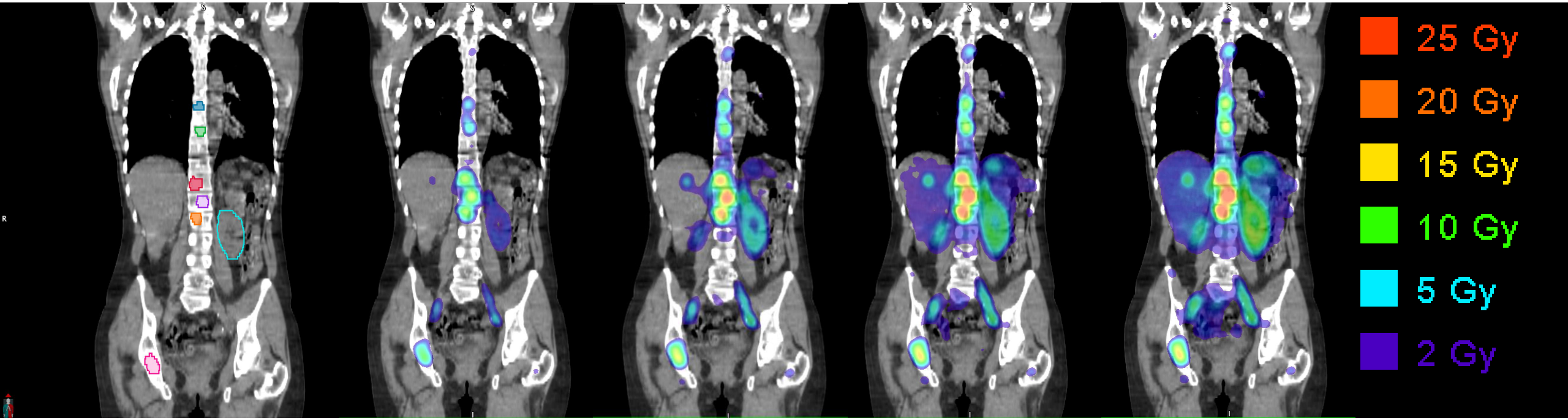
Calculating and Reporting Absorbed Dose from Radionuclide Therapies



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Introduction (to your speaker)

