Memorial Sloan Kettering Cancer Center

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!

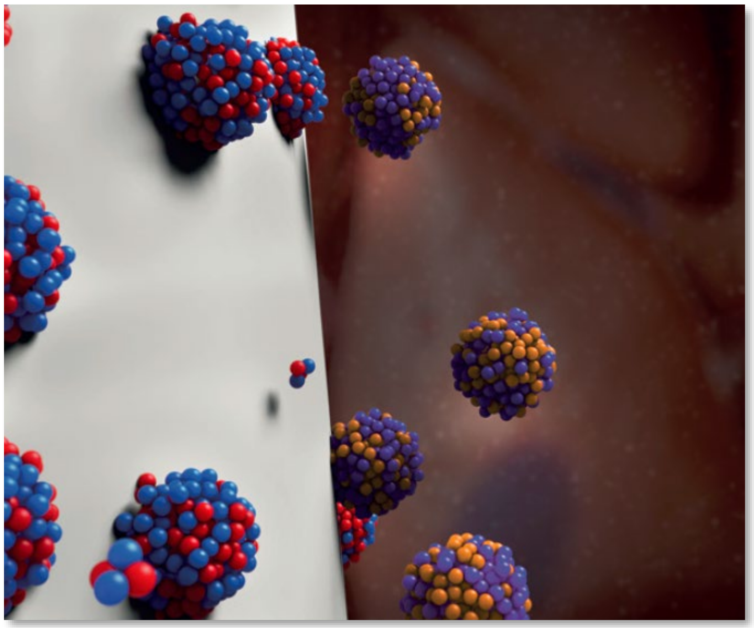
Alpha radiation?

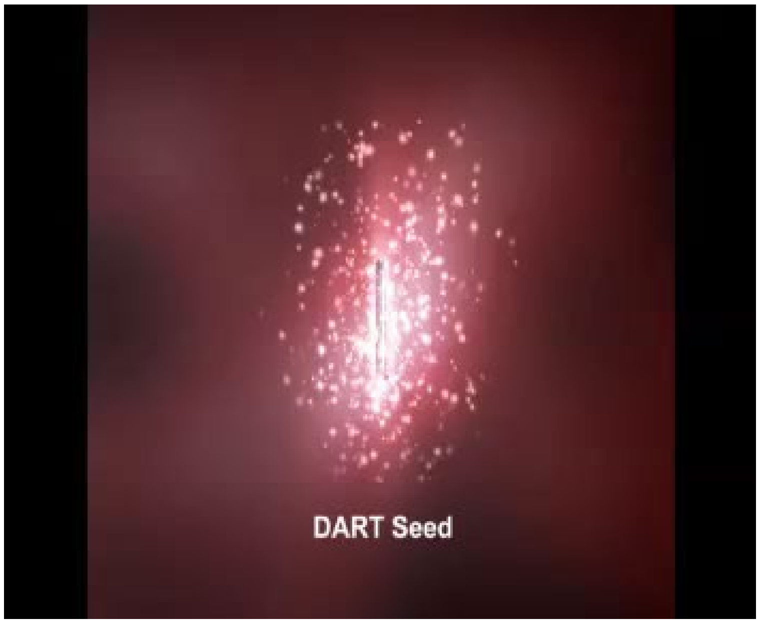
- High LET radiation:
  - Double-strand break
  - Effective against hypoxic tumors ***

- 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

Courtesy: Lior Arazi

Alpha DaRT:
Overcoming the short range of alpha particles

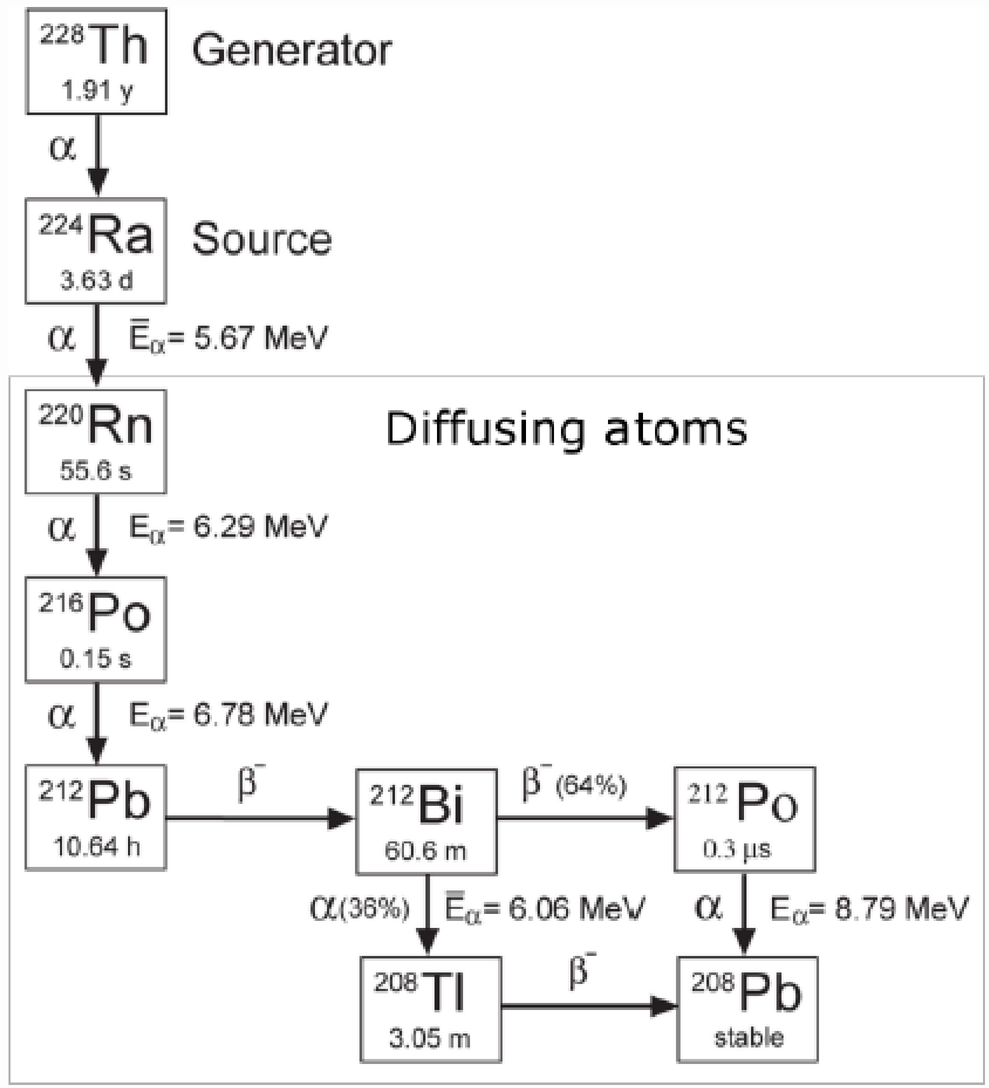




The DaRT seed emits from its surface **by recoil** a chain of alpha emitting *atoms* ***

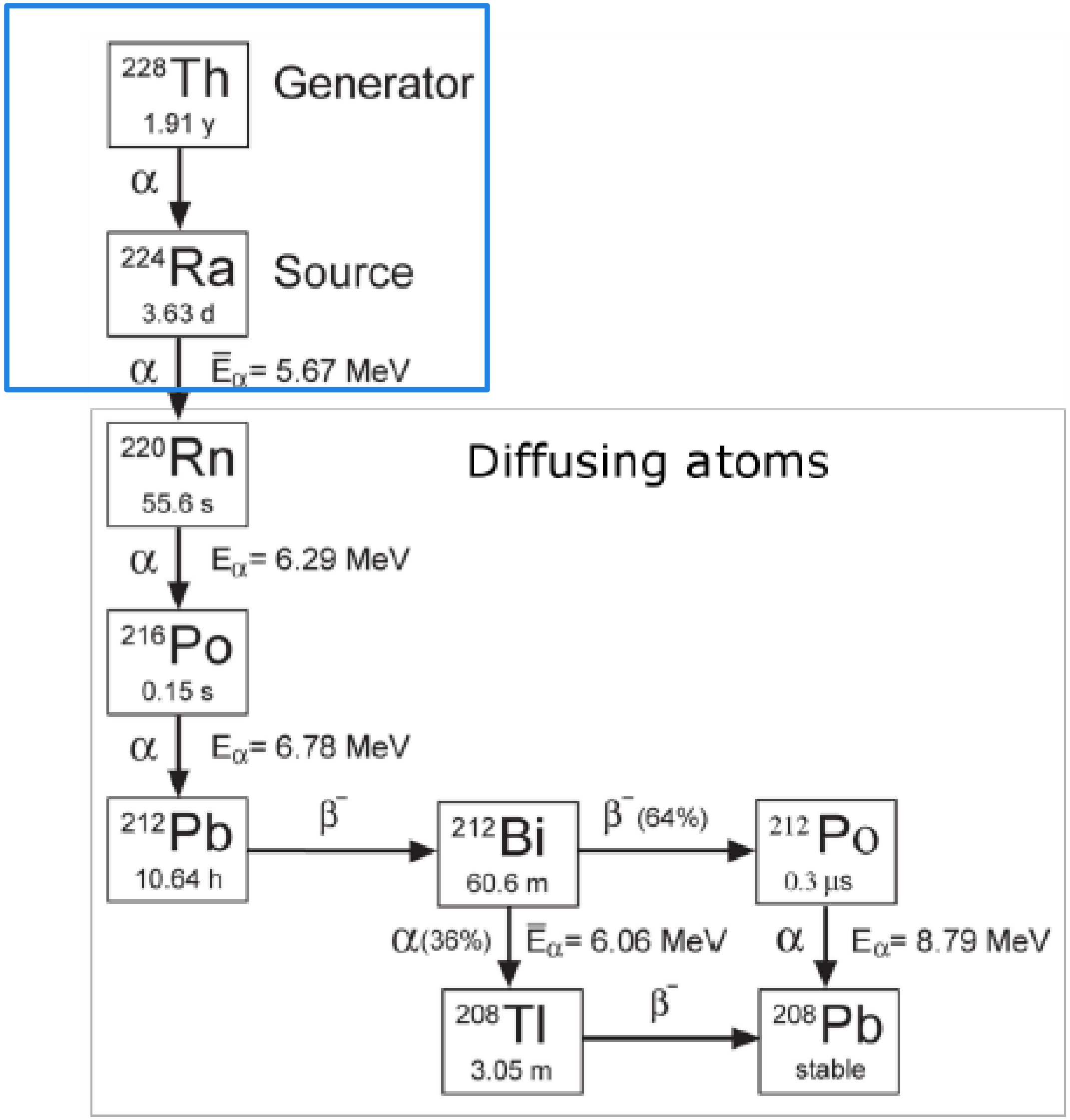
The atoms disperse by diffusion, creating a 'kill region' over several mm

