Desired SRT Dosimetry Methods/Approaches A clinician's wish list

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The promise of SRT

- Precise patient selection
- Personalized dosing
- Optimized therapeutic ratio

- Better care

Precise patient selection

- Can verify target expression
  - Potentially repeatedly
- Reduce futile treatments
  - Difficult to set bar

Personalized dosing

- Radiopharmaceuticals readily tracked in vivo
- Potential to determine patient-specific pharmacokinetics

Optimized therapeutic ratio

- Give maximal dose possible while avoiding toxicity

Overarching goals

- Pick the right patients
- Make treatments safer
- Make treatments more efficacious

Current status: Sodium iodide

- Wide therapeutic ratio in most cases
- Whole body & blood dosimetry used in isolated centers

Current status: Bone radiopharmaceuticals

- Ra-223, Sm-153, Sr-90 approved
- Weight based or flat dosing
  - 6 cycles for Ra-223
- Wide therapeutic window

Current status: PRRT

- Lu-177 DOTATATE recently approved
- Flat dosing
  - 4 cycles

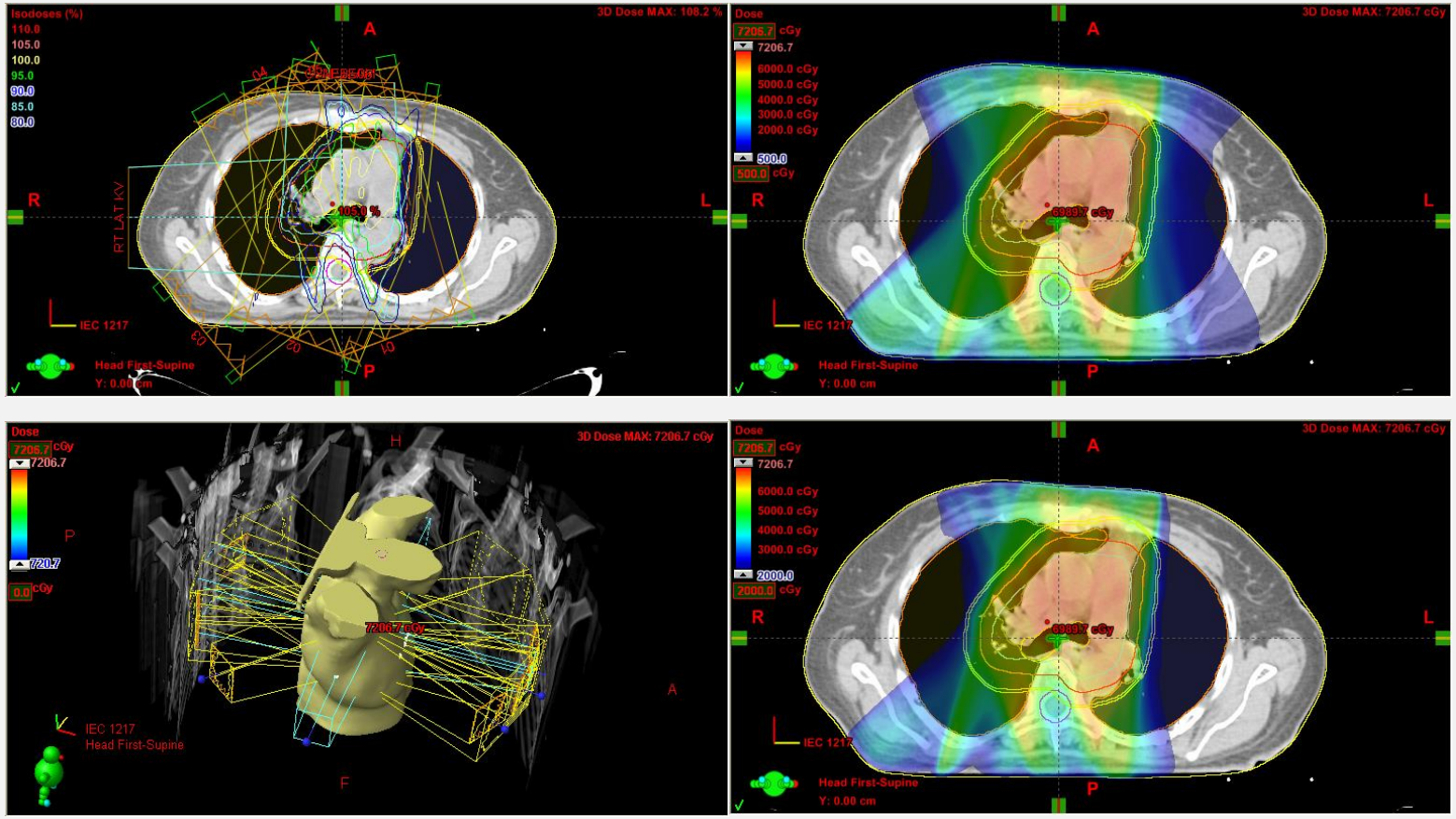
Current status: MIBG

- NDA under review
- Flat dose
  - 2 cycles
  - Organ dosimetry for reduction

Current status: Summary

- Most clinical uses flat or weight based dosing
- Rare use of rudimentary dosimetry

Complicated but rudimentary by comparison



Current status: Summary

- There is patient benefit
- Substantial room for improvement

What is holding us back?

