NCI Workshop on Dosimetry of Systemic Radionuclide Therapy (SRT) - ^{153}Sm

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JOHNS HOPKINS
MEDICINE

Overview

Characteristics

Use

Dosimetry

- planar
- 3D-RD
- Combination with Xbeam

Lessons and Limitations

^{153}Sm: the isotope

^{153}Sm emits β^- with a half-life of 46.7 h and 103 keV photon with 28.3 % frequency, which is used for quantitative imaging. Imaging typically uses triple energy window centered on 103 keV peak for scatter correction.

Higher branching ratio with lower energy photons ~ 50 keV are too low to distinguish from scatter background reliably

Q-value of β: 810 keV, average value 230 keV, average distance traveled in water: 0.6 mm.

Produced by neutron bombardment of Sm-152 enriched targets, includes small amount of long lived impurities and decay products (^{152}Eu, ^{154}Eu) estimated at 20-30 ppm.

Pharmaceuticals: ^{153}Sm-EDTMP

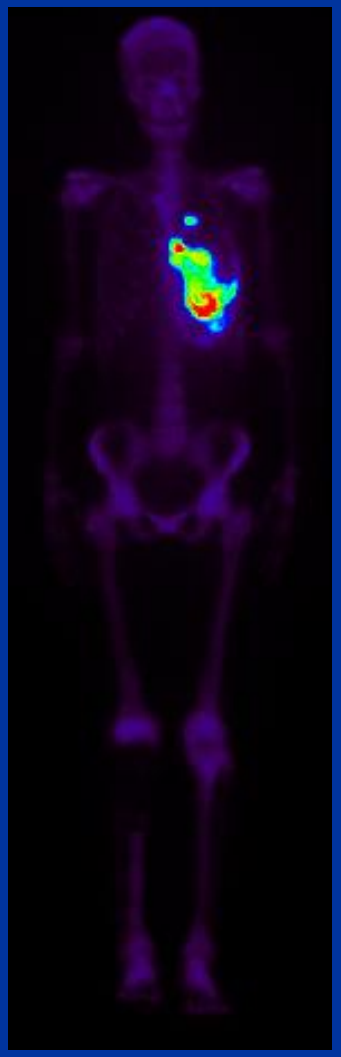
Sm-153-ethylenediaminetetramethylenephosphonic Acid aka Sm-153-lexidronam aka Quadramet

Chelate is bone seeking calcium mimetic

First approved by the FDA for palliation in 1997

Predominantly for bone pain palliation: mass-based administration, no dosimetry 1 mCi/kg.

Uptake is in bone and osteoblastic lesions. Excess clears through the kidneys in 4-8 h. Bone marrow is primary toxicity, concern for kidneys.



Pharmaceuticals: ^{153}Sm-EDTMP*

Currently owned by Lantheus (previously Cytogen, EUSAPharm)

Produced once per week, shipped in frozen 150 mCi vials, need to “thaw and draw”

*Cyclosam – new chelate by Cyclosam Therapeutics (IsoTherapeutics) not FDA approved.

*^{153}Sm-Hydroxyapatite for synovectomy

^{153}Sm-EDTMP use and dosimetry

Australia: Phase I/II study for skeletal mets using "AD"-based escalation. AD to bone marrow scaled directly from AA, max 2.8 Gy. Used planar imaging for tumor/background ratio

Mayo: up to **30 mCi/kg** for bone mets with stem cell support, with and without sensitizer. **No noted nephrotoxicity**. Mild hypocalcemia. Copper shielding for imaging.

Hutch: hormone refractory prostate carcinoma: a phase I/II trial up to 3 mCi/kg. **3 month OS improvement** from 0.5 mCi/kg group to 3 mCi/kg. AP-PA dosimetry. Noted similar uptake between ^{99m}Tc-MTP and ^{153}Sm-EDTMP.

MD Anderson: 1 mCi/kg for bone mets - dosimetry using blood and urine draws to determine WB activity. Use rat data to apportion activity to organs (mostly skeletal), use S values.

UCDavis-TJU: Phase 2 trial of ^{153}Sm-EDTMP followed by salvage prostatic fossa Xbeam Irradiation. No dosimetry other than claim that 2 mCi/kg is 50 Gy to bone surface (from Serafini et al.) did not meet goal of PSA response, propose combining XRT and Ra-223.

^{153}Sm-EDTMP use and dosimetry

SKCC: Repeat fractionation of docetaxl and 1 mCi/kg of ^{153}Sm-EDTMP. Median survival of 14.3 months.

Harvard: 152 patients with prostate bone mets treated for pain with 1 mCi/kg. Positive outcome.

NIH: Showed progression-free survival for ^{153}Sm-EDTMP 1 mCi/kg plus vaccine vs. ^{153}Sm-EDTMP alone versus mCRPC 1.7 vs 3.7 PFS. Will move to Ra-223.

Gustave Roussy: 43 patients added 1 mCi/kg with docetaxl. Well tolerated, pain relief, OS compares favorably **29 months compares** to 28 months in a multi-arm trial with Sr-89 as compared **to 17 months on chemo alone**

EANM: guidelines for beta-emitting bone met RPT – AA to organ dose conversion table from Eary et al. (1993)

Vigna *et al*.: 3 compartment model for PK and dosimetry based on 20 patients with 1 mCi/kg – see high variability, recommend patient specific dosimetry.