Memorial Sloan Kettering Cancer Center



Arazi, Phys. Med. Biol. 65(2020)

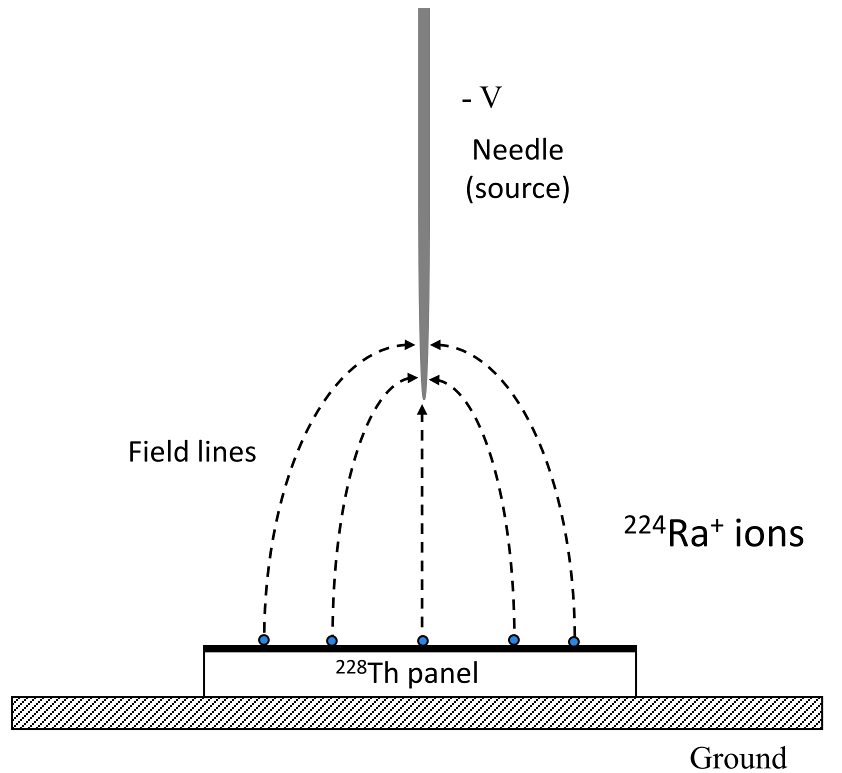
Memorial Sloan Kettering Cancer Center



Arazi, Phys. Med. Biol. 65(2020)