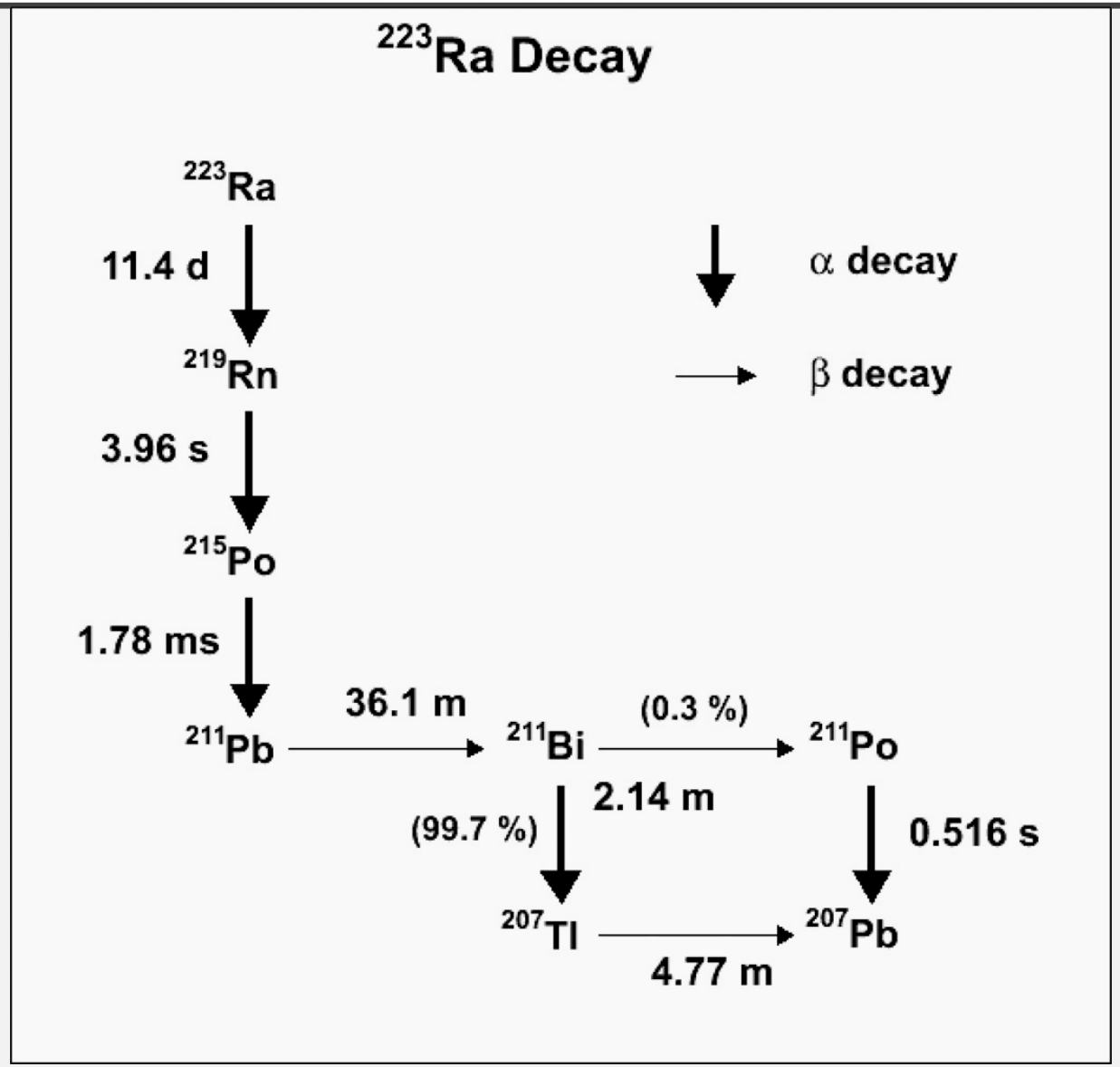
Basic radiobiology

- Poorly understood for unsealed sources
- Much dogma with clear contradictory evidence

Alpha decays are complicated

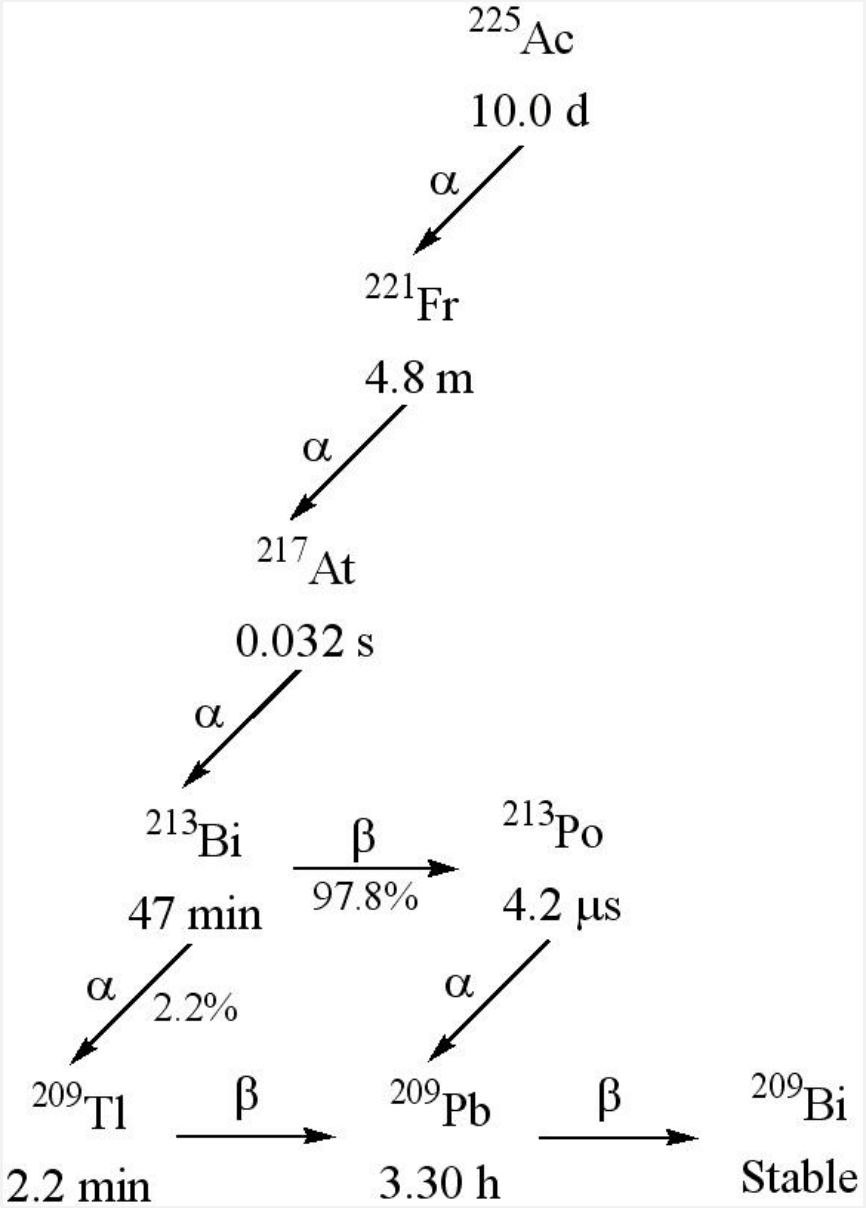
- Long decay chains
- Significant daughter half-lives
- Exponentially more complicated pharmacokinetics