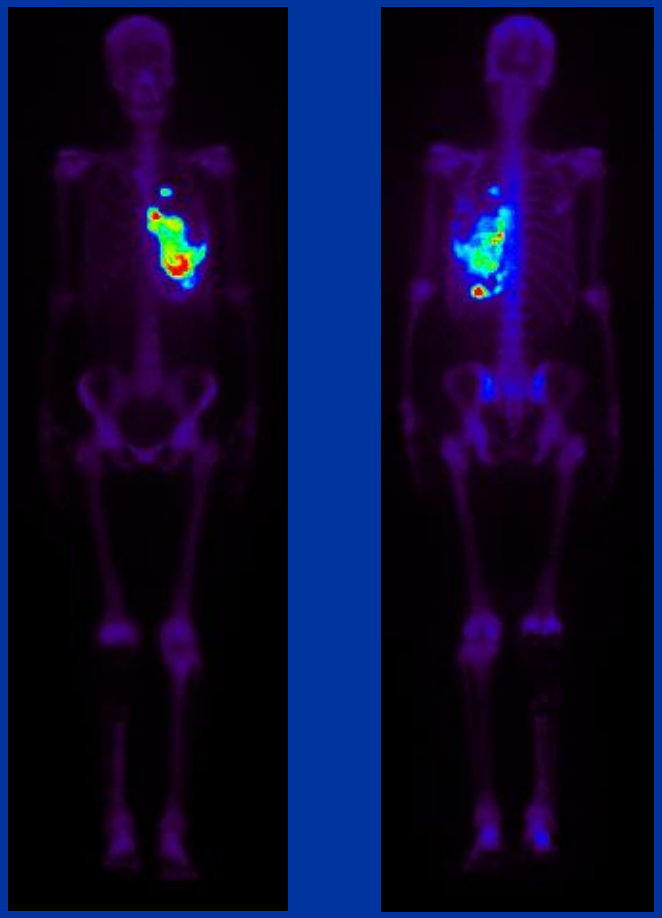
Hopkins experience ^{153}Sm

Therapy for high risk metastatic osteogenic sarcoma, pediatric soft tissue disease with calcification.

2 protocols – “low dose” Phase I escalation to determine AA that does not induce myelotoxicity. (1.21 mCi/kg)

- tandem protocol using low dose (1.0 mCi/kg) followed by “high dose” (6.0 mCi/kg) for linearity

Used planar and SPECT images for 2D and 3D quantification.

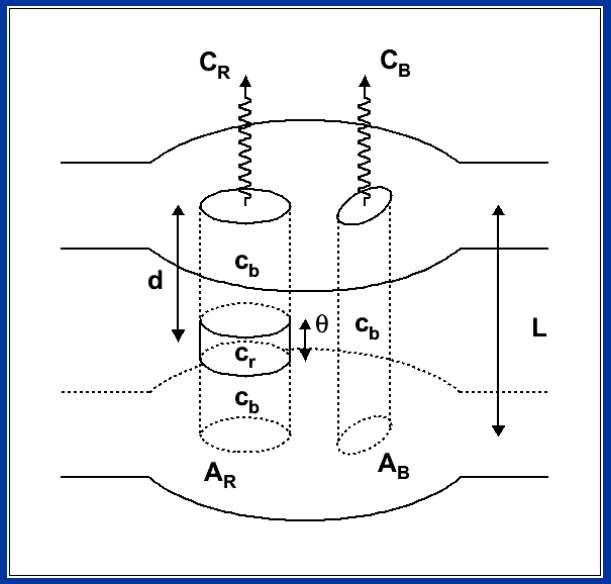


Loeb *et al.* Cancer ’09
Loeb *et al.* Cancer ’10

Planar dosimetry

Draw ROI and background contours on anterior and posterior images

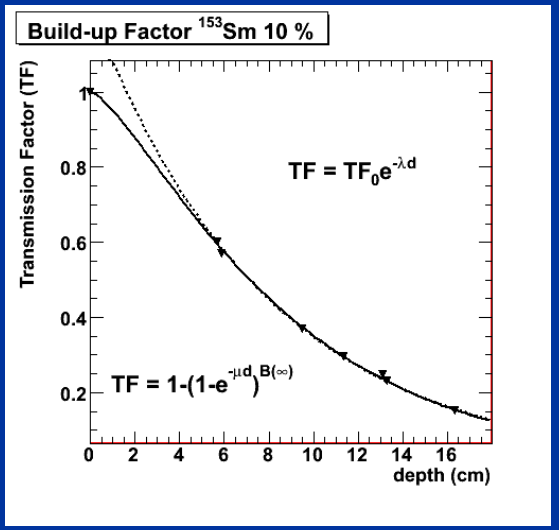
Use MIRD A/P methodology[a] and build-up method[b] for scatter correction to determine counts in tumors



$$\frac{C_R}{A_R} = \int_0^{d-\frac{\theta}{2}} c_b e^{-\lambda x} dx + \int_{d-\frac{\theta}{2}}^{d+\frac{\theta}{2}} c_r \left(1-\left(1-e^{-\mu x}\right)\right)^{B(\infty)} dx + \int_{d+\frac{\theta}{2}}^{L} c_b e^{-\lambda x} dx$$

$$\frac{C_B}{A_B} = \int_0^{L} c_b e^{-\lambda x} dx$$

$$\begin{cases} TF = TF_0 e^{-\lambda d} \\ TF = 1-\left(1-e^{-\mu d}\right)^{B(\infty)} \end{cases}$$