Courtesy: Lior Arazi

Source preparation: electrostatic collection of ^{224}Ra



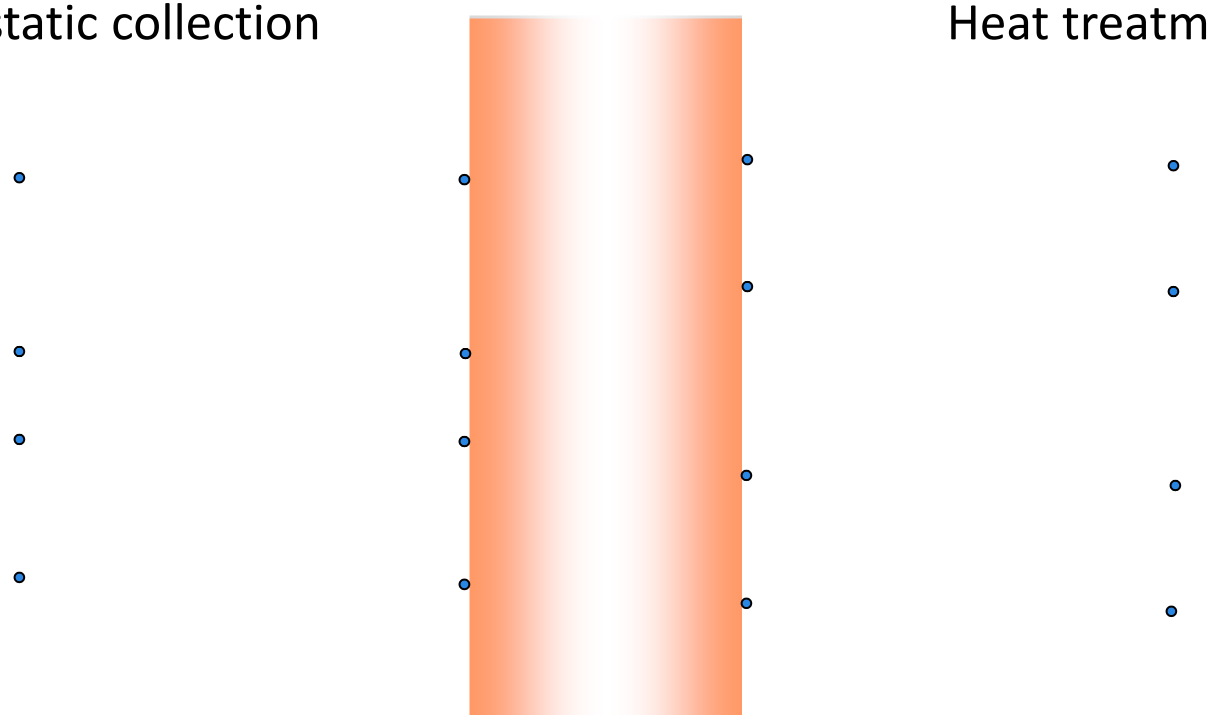
Memorial Sloan Kettering Cancer Center

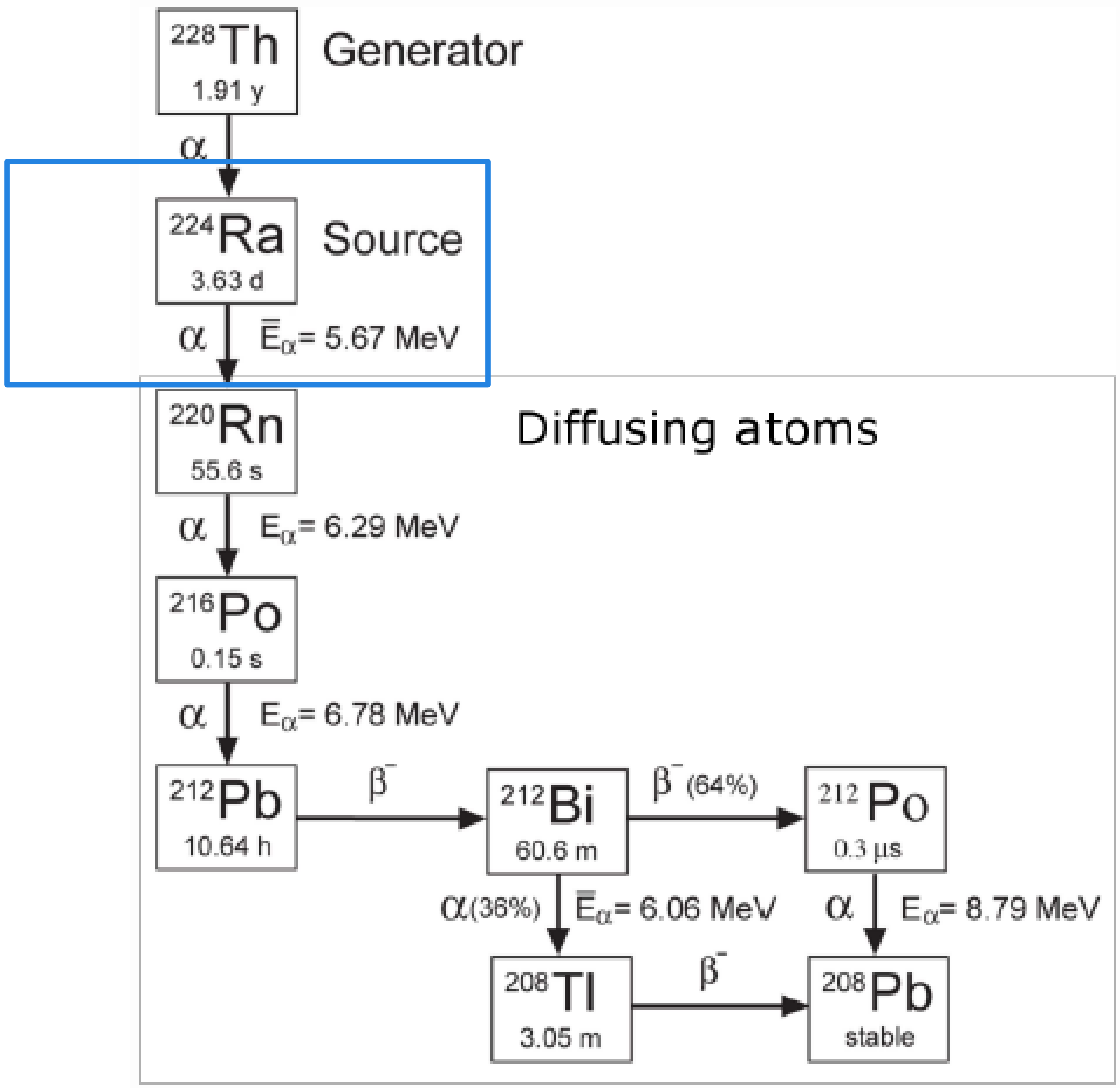
Courtesy: Lior Arazi

Source preparation:
^{224}Ra embedding on source

Electrostatic collection

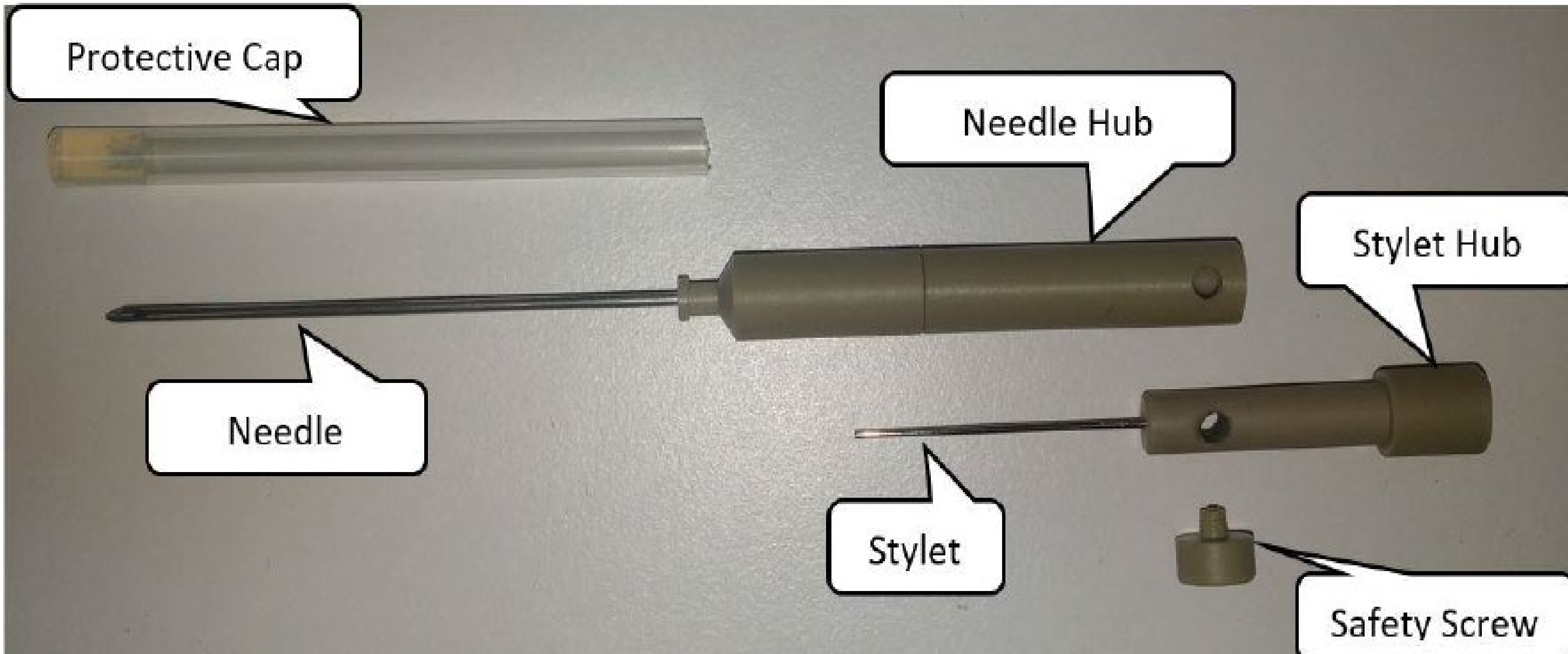
Heat treatment





Arazi, Phys. Med. Biol. 65(2020)

DaRT : a brachytherapy device



What is "emitted" at the source?***

- ^{220}Rn from backscatter α-decay ^{224}Ra (in source)
- ^{212}Pb from backscatter α-decay ^{216}Po (in source)

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

Memorial Sloan Kettering Cancer Center

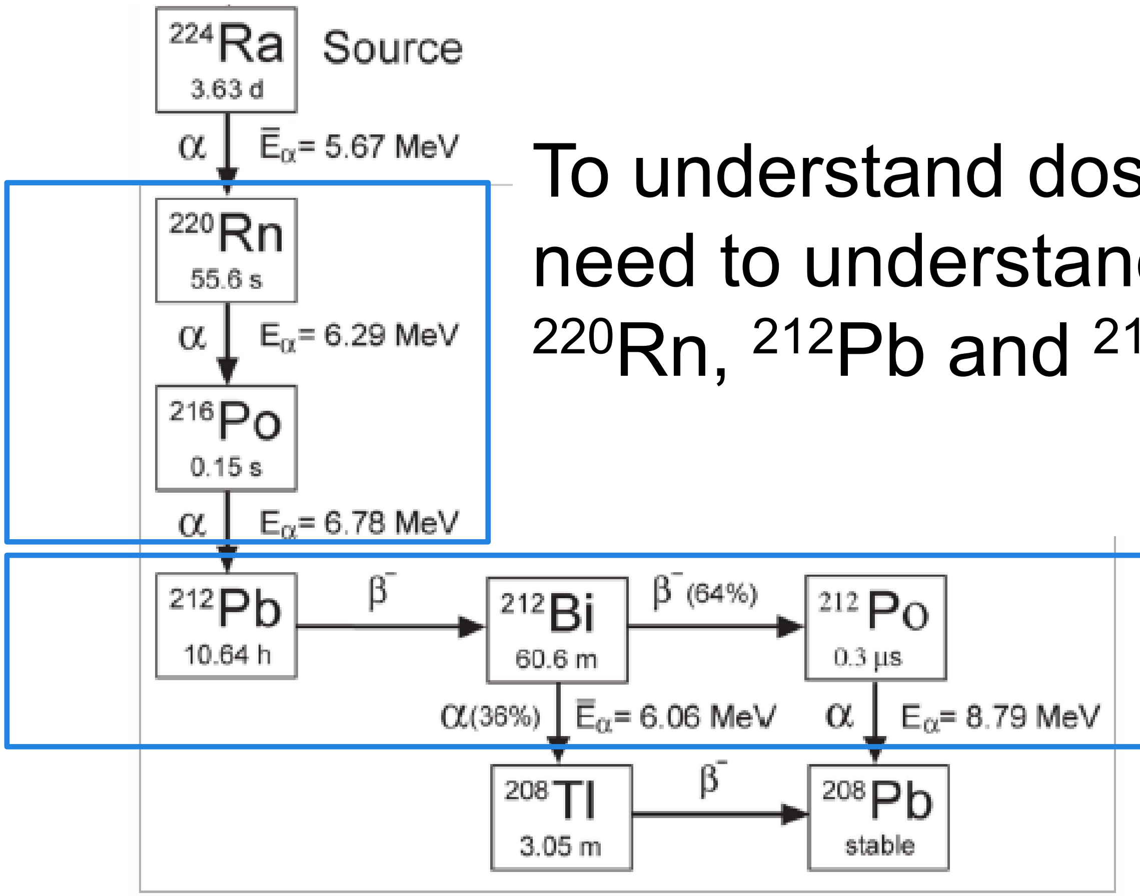
What is "emitted" at the source?