- Assistant Professor of Clinical Radiation Oncology at UCSF

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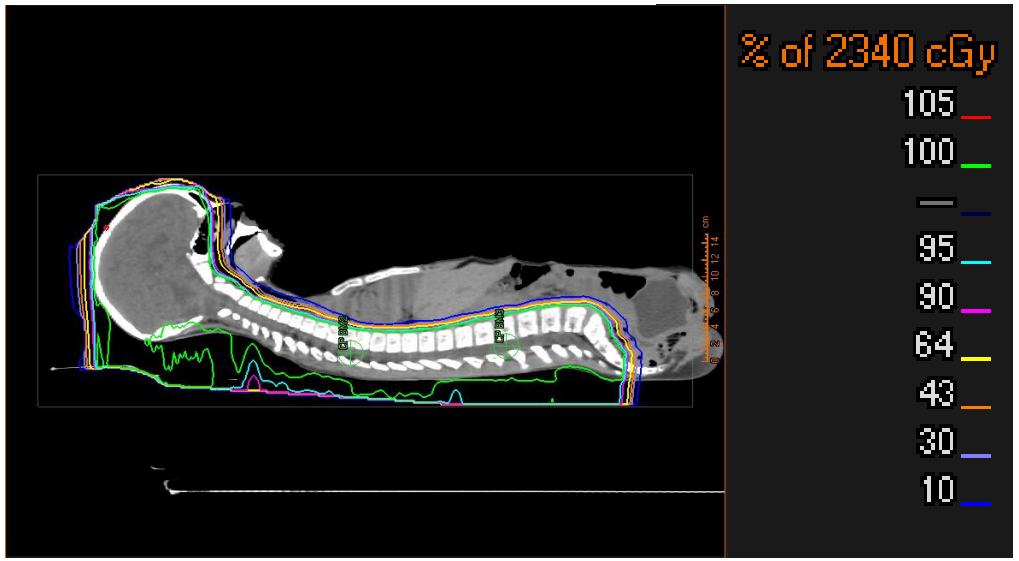
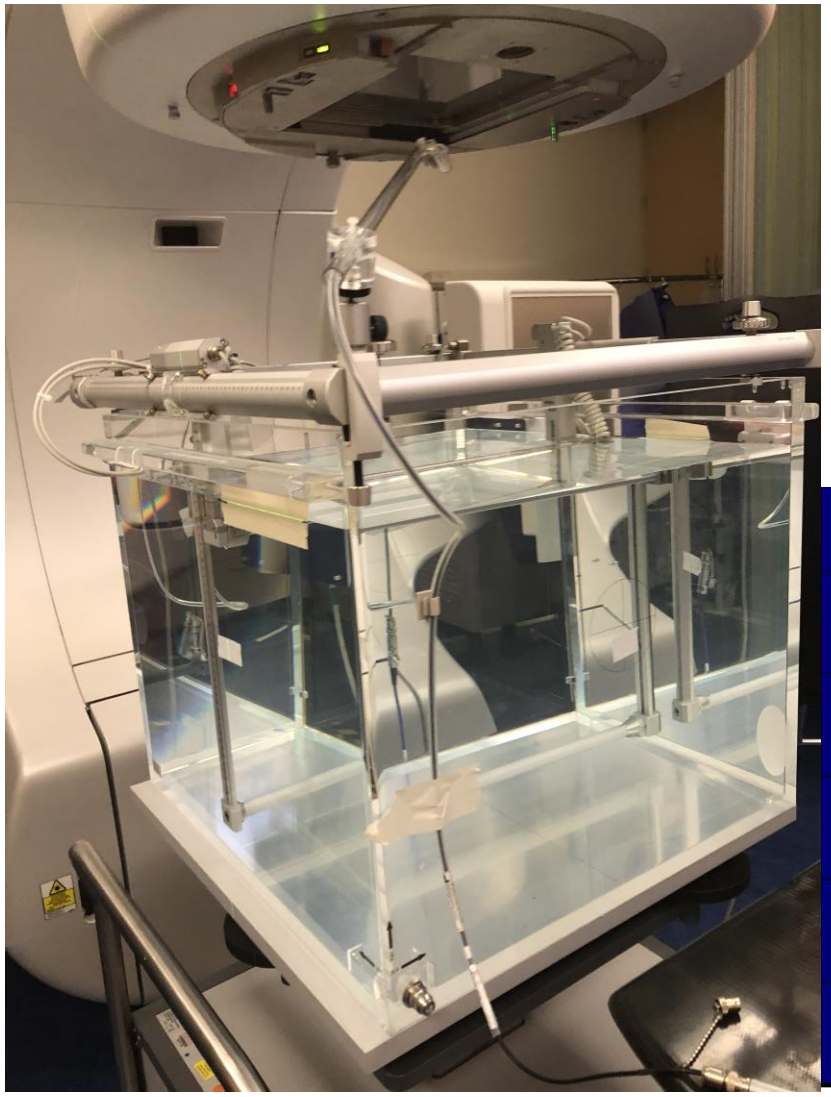
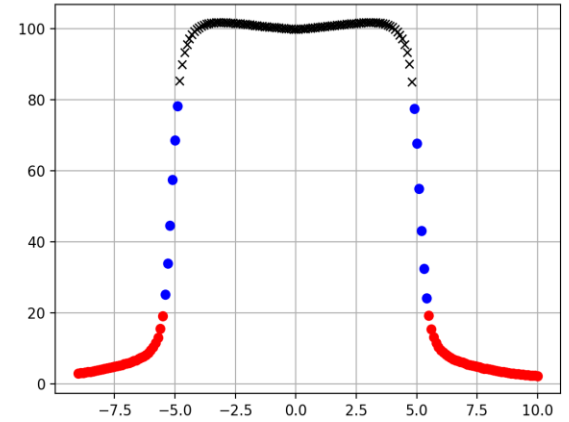
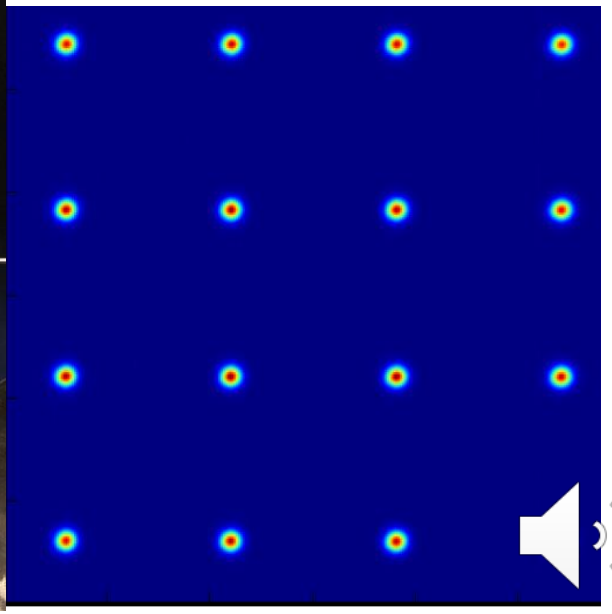
Disclosures