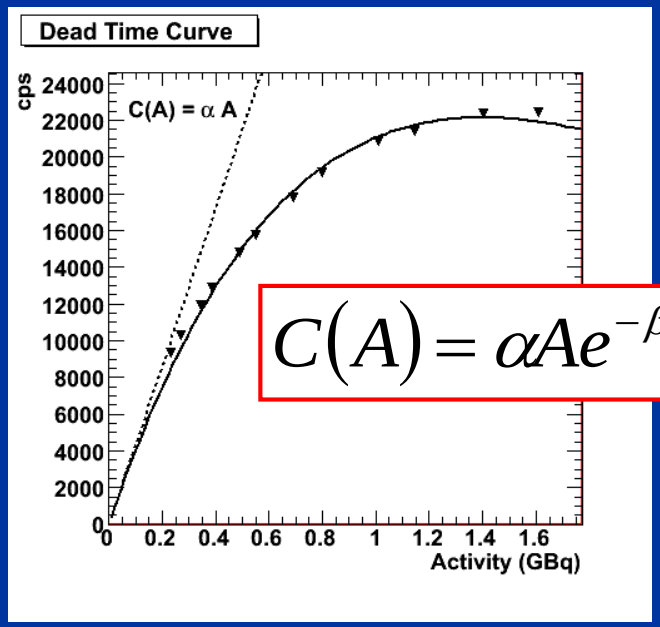
[a] MIRD Pamphlet #16 JNM '99

[b] Siegel *et al.* JNM '85

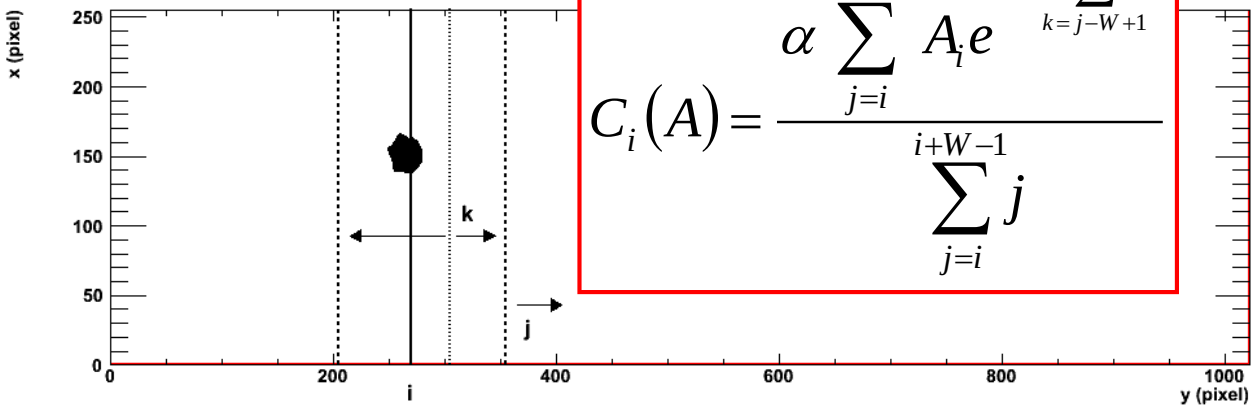
Camera Saturation

Convert counts to activity, BUT high activities (1.2-5 mCi/kg) cause camera saturation

AND patient is moving, so saturation is time dependent



$$C(A) = \alpha A e^{-\beta A}$$



$$C_i(A) = \frac{\alpha \sum_{j=i}^{i+W-1} A_i e^{-\beta \sum_{k=j-W+1}^{j} A_k}}{\sum_{j=i}^{i+W-1} j}$$

Correction Algorithm

Saturation compensation algorithm

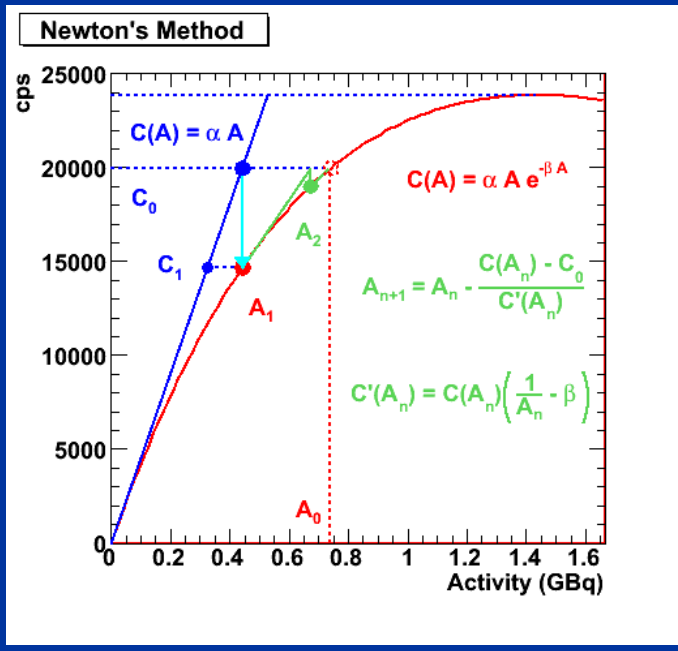
1. For each summed count rate per row $C_{i(0)}$, make a linear (or first order) approximation of the activity, A_i
2. Find the activity seen by the detector for each time point, j, by summing the activities A_i
3. Calculate each matrix element t_{ij}, the count rate measured in row i at time j attenuated by the activity A_j.
4. Take the average count rate
5. Calculate the next approximation of A_i
6. Repeat steps 2-5 and calculate the difference between successive values of A_i until the desired precision is reached for each A_i.