Radium-223



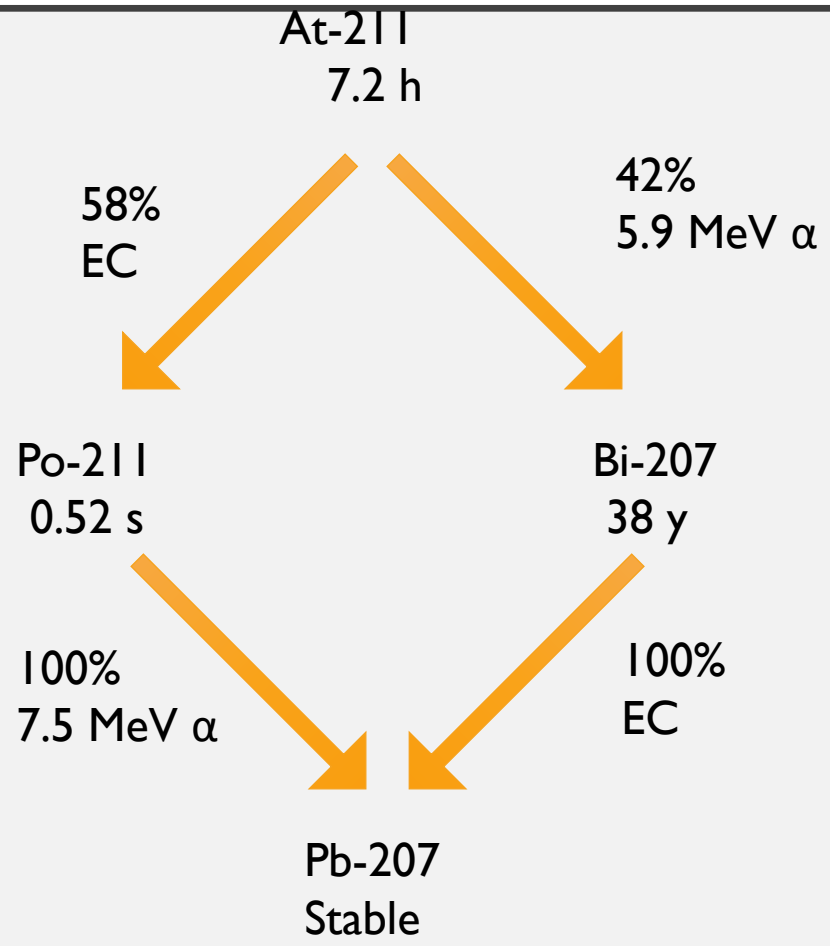
Robert F Hobbs et al Phys. Med. Biol. 2012