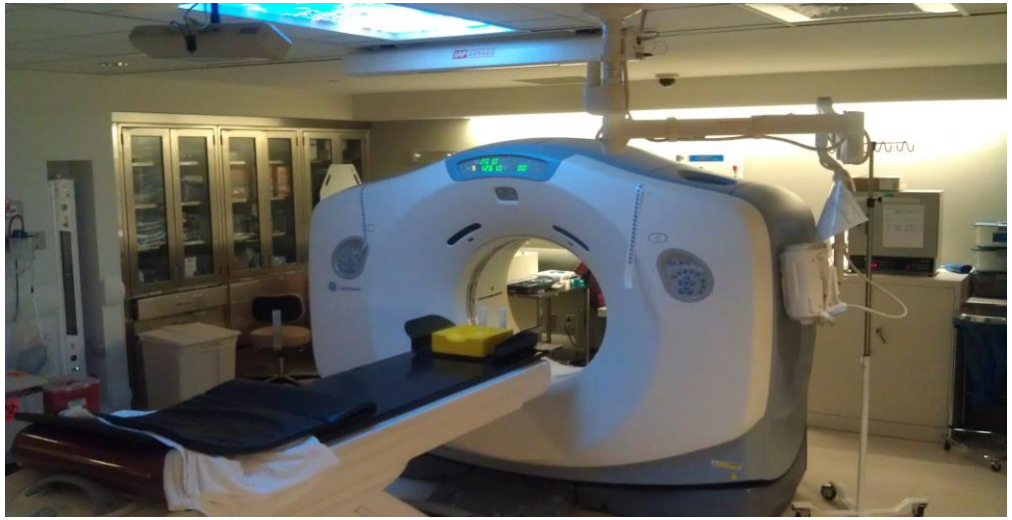
- No financial disclosures
- I work in therapeutic medical physics









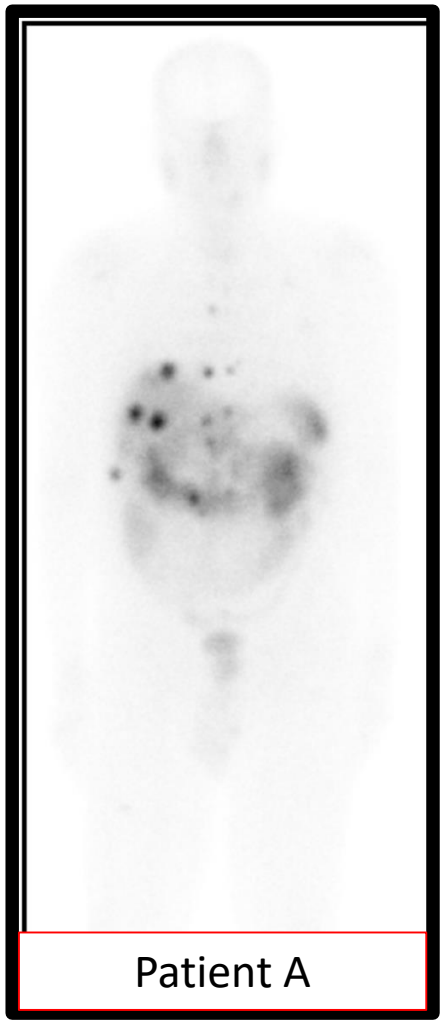


Motivation

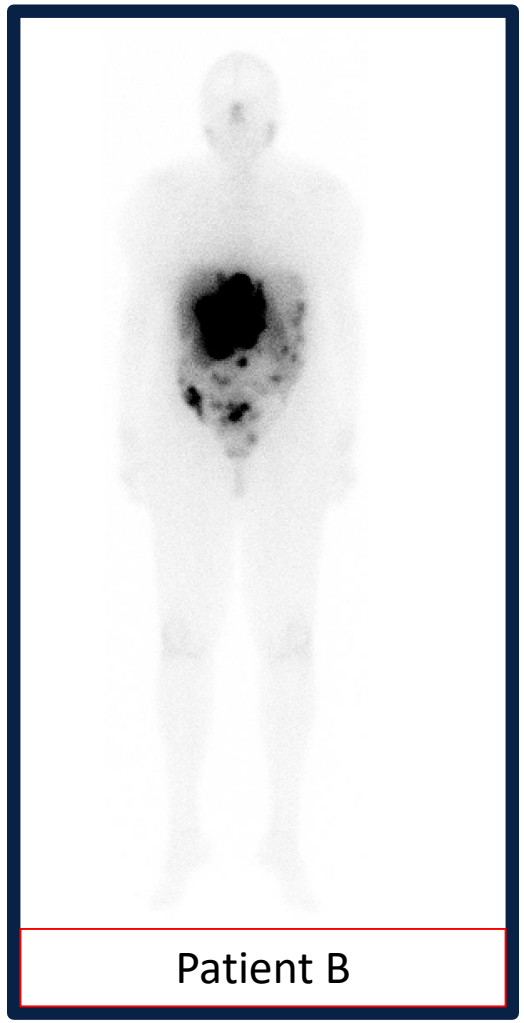
Patients treated with ^{177}Lu- DOTATATE at UCSF have a 24 hour post-administration SPECT/CT scan

What dose our patients are receiving?