$$A_{i(0)} = \frac{C_{i(0)}}{\alpha}$$

$$A_j = \sum_{k=j-W+1}^{j} A_k$$

$$t_{ij} = \alpha A_i e^{-\beta A_j}$$

$$C_i = \frac{\sum_{j=i-W+1}^{i} t_{ij}}{W}$$



$$A_{i(n+1)} = A_{i(n)}\left(1 + \frac{C_{i(0)} - C_i}{C_i\left(1 - \beta A_{i(n)}\right)}\right)$$

Hobbs *et al.* Phys Med Biol '10

Patient Results

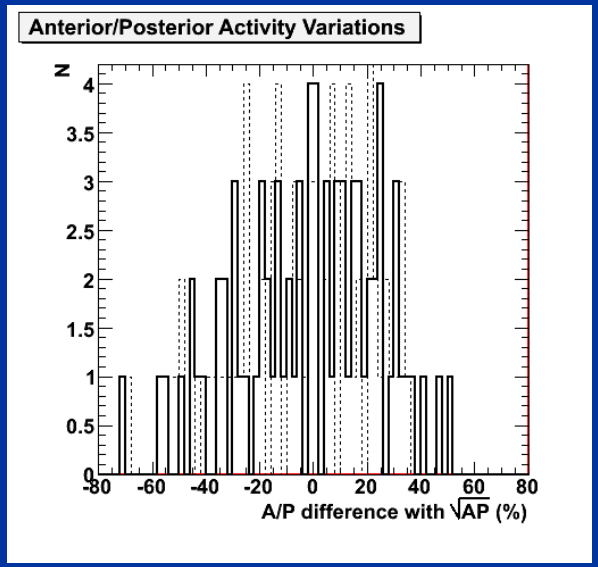
Compare anterior to posterior activities

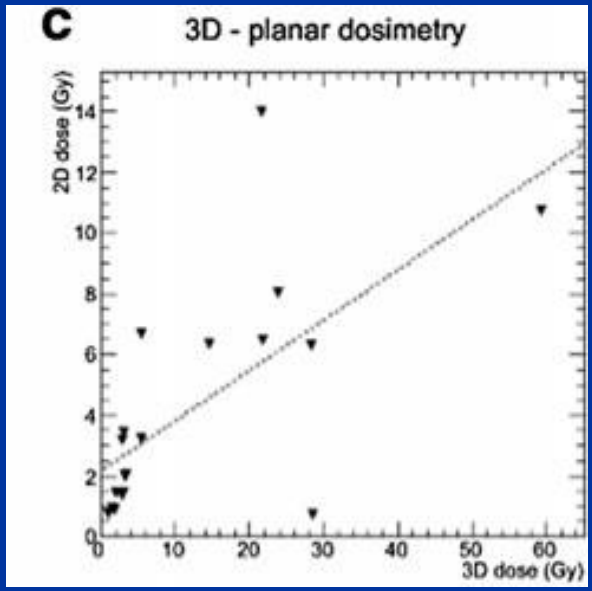
$$A = \sqrt{A_A A_P}$$

Should choose side closest to tumor? [a]

Compare 2D to 3D dosimetry

Great variability, most likely due to inaccuracy of planar quantification



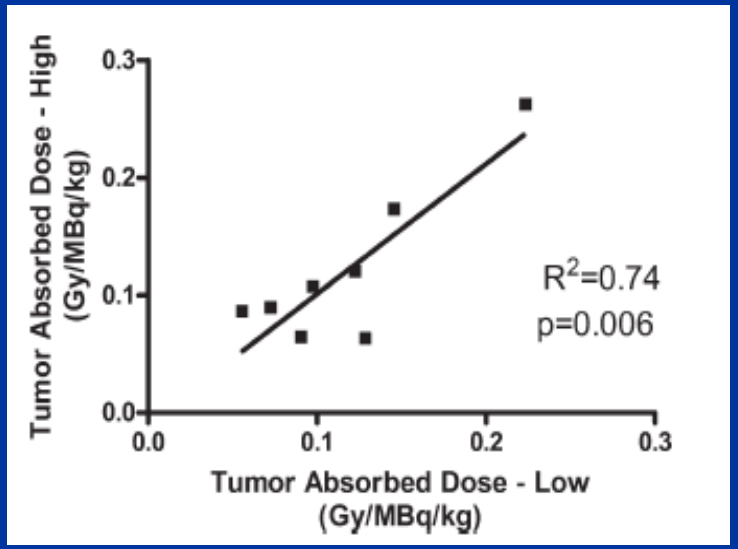


Plyku *et al.* CBR '15

[a] Baechler *et al.* CBR '08

Clinical Conclusions

- Systematic errors are expected to be consistent for the same patient. So kinetics and low dose-high dose correlations are more reliable (Hybrid method)
- Projection from low to high dose good on average, but not reliable on an individual basis
- Variations may still be due to “bad” dosimetry, saturation effects, chrono-biological variations.