- ^{220}Rn from backscatter α-decay ^{224}Ra (in source)
- ^{212}Pb from backscatter α-decay ^{216}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}Rn
  - ~55% for ^{212}Pb

Dose Deposition

- $^{220}Rn/^{216}Po$ in <u>local</u> secular equilibrium
- ^{212}Bi transport after ^{212}Pb decay
- $^{212}Bi/^{212}Po$ in <u>local</u> secular equilibrium



To understand dose deposition, we need to understand the transport of ^{220}Rn, ^{212}Pb and ^{212}Bi

Arazi, Phys. Med. Biol. 65(2020)

Memorial Sloan Kettering Cancer Center

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)

[1]Arazi et al., Phys. Med. Biol. 52(2007) [2]Arazi, Phys. Med. Biol. 65(2020)

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)

[1]Arazi et al., Phys. Med. Biol. 55(2007) [2]Arazi, Phys. Med. Biol. 65(2020)

Memorial Sloan Kettering Cancer Center

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.

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

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

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

Arazi, Phys. Med. Biol. 65(2020)

^{220}Rn

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

Arazi, Phys. Med. Biol. 65(2020)

^{220}Rn

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

Change in time of the number density of ^{220}Rn at a given position

Arazi, Phys. Med. Biol. 65(2020)

^{220}Rn

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

Diffusion of ^{220}Rn, where D_{Rn} is the local effective diffusion coefficient

Arazi, Phys. Med. Biol. 65(2020)

^{220}Rn

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

^{220}Rn generated (at DaRT surface only) given by desorption probability multiplied by decayed ^{224}Ra activity.

^{220}Rn

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

^{220}Rn decay.

Arazi, Phys. Med. Biol. 65(2020)

^{212}Pb and ^{212}Bi

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

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

Arazi, Phys. Med. Biol. 65(2020)

^{212}Pb and ^{212}Bi

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

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

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

Arazi, Phys. Med. Biol. 65(2020)

Memorial Sloan Kettering Cancer Center

^{212}Pb and ^{212}Bi

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

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

Additional sink term – elimination due to vasculature

Arazi, Phys. Med. Biol. 65(2020)

Memorial Sloan Kettering Cancer Center

From transport to α macroscopic dose

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

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

Arazi, Phys. Med. Biol. 65(2020)

From transport to α macroscopic dose

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

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

Energy deposition from α-decay in tissue per decay

Arazi, Phys. Med. Biol. 65(2020)

From transport to α macroscopic dose

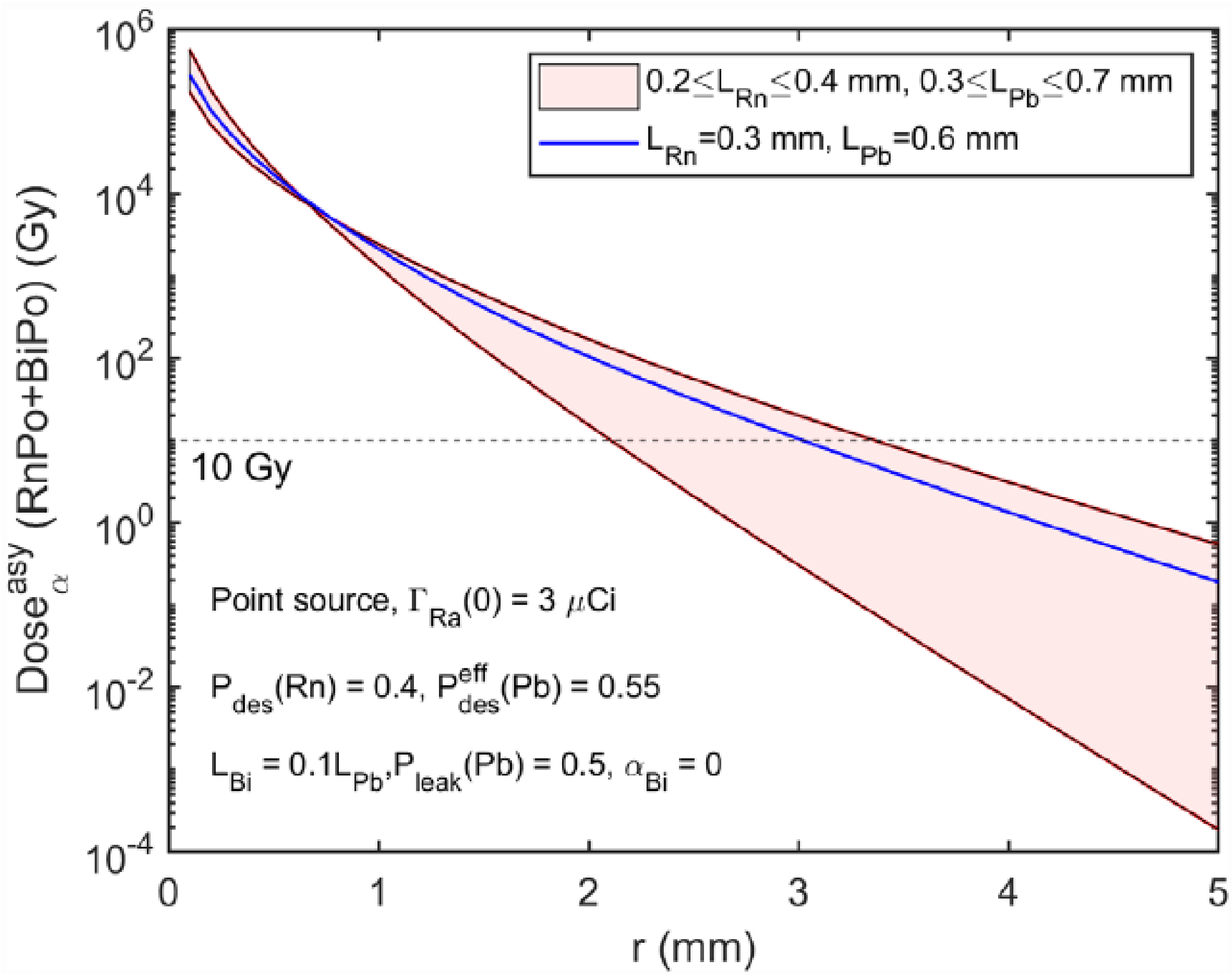
$$Dose_\alpha(\mathrm{RnPo};\,\mathbf{r},t) = \frac{E_\alpha(\mathrm{RnPo})}{\rho}\int_0^t \lambda_{\mathrm{Rn}} n_{\mathrm{Rn}}(\mathbf{r},t')dt'$$

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

Number of α-decays over time

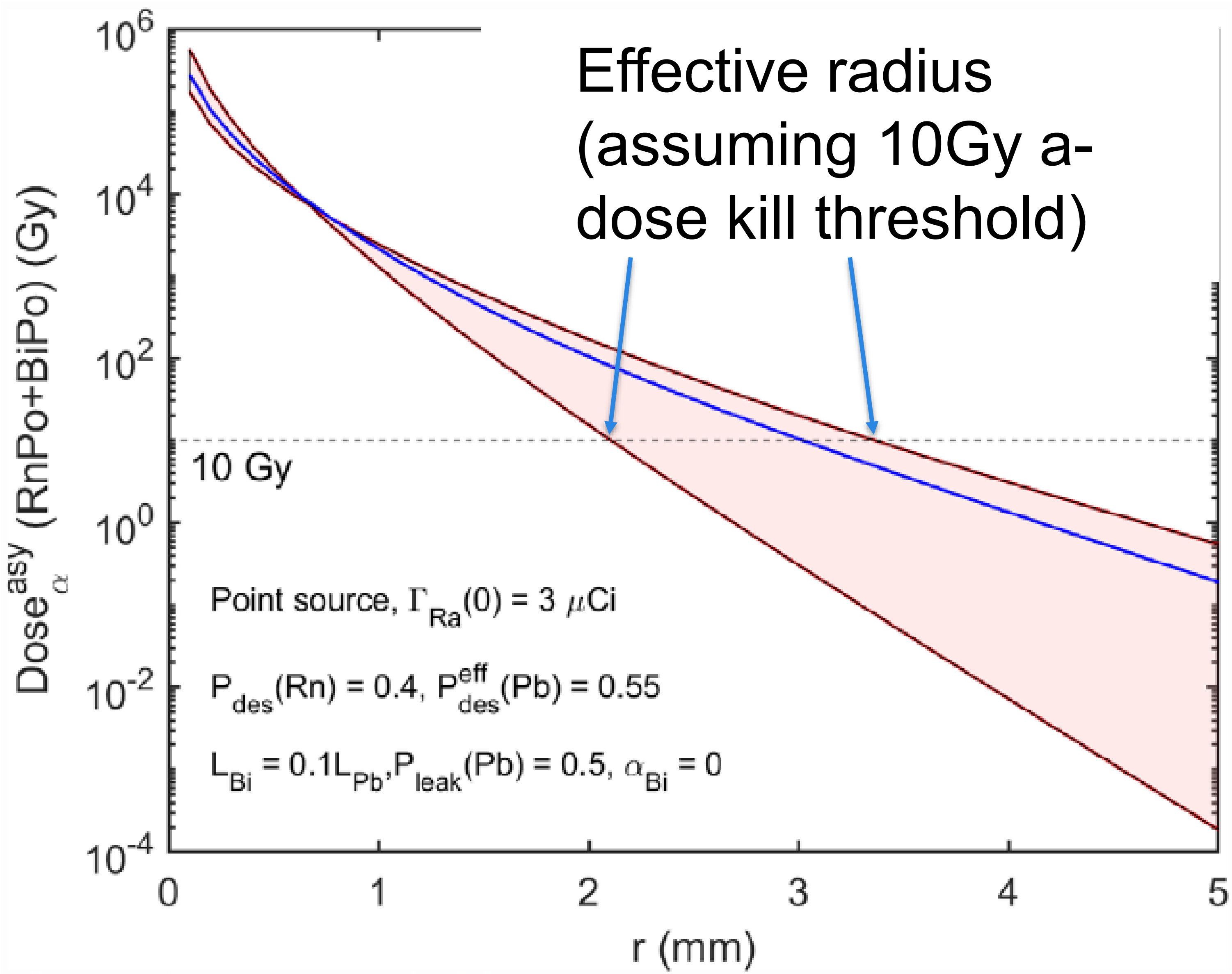
Memorial Sloan Kettering Cancer Center

Arazi, Phys. Med. Biol. 65(2020)