Actinium-225

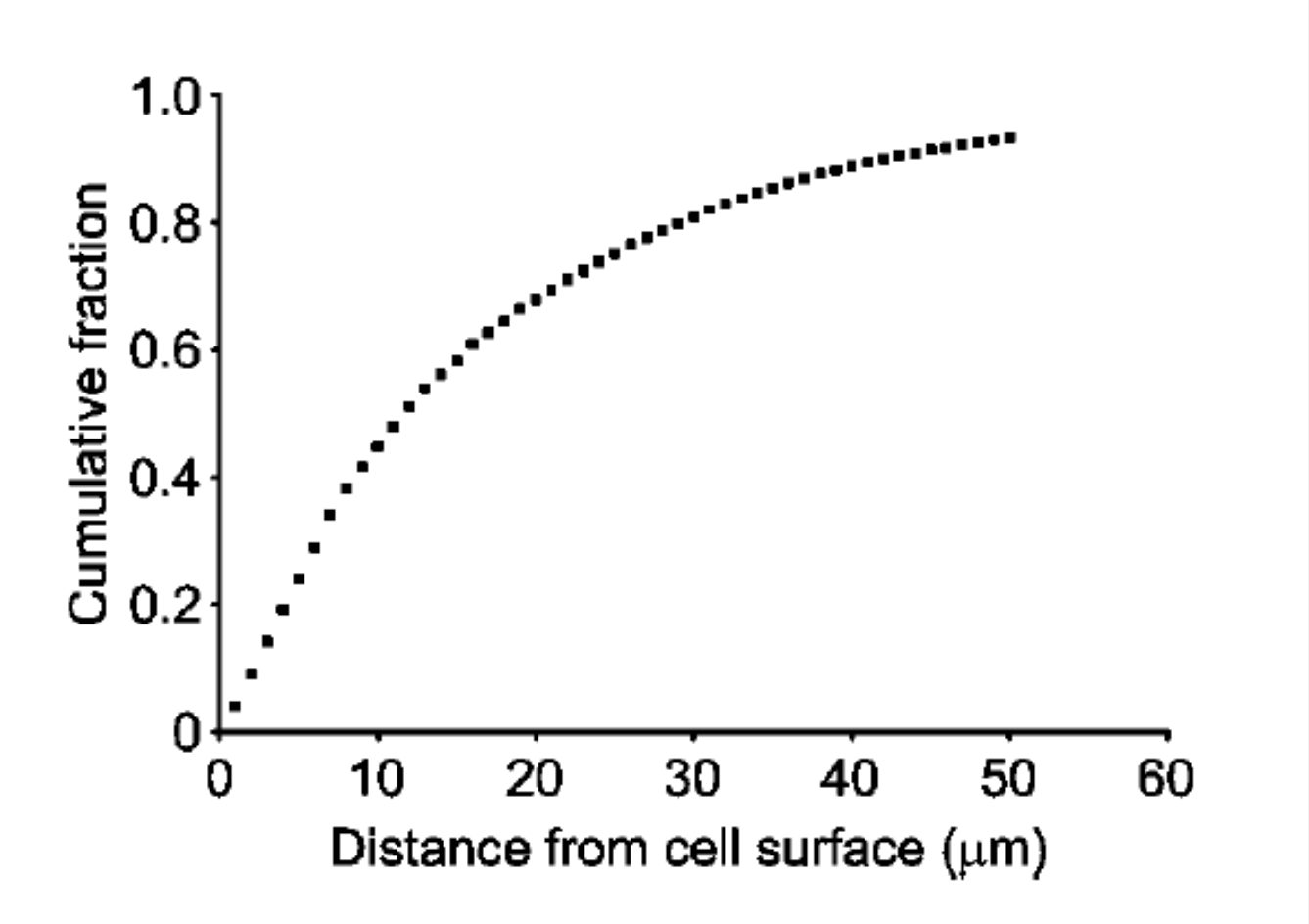


Brechbiel. Dalton Trans 2007

Astatine-211

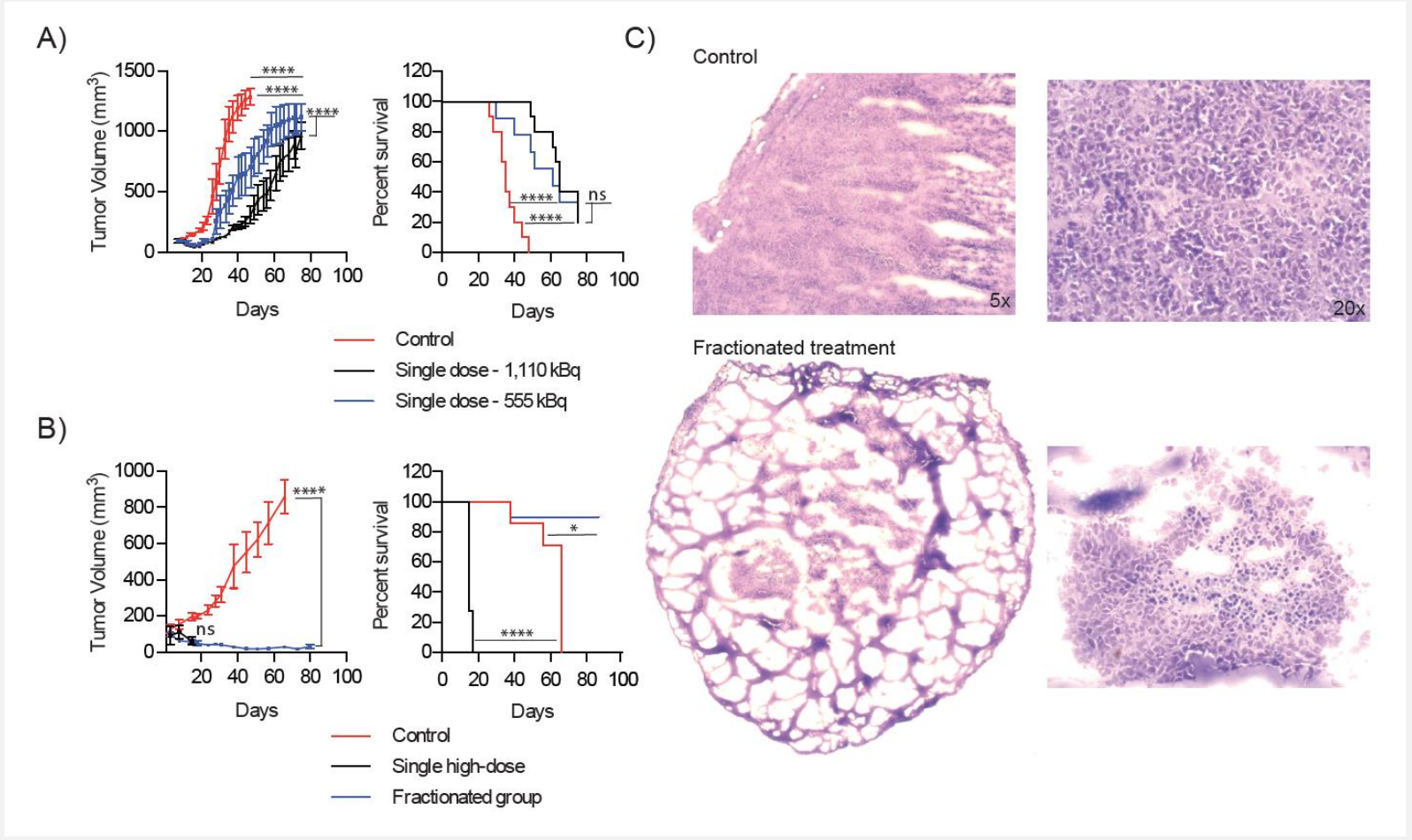


Nothing can happen in 0.52 seconds, right?