Loeb *et al.* Cancer ’10

3D dosimetry

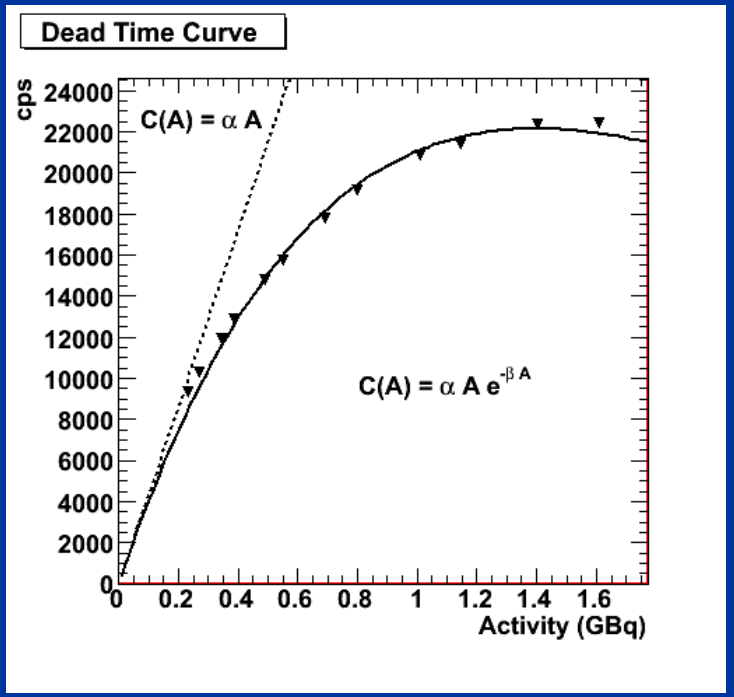
Camera saturation still a factor, but curve response applied to each frame.

An in-house quantitative SPECT reconstruction method was used [a] with a TEW scatter correction and a primary energy peak of 103 keV +/- 10 %.

Iterative ordered subsets expectation–maximization (OS-EM) algorithm, collimator-detector response function.

Accuracy expected to be comparable to the ^{111}In study

3D-RD patient specific dosimetry with 3 time points (4 h, 24 h, 48 h)



Senthamizhchelvan *et al.* JNM '12

[a] He *et al.* PMB '05

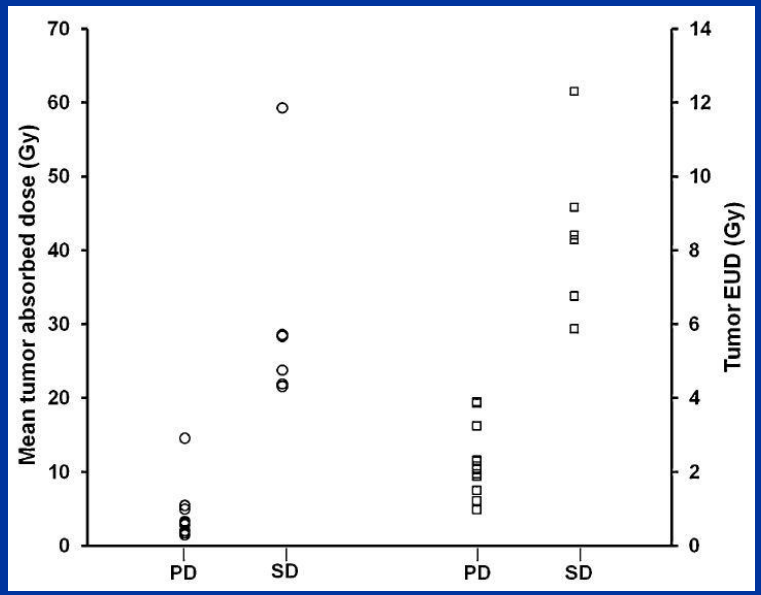
3D results

Tumor dosimetry

1. compared to OLINDA/EXM

3D-RD tumor doses higher (2%-4%) due to photon dose from outside the tumor (higher for small tumors, up to 10%-15%)

2. correlated AD/EUD to response as measured by tumor volume reduction from pre- and post- MRI images.



Senthamizhchelvan *et al.* JNM '12

Equivalent Uniform Dose (EUD)

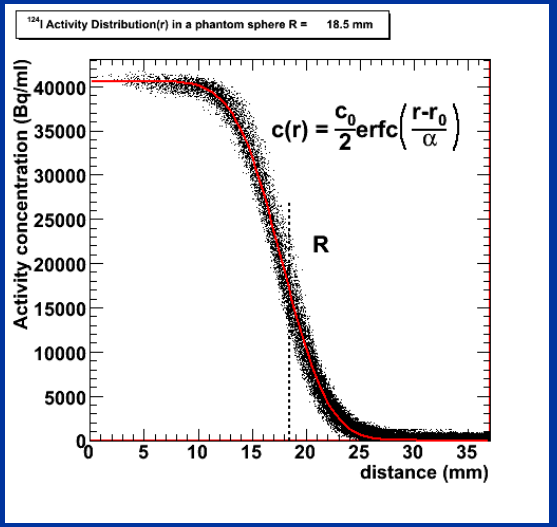
- For non-uniform distributions of dose values provides the uniform dose value that would results in the same surviving fraction [a]
- Radiobiologically driven, use equivalent uniform BED [b]
- Accounts for non-uniform absorbed dose distribution
- Provides a single value that may be used to compare different dose distributions [c]
- Scales with α
- Depends on the accuracy of each individual dose value

