn}} n_{\text{Rn}}(\mathbf{r}, t') dt'
\]

\[
Dose_\alpha(\text{BiPo}; \mathbf{r}, t) = \frac{E_\alpha(\text{BiPo})}{\rho} \int_0^t \lambda_{\text{Bi}} n_{\text{Bi}}(\mathbf{r}, t') dt'
\]

Number of $\alpha$-decays over time
Dose\(_{\text{asy}}\) (RnPo+BiPo) (Gy)

- 0.2 \(\leq L_{\text{Rn}} \leq 0.4\) mm, 0.3 \(\leq L_{\text{Pb}} \leq 0.7\) mm
- \(L_{\text{Rn}} = 0.3\) mm, \(L_{\text{Pb}} = 0.6\) mm

10 Gy

Point source, \(\Gamma_{\text{Ra}}(0) = 3\) \(\mu\)Ci

- \(P_{\text{des}}(\text{Rn}) = 0.4\), \(P_{\text{des}}^{\text{eff}}(\text{Pb}) = 0.55\)
- \(L_{\text{Bi}} = 0.1L_{\text{Pb}}, P_{\text{leak}}(\text{Pb}) = 0.5, \alpha_{\text{Bi}} = 0\)

\(r\) (mm)
Effective radius (assuming 10Gy adose kill threshold)

- Point source, $\Gamma_{Ra}(0) = 3 \, \mu$Ci
- $P_{des}(Rn) = 0.4$, $P_{eff}(Pb) = 0.55$
- $L_{Bi} = 0.1L_{Pb}$, $P_{leak}(Pb) = 0.5$, $\alpha_{Bi} = 0$
Effective Diameter for a 2µCi DaRT***

Dose_{\alpha}^{asy}(BiPo) > 10 Gy
0.2 mm < L_{Rn} < 0.4 mm
0.5 mm < L_{Pb} < 0.8 mm

All dose components:

- 3 μCi $^{224}$Ra 10 mm seed

**Graph:**
- $^{220}$Rn+$^{216}$Po α dose
- $^{212}$Bi+$^{212}$Po α dose
- β dose
- γ dose
- Data 1

- Asymptotic dose (Gy)

- $P_{\text{des}}(\text{Rn})=0.4$, $P_{\text{eff}}(\text{Pb})=0.55$
- $L_{\text{Rn}}=0.3 \text{ mm}$, $L_{\text{Pb}}=0.6 \text{ mm}$, $L_{\beta_{\text{Bi}}}=0.1L_{\text{Pb}}$
- $P_{\text{leak}}(\text{Pb})=0.5$, $\alpha_{\beta_{\text{Bi}}}=0$

Beta and gamma doses calculated using EGSnrc, insensitive to diffusion
“TG43” distribution

\[ \alpha \text{ dose (Gy)} \]
\[ 3 \mu \text{Ci} \ ^{224}\text{Ra} \]

\[ Y \text{ (mm)} \]
\[ X \text{ (mm)} \]

\[ L_{\text{Rn}} = 0.3 \text{ mm}, \quad L_{\text{Pb}} = 0.6 \text{ mm} \]
\[ P_{\text{leak}} (\text{Pb}) = 0.5 \]

\[ \beta+\gamma \text{ dose (Gy)} \]
\[ 3 \mu \text{Ci} \ ^{224}\text{Ra} \]

\[ Y \text{ (mm)} \]
\[ X \text{ (mm)} \]

\[ 3 \mu \text{Ci} \ ^{224}\text{Ra} \]
\[ P_{\text{leak}} (\text{Pb}) = 0.5 \]

Courtesy: L. Arazi
Safety – adjacent healthy tissue

- Negligible beta and gamma dose; rapid clearance of $^{212}\text{Pb}$ by ordered vasculature limits the kill region

Courtesy: Lior Arazi
A biokinetic model can be used to calculate a maximum activity implantable, therefore a maximum theoretical size of tumor treatable with DaRT. ***

The tolerated $^{224}$Ra activity for DaRT can be expected to be 2-4 mCi.

Hematoxylin-eosin (H&E) stained 5µm 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.

The radiation pattern of the same section.
Ra-224 DaRT wires inhibit the growth of squamous cell carcinoma (SCC) mouse tumors

DaRT wires were inserted into skin tumors and the growth of the tumors was measured for 32 days.
**Tumor Destruction by DaRT is Primarily Mediated by Alpha Particles**

Average of CT26 Tumor Volumes

- **DaRT (n=8)**
- **Sealed (n=7)**
- **Inert (n=7)**

PSL (Photostimulated Luminescence) Average

- DaRT (n=3)
- Sealed (n=4)

**p<0.05 DaRT vs. controls**

**p<0.05 DaRT vs. sealed**

Courtesy: Keisari
DaRT Wires Eradicating Human SCC in Nude mice

Effect of a single DART wire

A

HNSCC

B

Lung SCC

Memorial Sloan Kettering Cancer Center
DaRT Wires Eradicating Human Tumors in Nude mice

- Inert wire
- Ra-224 wire

Tumor size after 11 days

GBM

Human Prostate in Nude Mice

45 days after tumor HNSCC transplantation
Conclusion

• Promising initial clinical results
  • Novel device with brachytherapy and nuclear medicine aspects
  • Clinical protocols starting in the US; used clinically elsewhere

• Need a primary standard
  • How to operate while we don’t have one

• Dose calculation
  • Simplified model developed by BGU/TAU
  • More complex model active area of research