Palm et al, Medical Physics 2004

Alpha particle damage cannot be repaired



Cross-fire effect is an advantage of beta over alpha

- Mostly applied to bulky disease
- Little to no empirical evidence of truth

23 Gy renal dose limit

- Derived from EBRT experience
  - Old and anecdotal data
- Clearly not optimal

Improving dose limits

- Requires clear understanding of biodistribution and kinetics
  - Micro/macro heterogeneity

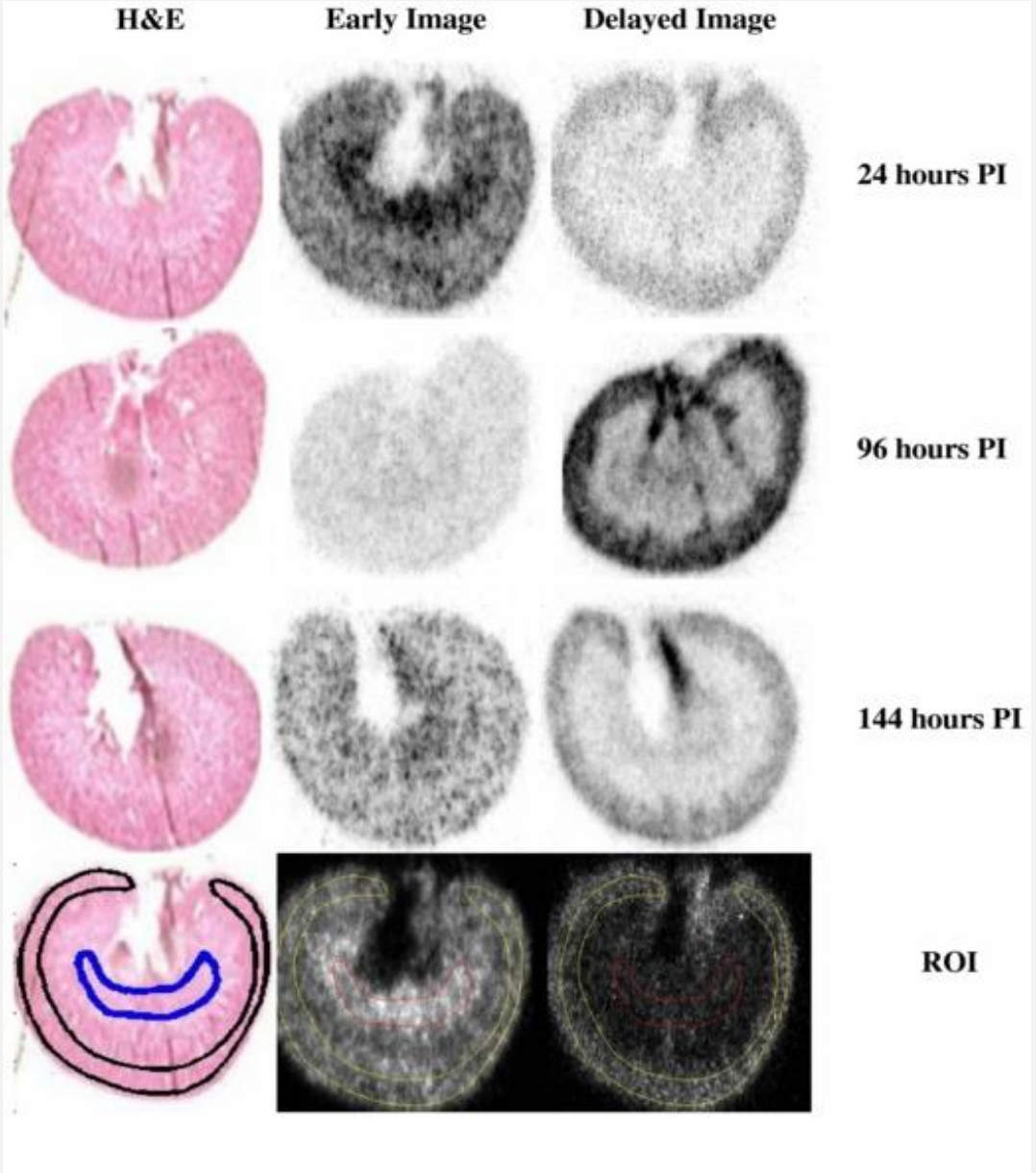


Figure 4 from Renal uptake of bismuth-213 and its contribution to kidney radiation dose following administration of actinium-225-labeled antibody
J Schwartz et al 2011 Phys. Med. Biol. 56 721 doi:10.1088/0031-9155/56/3/012

Dose limits: Population or individual

- Do we need population-based constraints?
- Could dose limits be determined on a per patient basis?

Dose needs: Population or individual

- Can we utilize predictors of tumor response/normal tissue toxicity to optimize dose?

Adaptive therapy

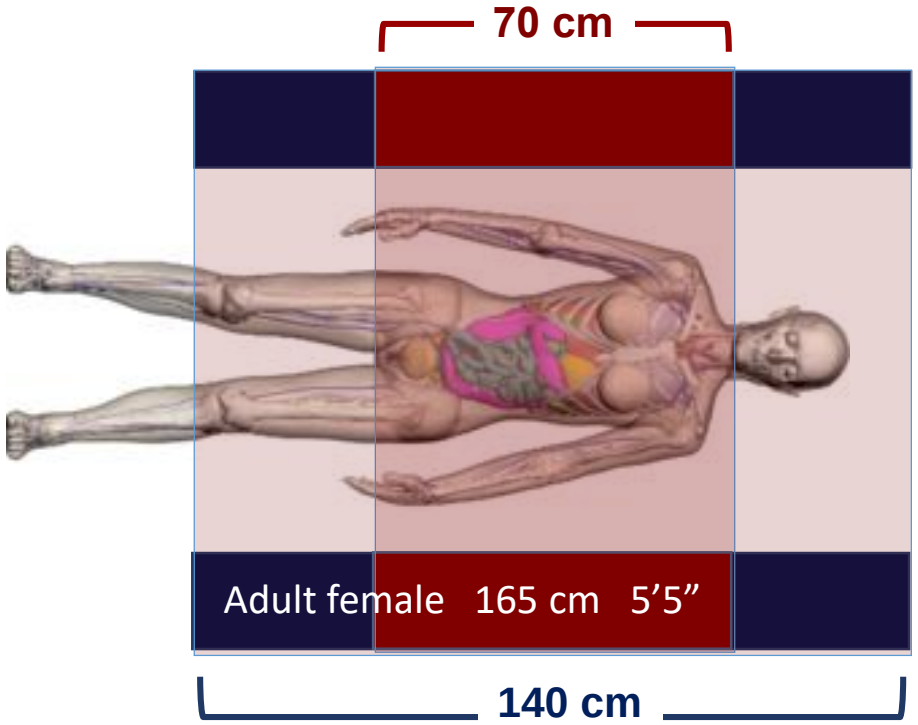
- Utilize input data from prior fraction(s) to determine subsequent
  - Efficacy
  - Toxicity