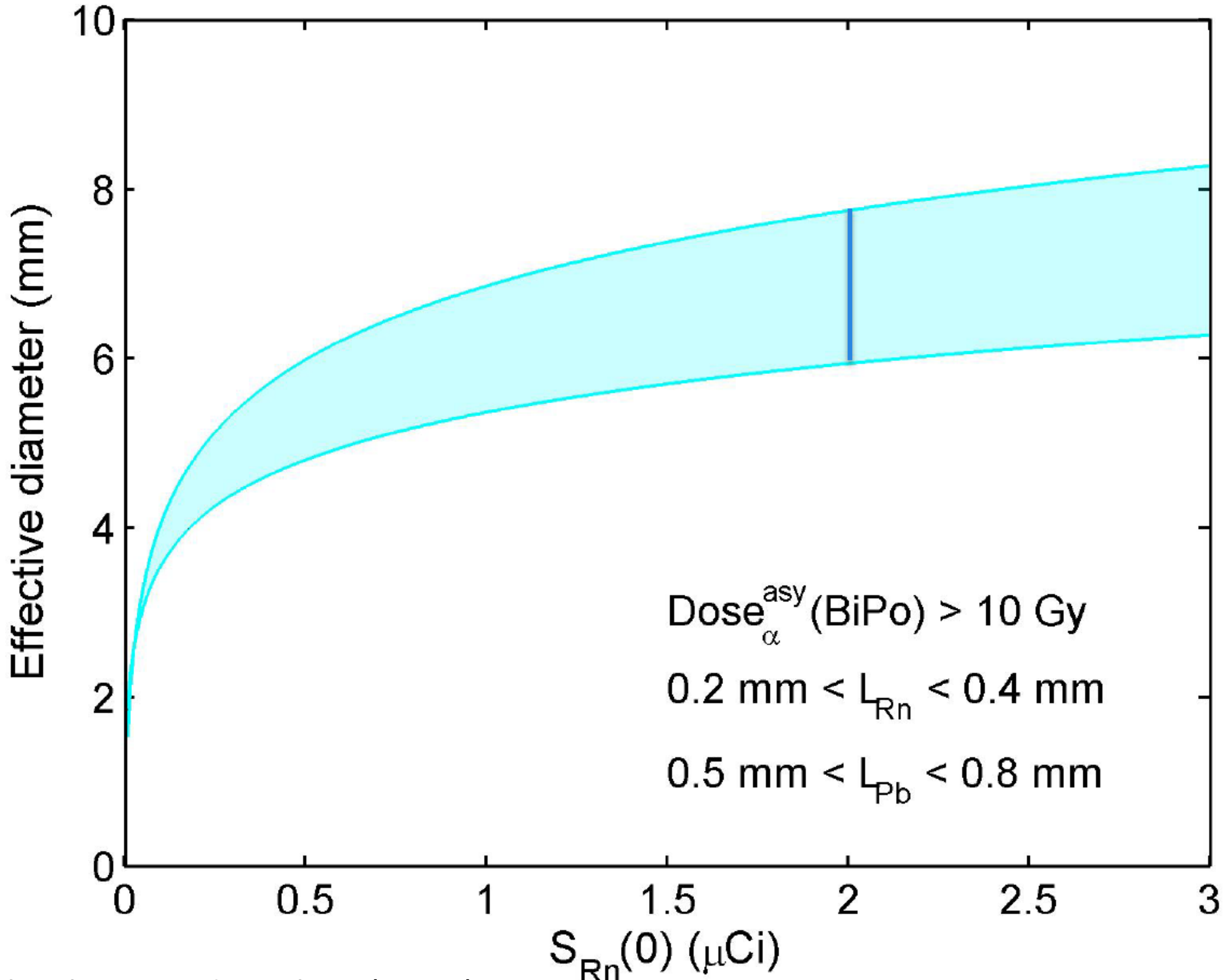
Arazi, Phys. Med. Biol. 65(2020)

Memorial Sloan Kettering Cancer Center



Arazi, Phys. Med. Biol. 65(2020)

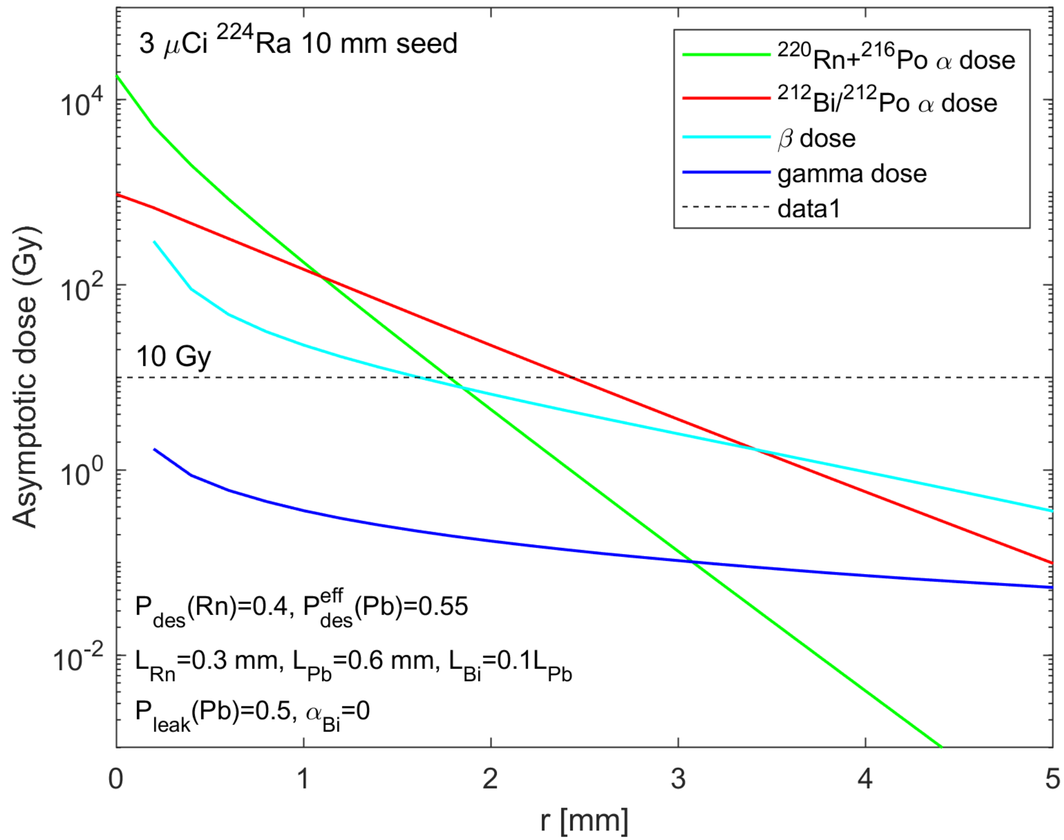
Effective Diameter for a 2μCi DaRT***



Arazi et al., Phys. Med. Biol. 52(2007)

an Kettering
r

All dose components:

