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

$^{223}\text{Ra Decay}$

$^{223}\text{Ra}$

11.4 d

$^{219}\text{Rn}$

3.96 s

$^{215}\text{Po}$

1.78 ms

$^{211}\text{Pb}$

36.1 m

$^{211}\text{Bi}$

(99.7 %)

2.14 m

$^{207}\text{Tl}$

4.77 m

$^{207}\text{Pb}$

$^{211}\text{Po}$

(0.3 %)

$^{211}\text{Po}$

0.516 s

Actinium-225

$^{225}\text{Ac}$
- 10.0 d
- $^\alpha$
- $^{221}\text{Fr}$
- 4.8 m
- $^\alpha$
- $^{217}\text{At}$
- 0.032 s
- $^\alpha$
- $^{213}\text{Bi}$
- 47 min
- $^\beta$ 97.8% 4.2 μs
- $^\alpha$
- $^{213}\text{Po}$
- $^{209}\text{Tl}$
- 2.2 min
- $^\beta$
- $^{209}\text{Pb}$
- 3.30 h
- $^\beta$
- $^{209}\text{Bi}$
- Stable

Astatine-211

$^\text{At-211}$
7.2 h

58% EC

$^\text{Po-211}$
0.52 s

100%
7.5 MeV α

$^\text{Bi-207}$
38 y

42%
5.9 MeV α

$^\text{Pb-207}$
Stable

100%
EC
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
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

![Diagram of PennPET Explorer Design](image)

*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
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


N Engl J Med
Volume 378(1):11-21
January 4, 2018
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!