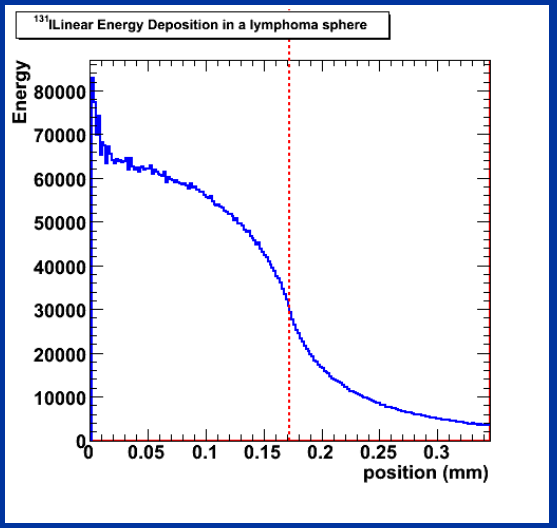
$$EUD = -\frac{1}{\alpha}\ln\left(\sum_{i=1}^{N}\frac{e^{-\alpha BED_i}}{N}\right)$$

[a] Niemierko *et al.* Med Phys '97
[b] O'Donoghue *et al.* J Nucl Med '97
[c] Dewaraja *et al.* JNM '10

Lesion Dosimetry: EUD and PVE

- PVE alters shape of activity distribution – edge effect (not to be confused with dose edge effect)
- Low dose value voxels dominate EUD at higher dose – low dose edge underestimates EUD, more so than AD
- RC are reasonable for AD calculated from self-dose, but not for EUD
- Overall effect is dependent on lesion size, VOI delineation, S/B ratio and scale of AD values
- Voxelized re-distribution of activity necessary; current methods assume spherical symmetry and homogenous activity





Combined ^{153}Sm-EDTMP RPT with XRT

Why?

- Originally one patient returned for XRT palliation after earlier RPT with ^{153}Sm-EDTMP, questions of combined toxicity

Idea!

- XRT can deliver precise amounts of radiation dose to tumors but limited by adjacent normal tissues (e.g. spinal cord)
- RPT delivers radiation dose to all tumor sites including micro-metastases very conformal but can not escalate radiation dose to tumor limit

How?

- The combination XRT with RPT requires accurate 3D radiation dose calculations to avoid toxicity and evaluate potential efficacy
- Deliver RPT (1.0 mCi/kg) and make 3D dose map in 3D-RD, convert to XRT AD values (1.8 Gy fractions) and import into XRT software and include in combined treatment plan with goal of 70 Gy to tumor

RPT-XRT AD equivalence

- AD from XRT fractionated
- AD from RPT over time
- What about biological equivalence?
- Use BED as a bridge
- (Equivalent linear dose compared to the linear-quadratic absorbed dose with a repair term)
- EQD2, equivalent 2-Gy fraction [a]

RPT

$$BED_i = D_i\left(1+\frac{D_i}{\alpha_i/\beta_i}\cdot G_i(\infty)\right)$$

XRT

$$BED_i = D_i\left(1+\frac{d}{\alpha_i/\beta_i}\right)$$

$$EQD2_i = \frac{D_{RPTi}\left(\alpha_i/\beta_i + D_{RPTi}\cdot G_i(\infty)\right)}{\alpha_i/\beta_i + 2}$$

Hobbs *et al.* IJROBP '10
Bodey *et al.* IJROBP '04
[a] Bentzen *et al.* Radiother Oncol '12

Protocol

(a.) ^{18}F-MISO PET/CT for baseline

b. Stem cell collection for autologous transplant

c. CT-sim used for both XRT and RPT treatment planning

d. Low dose ^{153}Sm-EDTMP (1 mCi/kg)

e. SPECT/CT imaging at 4, 24 and 48 h, image reconstruction and dosimetry calculations.

f. Import EQD2 RPT dose map into Pinnacle and make combined treatment plan. High dose ^{153}Sm-EDTMP determined (max 20 mCi/kg)

g. High dose imaging at 4, 24 and 48 h, image reconstruction and dosimetry calculations

h. Re-import high dose + low dose EQD2 dose map for final IMRT treatment plan

i. Autologous stem cell transplant (recovery) after bone marrow dose calc below threshold

(j.) ^{18}F-MISO PET/CT for treatment response

RPT-Dosimetry

Patient 2:

- Dose limiting organ is spinal cord and heart.
- Wanted absorbed dose to the tumor > 70 Gy

^{153}Sm-EDTMP Pelvis	Low AD (Gy)	Low EQD2 (Gy)	Predicted AD (Gy)	High AD (Gy)	High EQD2 (Gy)
Tumor	4.5	3.3	45.0	25.6	20.1
Spine	0.90	0.6	9.0	2.7	1.8

^{153}Sm-EDTMP Chest	Low AD (Gy)	Low EQD2 (Gy)	Predicted AD (Gy)	High AD (Gy)	High EQD2 (Gy)
Tumor (R.)	2.6	1.9	26.0	6.4	4.7
Spine	1.0	0.7	10.0	4.7	3.0
Heart	0.22	0.13	2.2	0.74	0.45

Low = 1 mCi/kg = 58.7 mCi

High = 10 mCi/kg = 600 mCi

XRT - Treatment plan (Patient 2)

Chest Tumor R.