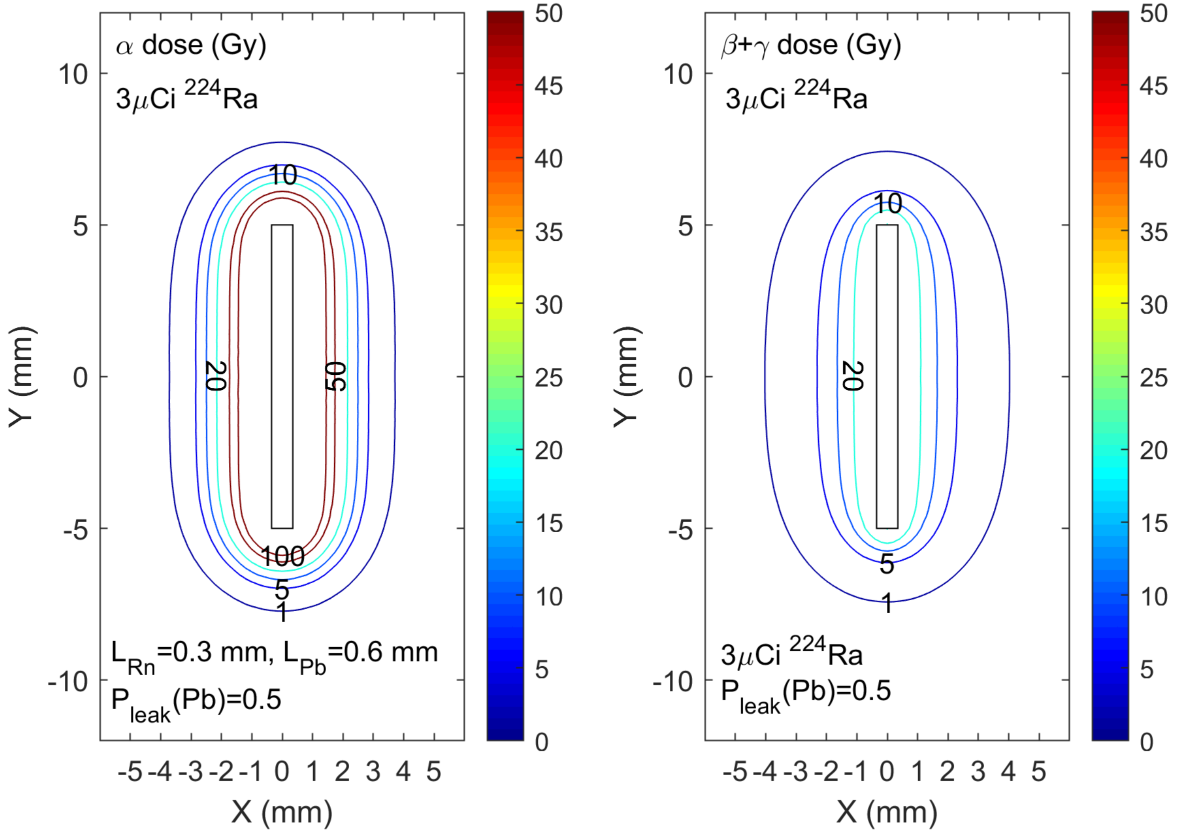


Beta and gamma doses calculated using EGSnrc, insensitive to diffusion

Courtesy: L. Arazi

Memorial Sloan Kettering Cancer Center

“TG43” distribution



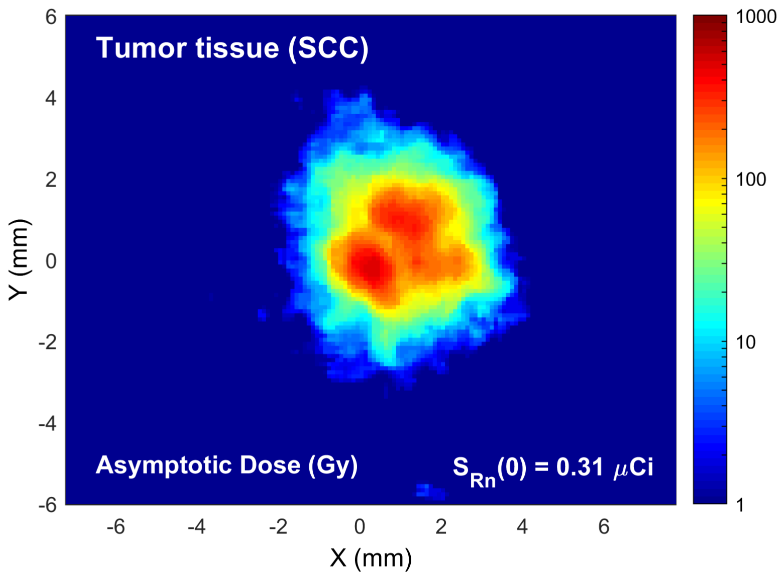
Courtesy: L. Arazi

Memorial Sloan Kettering Cancer Center

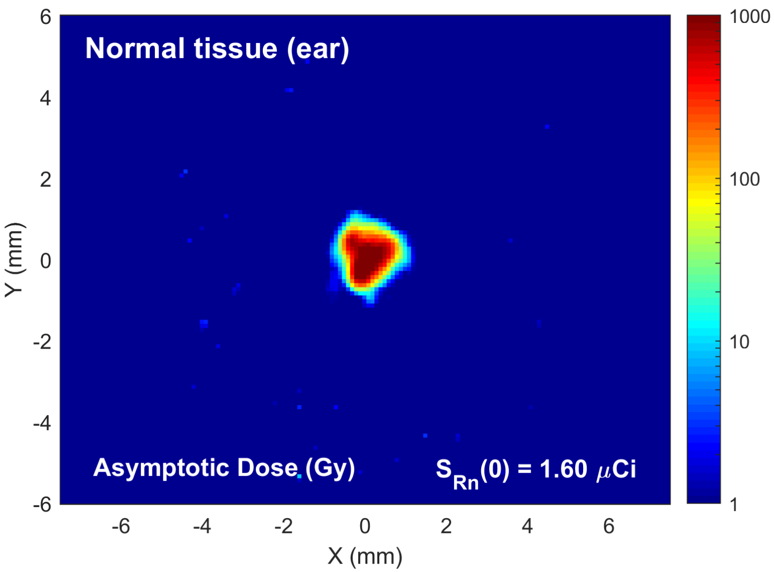
Courtesy: Lior Arazi

Safety – adjacent healthy tissue

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



Mouse SCC tumor



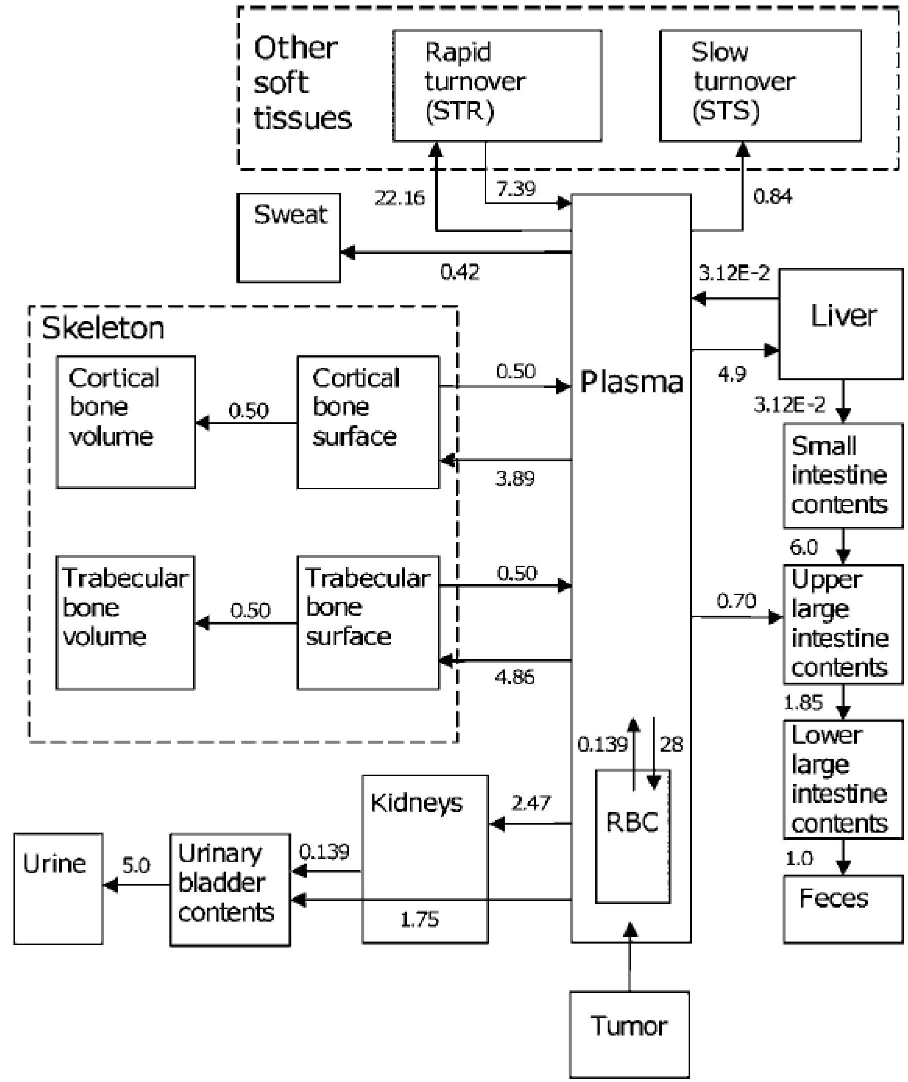
Pig's ear

Memorial Sloan Kettering Cancer Center

Internal dosimetry analysis

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.