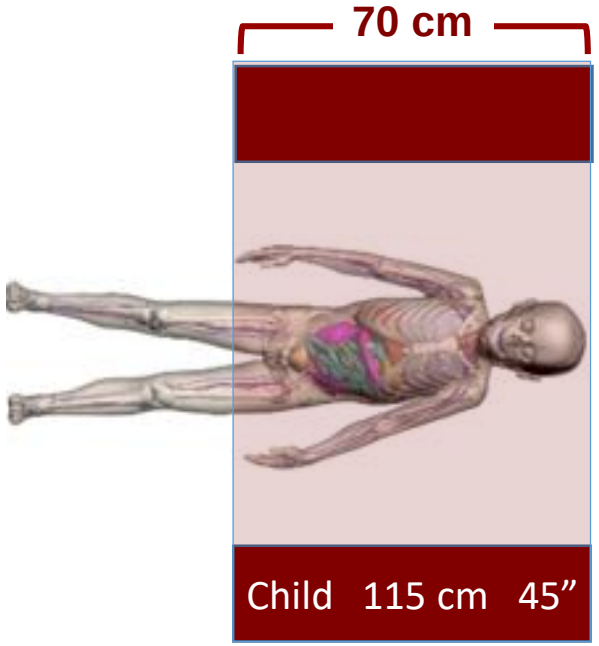
Many therapeutic isotopes are poor for imaging

- Low administered activity with alphas
- PET continues to improve
  - Better to use PET diagnostic

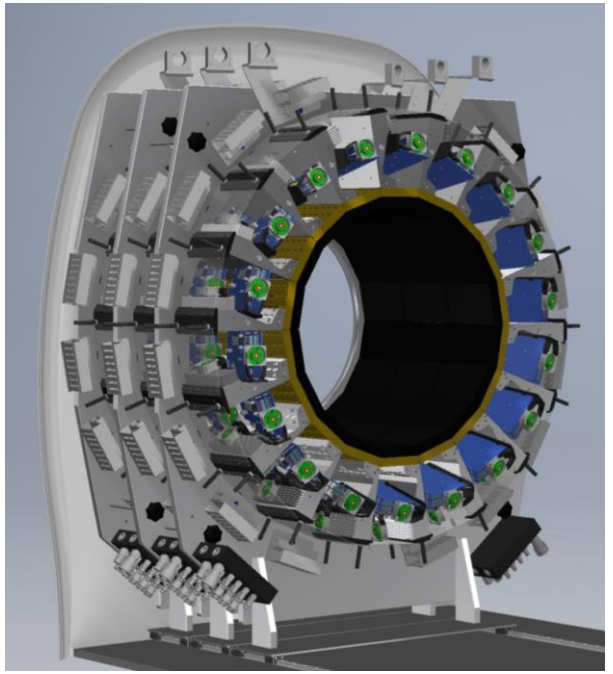
PennPET Explorer Design: *Multi-ring*

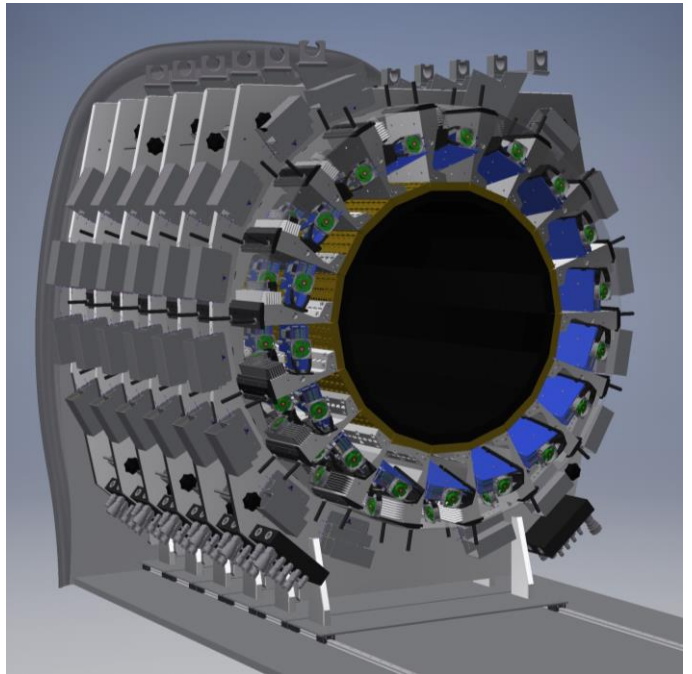
- Multi-ring construction for variable axial FOV
  - **3 rings 70 cm** – torso, pediatric
  - **6 rings 140 cm** – full body
- Detector module design with small gaps between rings