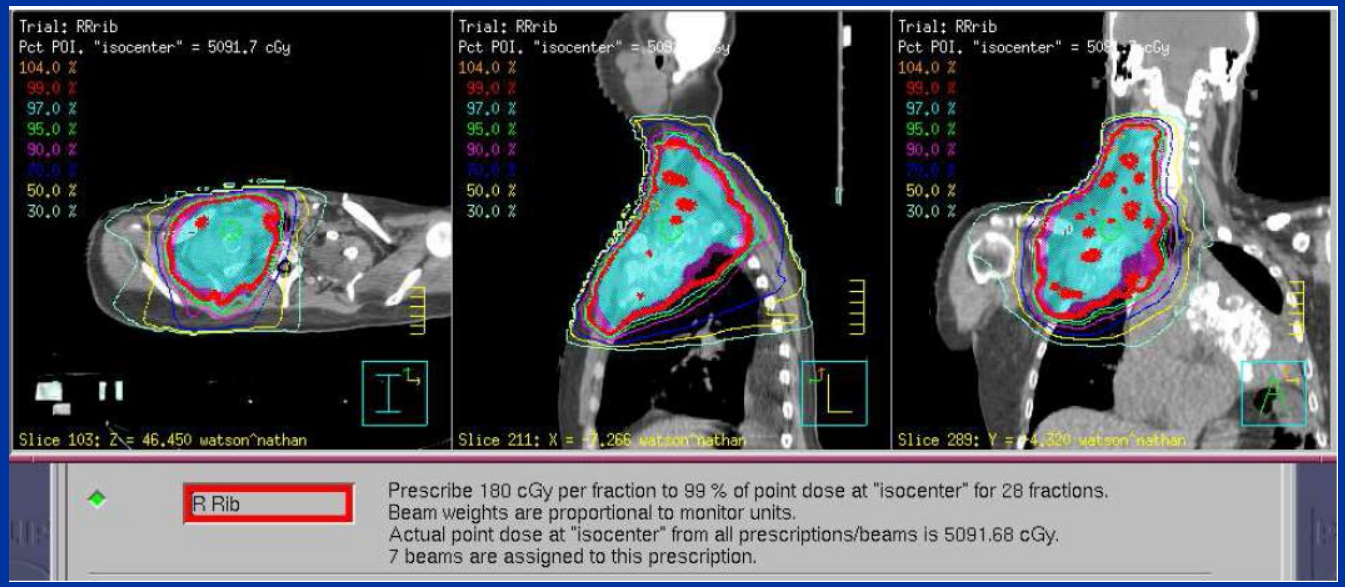
50.9 Gy (XRT)
6.6 Gy (RPT)

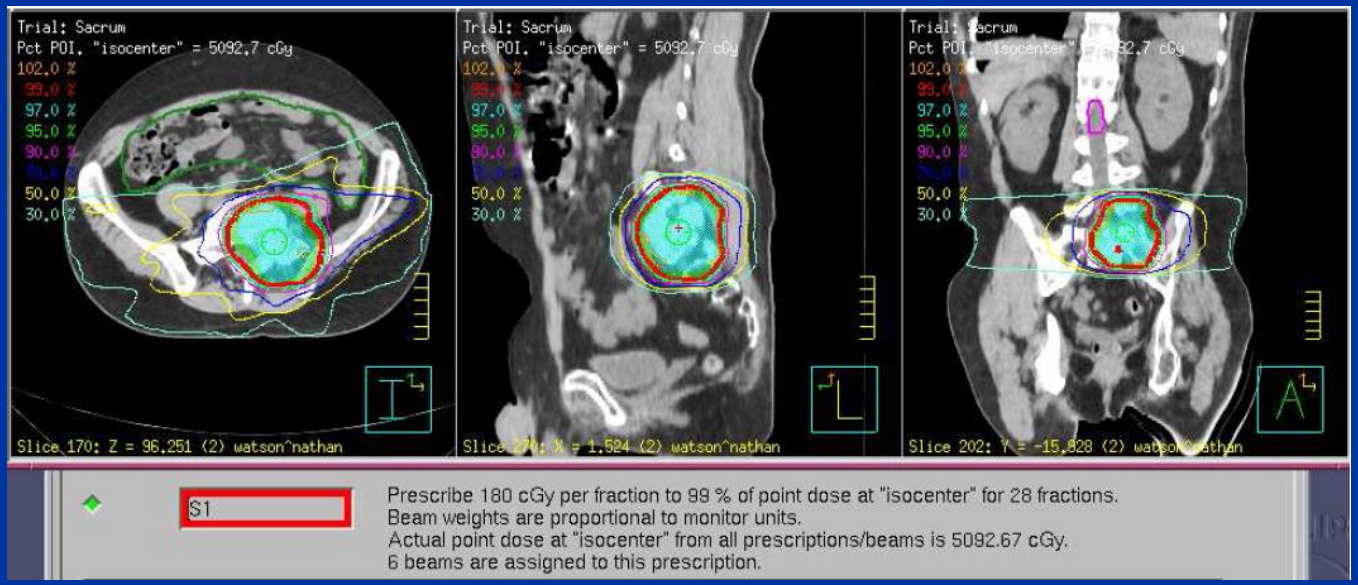
Spinal cord

34 Gy (XRT)
3.7 Gy (RPT)

Heart

18 Gy (XRT)
0.58 Gy (RPT)





Pelvis Tumor

50.9 Gy (XRT)
19.9 Gy (RPT)

Spinal cord

46 Gy (XRT)
2.4 Gy (RPT)

RPT-Dosimetry

Patient 2:

- Dose limiting organ is spinal cord and heart.
- Wanted dose to the tumor is 70 Gy