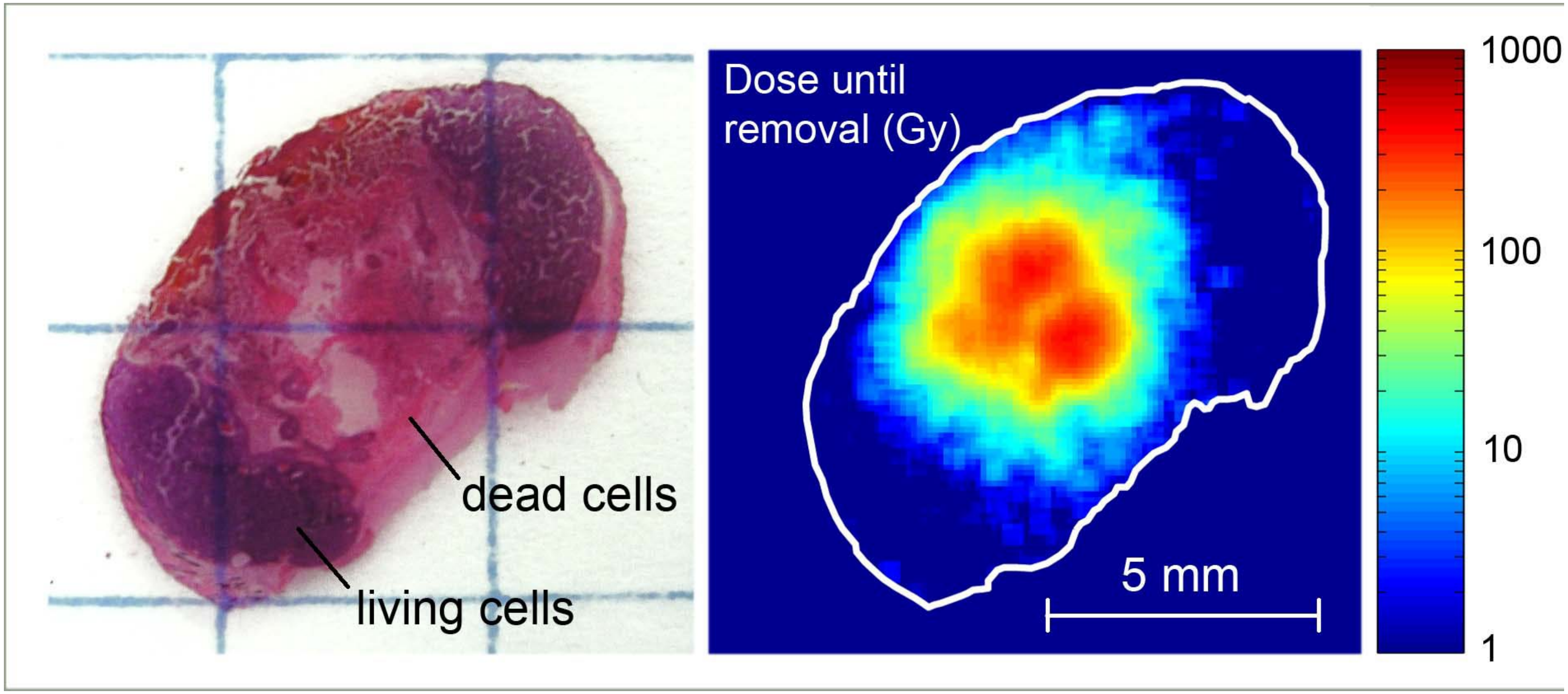


Arazi et al., Phys. Med. Biol. 55(2010)

Memorial Sloan Kettering Cancer Center

Lior Arazi and Tomer Cooks

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



(Left) 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.

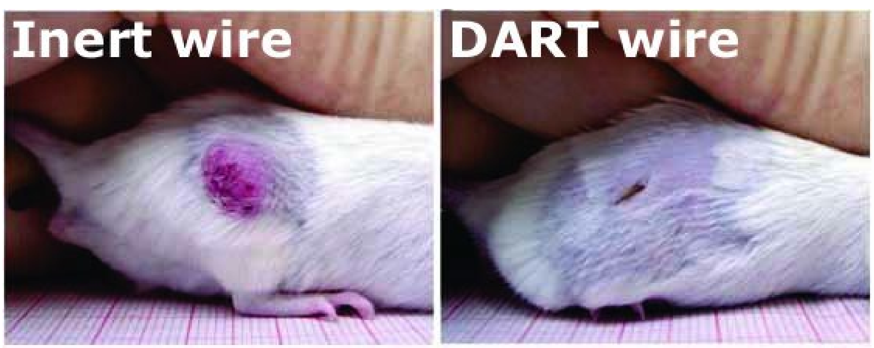
(Right) The radiation pattern of the same section.

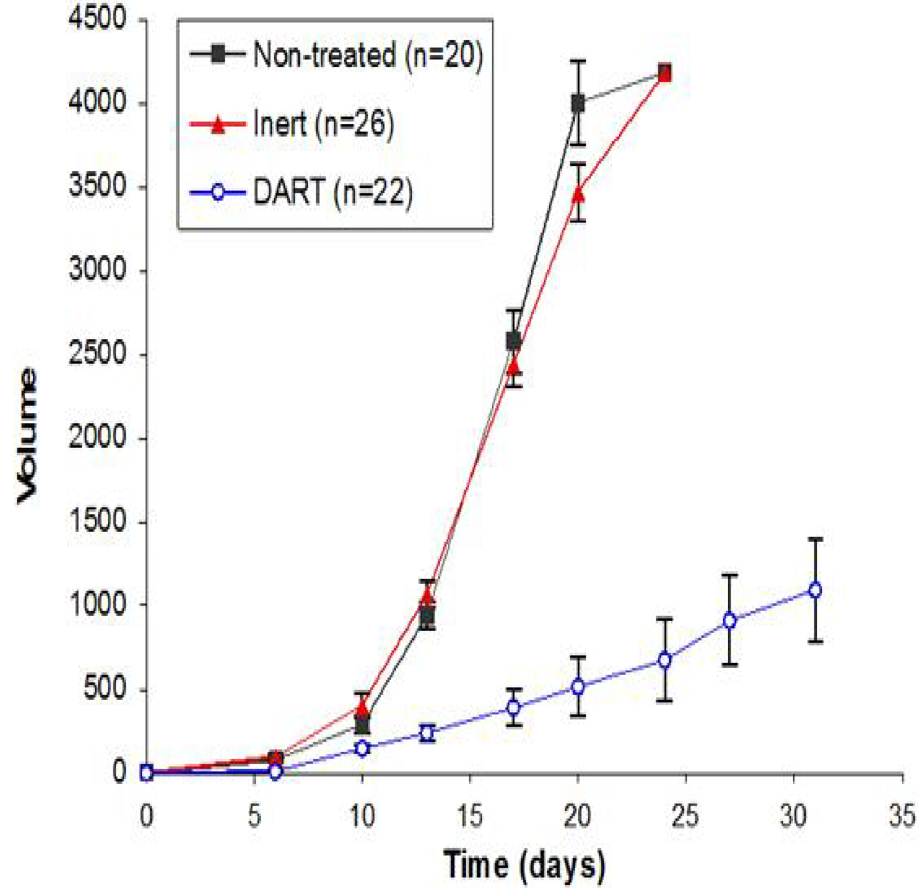
Memorial Sloan Kettering Cancer Center

Courtesy: Keisari

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.