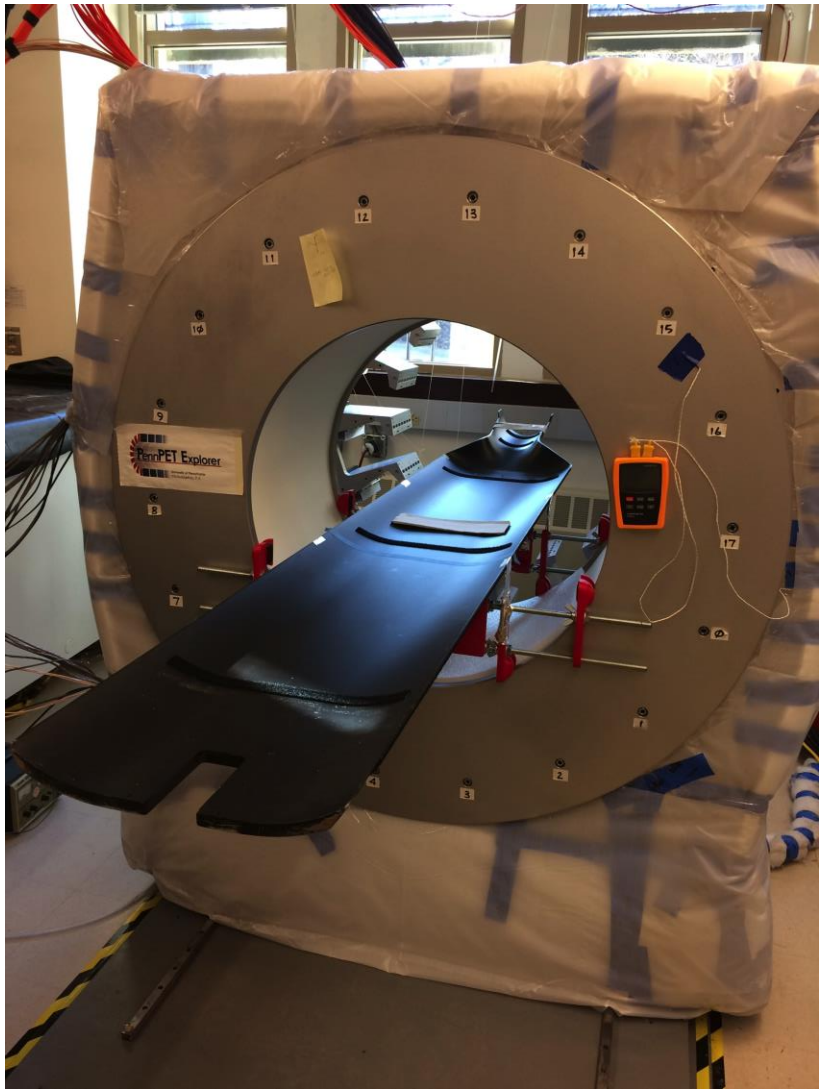


Courtesy of Joel Karp, PhD





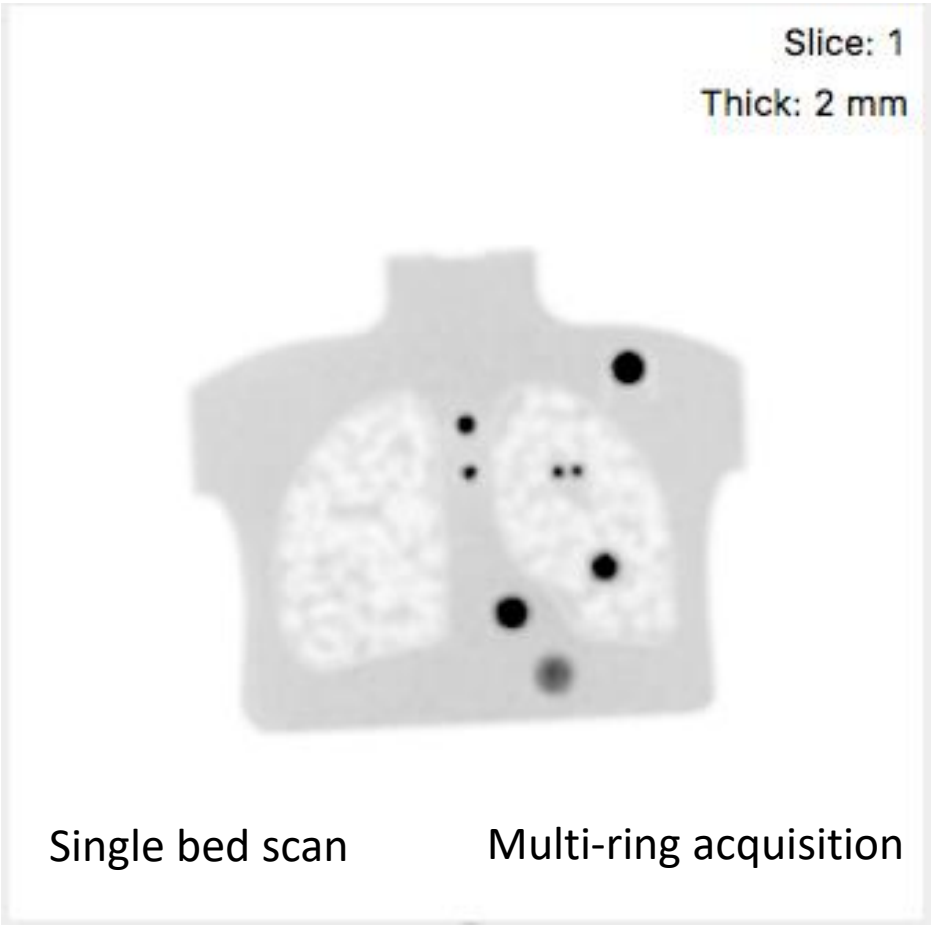
PennPET Explorer: Preliminary Measurements



Timing resolution: 250 ps
Energy resolution: 11%
Spatial resolution: 3.9 mm

SNM CTN phantom

Courtesy of Joel Karp, PhD



Single bed scan

Multi-ring acquisition

Companion diagnostics

- Better diagnostic imaging
- Does not imply better prediction of therapeutic efficacy
- Different optimization goals

Companion diagnostics

- Can they be used to predict therapeutic dose?
- How reliable are the estimates?