^{153}Sm-EDTMP Pelvis	Low AD (Gy)	Low EQD2 (Gy)	Predicted AD (Gy)	High AD (Gy)	High EQD2 (Gy)
Tumor	4.5	3.3	45.0	25.6	20.1
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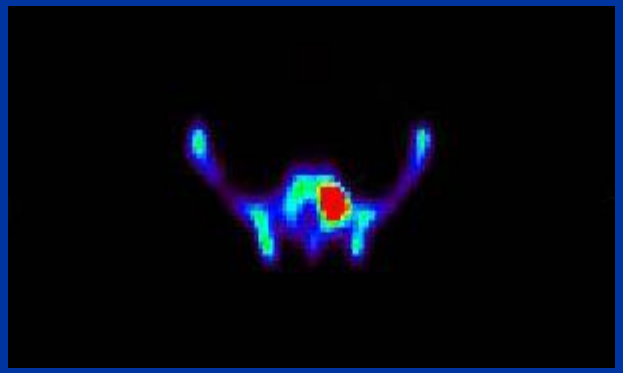
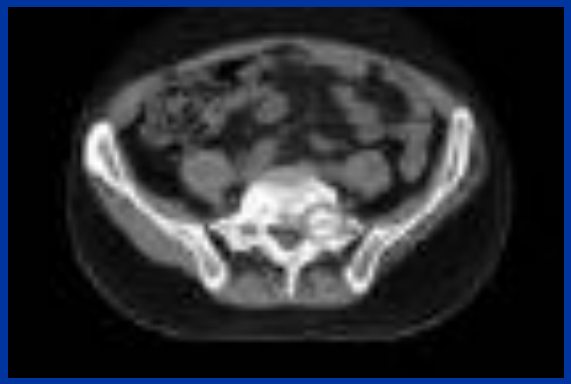




Low = 1 mCi/kg = 58.4 mCi

High = 10.0 mCi/kg = 600 mCi

XRT-RPT Results

- The created treatment planning protocol combining RPT and XRT for metastatic osteosarcoma in pediatric patients showed potential. Targeted tumors received a prescribed tumoricidal absorbed dose (> 70 Gy) due to the RPT boost

- Choice of tumors and location, can't treat the tumors around the trachea/heart/major vessels, which were life threatening and were the cause of death. In future be more selective of the patients and tumor location and burden.

XRT-RPT Conclusions

Currently many new approaches (including RPT) tested alone after multiple other therapies

Sequential likely not as effective as concurrent, final stage is difficult to treat, better patient recruitment when concurrent with other modalities, low dose (1 mCi/kg) shows clinical improvement

Need rational methodologies for safe and effective therapies, especially when combining.

Other Conclusions

Limitations (wish list):

1. Voxel activity accuracy for radiobiology
2. Radiobiological parameters for BED
3. Early time point data for kidney dosimetry

Lessons:

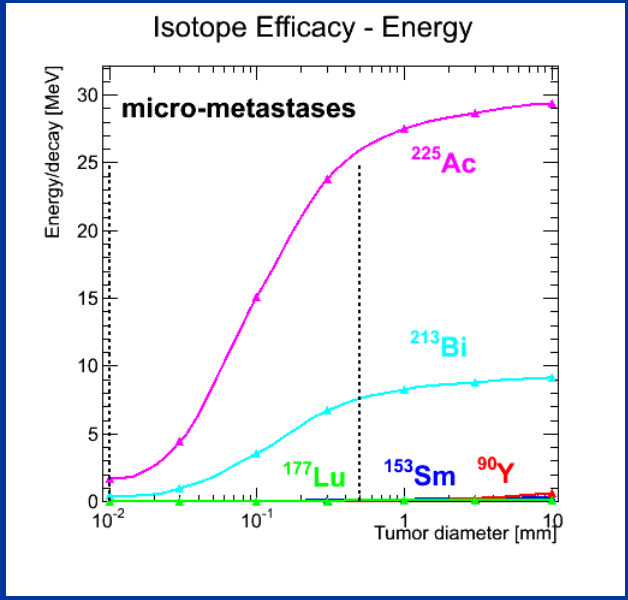
1. Planar dosimetry complicated
2. Patient-specific dosimetry accounts for external source of dose
3. Need concurrent protocols for recruitment
4. Caution with EUD values
5. Camera dead-time effects for high activity

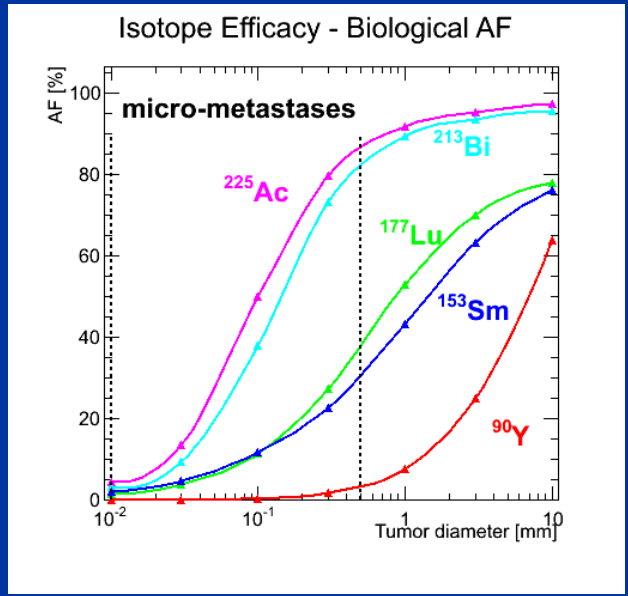
β-emitter vs. α-emitter

- range of emission indicates optimal tumor size for therapy [a]

-Alpha better for micro-metastases, betas better for larger tumors.

- upper edge of effectiveness depends on many criteria





[a] O'Donoghue *et al*. J Nucl Med '95

THANK YOU FOR YOUR ATTENTION