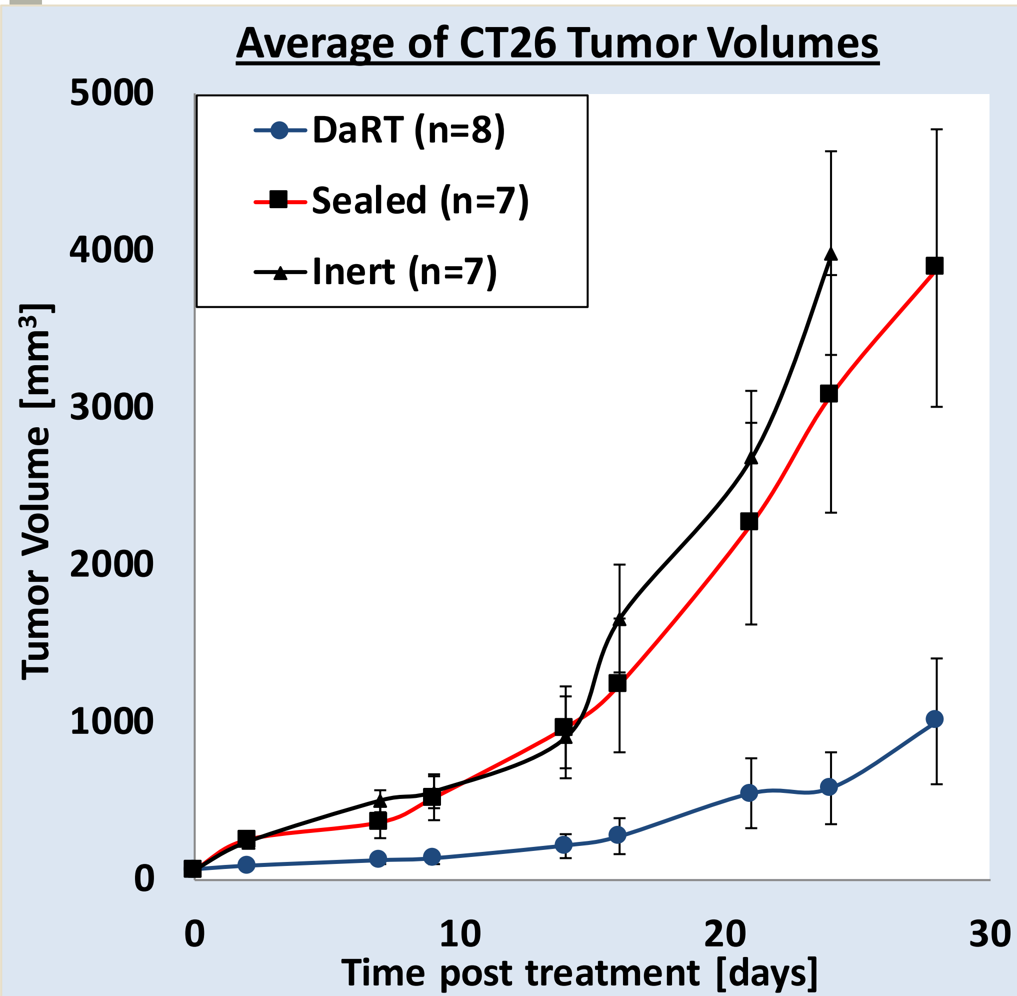


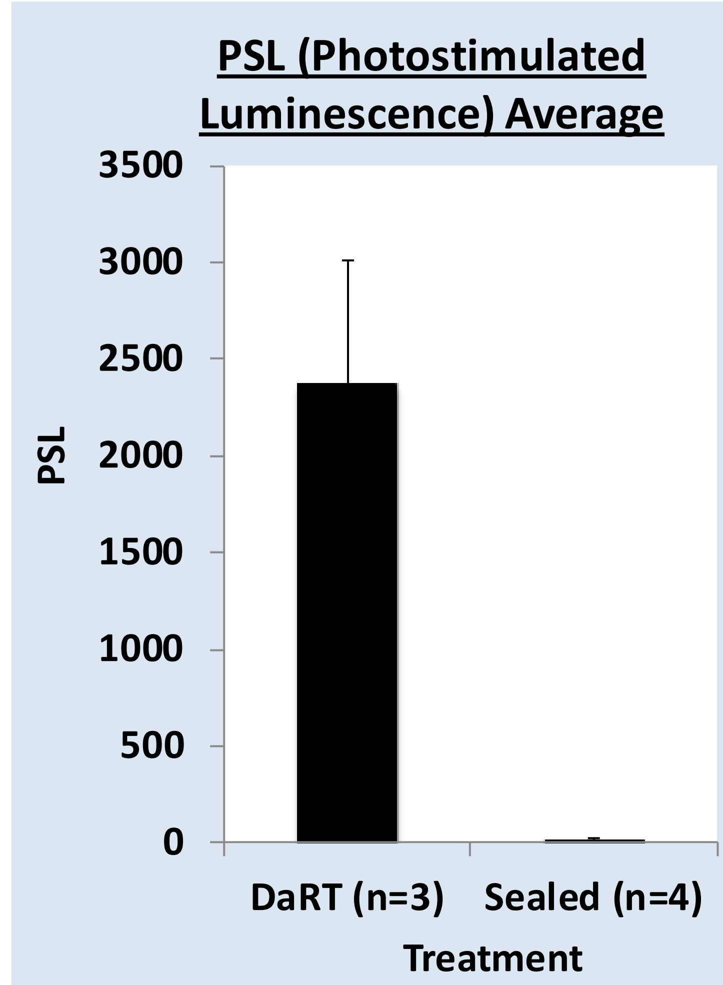


Memorial Sloan Kettering Cancer Center

Courtesy: Keisari

Tumor Destruction by DaRT is Primarily Mediated by Alpha Particles





$p<0.05$ DaRT vs. controls

$p<0.05$ DaRT vs. sealed

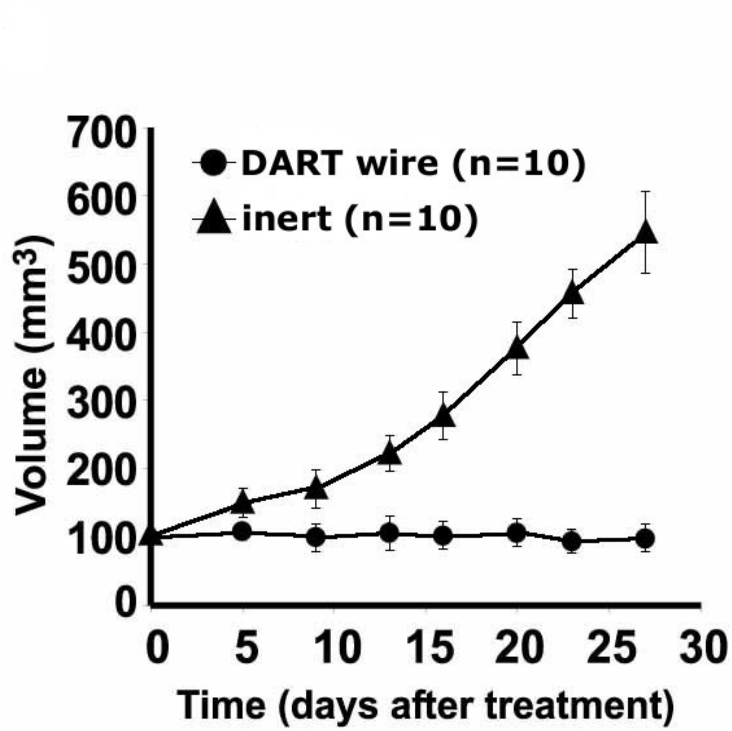
Memorial Sloan Kettering Cancer Center

T. Cook

DaRT Wires Eradicating Human SCC in Nude mice

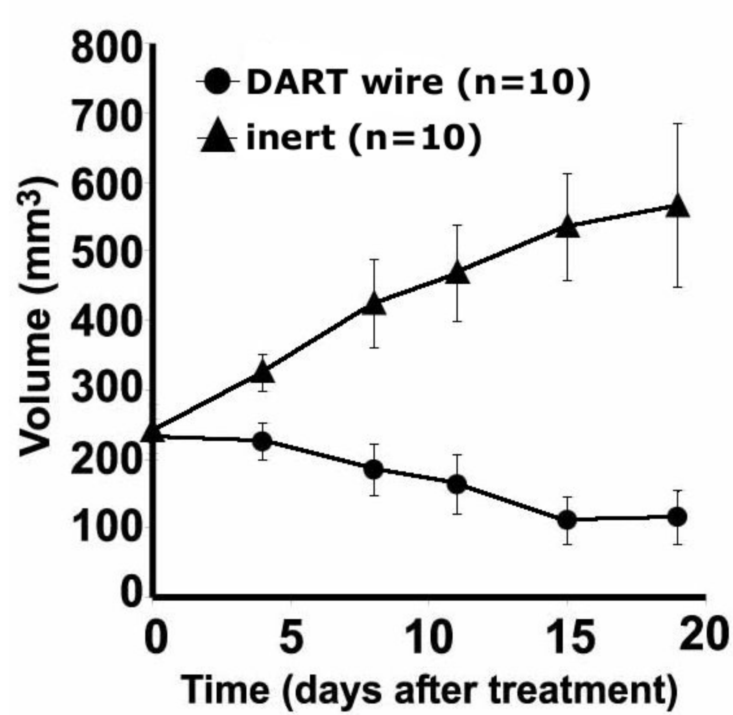
Effect of a single DART wire

A



HNSCC

B



Lung SCC

Memorial Sloan Kettering Cancer Center

T. Cook

DaRT Wires Eradicating Human Tumors in Nude mice

Tumor size after 11 days

GBM

Human Prostate in Nude Mice

45 days after tumor transplantation HNSCC

Memorial Sloan Kettering Cancer Center

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

1. Arazi, L., et al., *Treatment of solid tumors by interstitial release of recoiling short-lived alpha emitters.* Phys Med Biol, 2007. **52**(16): p. 5025-42.
2. Arazi, L., et al., *The treatment of solid tumors by alpha emitters released from (224)Ra-loaded sources-internal dosimetry analysis.* Phys Med Biol, 2010. **55**(4): p. 1203-18.
3. Cooks, T., et al., *Interstitial wires releasing diffusing alpha emitters combined with chemotherapy improved local tumor control and survival in squamous cell carcinoma-bearing mice.* Cancer, 2009. **115**(8): p. 1791-801.
4. Cooks, T., et al., *Growth retardation and destruction of experimental squamous cell carcinoma by interstitial radioactive wires releasing diffusing alpha-emitting atoms.* Int J Cancer, 2008. **122**(7): p. 1657-64.
5. Cooks, T., et al., *Local control of lung derived tumors by diffusing alpha-emitting atoms released from intratumoral wires loaded with radium-224.* Int J Radiat Oncol Biol Phys, 2009. **74**(3): p. 966-73.
6. Cooks, T., et al., *Intratumoral 224Ra-loaded wires spread alpha-emitters inside solid human tumors in athymic mice achieving tumor control.* Anticancer Res, 2012. **32**(12): p. 5315-21.