Kinetic optimization

- Single big dose not optimal (solid tumors)
- 4-6 cycles at 4-8 week intervals better
  - Still not optimal

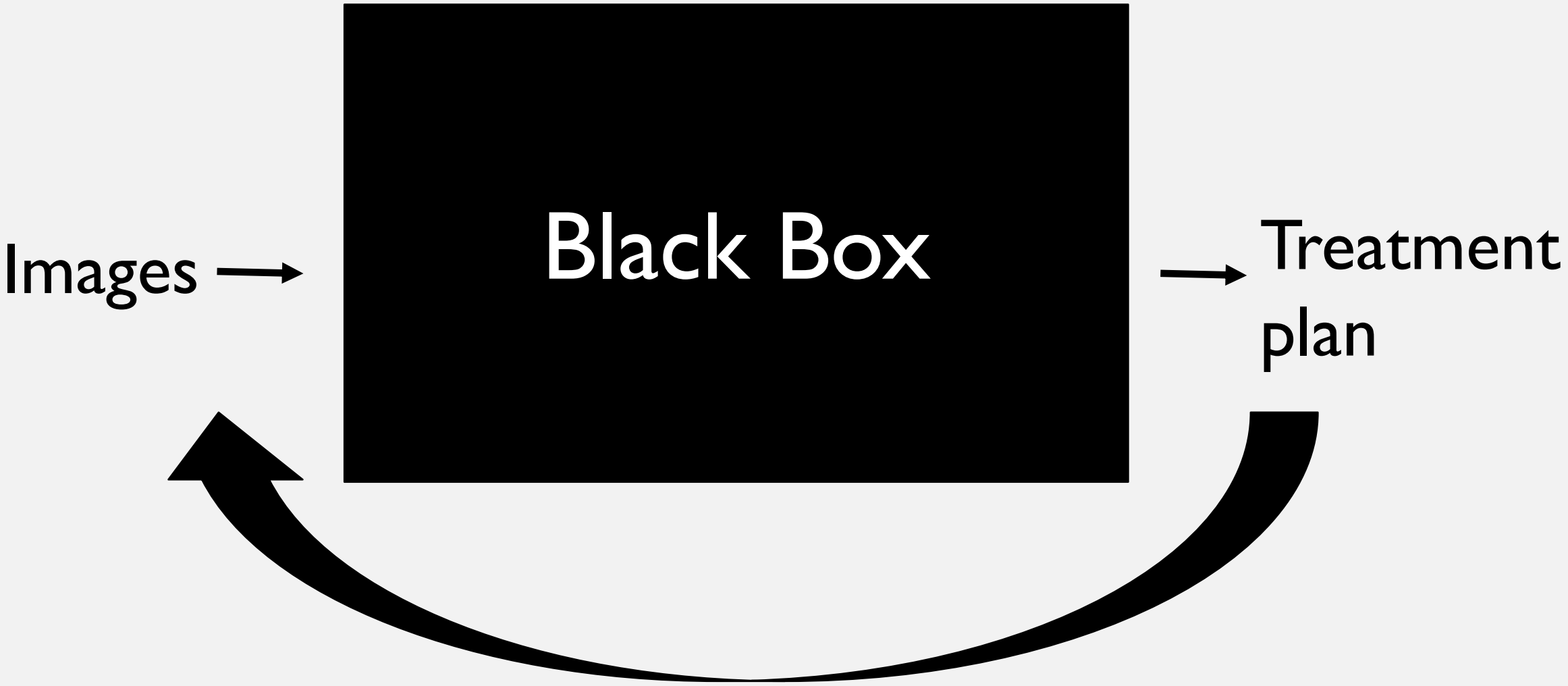
Kinetic optimization

- Can we achieve advantages from fractionation?
  - As EBRT moves to hypofractionation

Combination therapies

- How does radiation (from SRT) interact with other therapeutics?
- Can we achieve synergy?

The wish list


Images
Black Box
Treatment plan

A black box incorporating:

- Image analysis/segmentation
- Dose calculation
- Response prediction
- Dose adaptation

Original Article

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

Raul G. Nogueira, M.D., Ashutosh P. Jadhav, M.D., Ph.D., Diogo C. Haussen, M.D., Alain Bonafe, M.D., Ronald F. Budzik, M.D., Parita Bhuva, M.D., Dileep R. Yavagal, M.D., Marc Ribo, M.D., Christophe Cognard, M.D., Ricardo A. Hanel, M.D., Cathy A. Sila, M.D., Ameer E. Hassan, D.O., Monica Millan, M.D., Elad I. Levy, M.D., Peter Mitchell, M.D., Michael Chen, M.D., Joey D. English, M.D., Qaisar A. Shah, M.D., Frank L. Silver, M.D., Vitor M. Pereira, M.D., Brijesh P. Mehta, M.D., Blaise W. Baxter, M.D., Michael G. Abraham, M.D., Pedro Cardona, M.D., Erol Veznedaroglu, M.D., Frank R. Hellinger, M.D., Lei Feng, M.D., Jawad F. Kirmani, M.D., Demetrius K. Lopes, M.D., Brian T. Jankowitz, M.D., Michael R. Frankel, M.D., Vincent Costalat, M.D., Nirav A. Vora, M.D., Albert J. Yoo, M.D., Ph.D., Amer M. Malik, M.D., Anthony J. Furlan, M.D., Marta Rubiera, M.D., Amin Aghaebrahim, M.D., Jean-Marc Olivot, M.D., Wondwossen G. Tekle, M.D., Ryan Shields, M.Sc., Todd Graves, Ph.D., Roger J. Lewis, M.D., Ph.D., Wade S. Smith, M.D., Ph.D., David S. Liebeskind, M.D., Jeffrey L. Saver, M.D., Tudor G. Jovin, M.D., for the DAWN Trial Investigators

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It makes sense

- Accurate dosimetry paired with radiobiologic knowledge should improve outcomes

It must be approachable

- Needs to be virtually as easy as giving 4-6 cycles of fixed or weight based dose

It is feasible

Patients will thank you

Thank you!