Is this the right dose for them?



Patient A

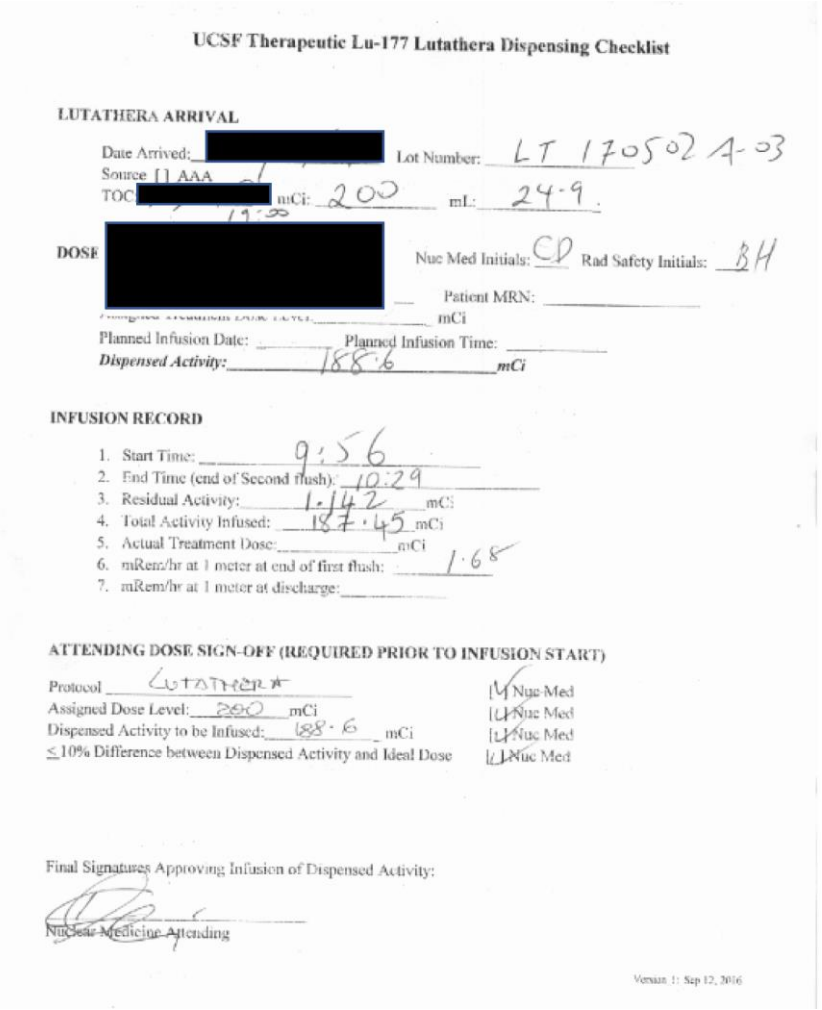


Patient B

Motivation

Patients treated with Lu-^{177} DOTATATE at UCSF have a 24 hour post-administration SPECT/CT scan

These scans are used qualitatively, but they may be used to calculate the received radiation dose



UCSF Therapeutic Lu-177 Lutathera Dispensing Checklist

LUTATHERA ARRIVAL

Date Arrived: [redacted] Lot Number: LT 170502 A-03
Source [] AAA
TOC [redacted] mCi: 200 mL: 24.9

DOSE [redacted] Nuc Med Initials: CD Rad Safety Initials: BH

Patient MRN:
mCi
Planned Infusion Date: Planned Infusion Time:
Dispensed Activity: 188.6 *mCi*

INFUSION RECORD

1. Start Time: 9:56
2. End Time (end of Second flush): 10:29
3. Residual Activity: 1.42 mCi
4. Total Activity Infused: 187.45 mCi
5. Actual Treatment Dose: mCi
6. mRem/hr at 1 meter at end of first flush: 1.68
7. mRem/hr at 1 meter at discharge:

ATTENDING DOSE SIGN-OFF (REQUIRED PRIOR TO INFUSION START)

Protocol LUTATHER*
Assigned Dose Level: 200 mCi
Dispensed Activity to be Infused: 188.6 mCi
≤10% Difference between Dispensed Activity and Ideal Dose

[✓] Nuc Med
[ ] Nuc Med
[✓] Nuc Med
[ ] Nuc Med

Final Signatures Approving Infusion of Dispensed Activity:

Nuclear Medicine Attending

Version 1: Sep 12, 2016

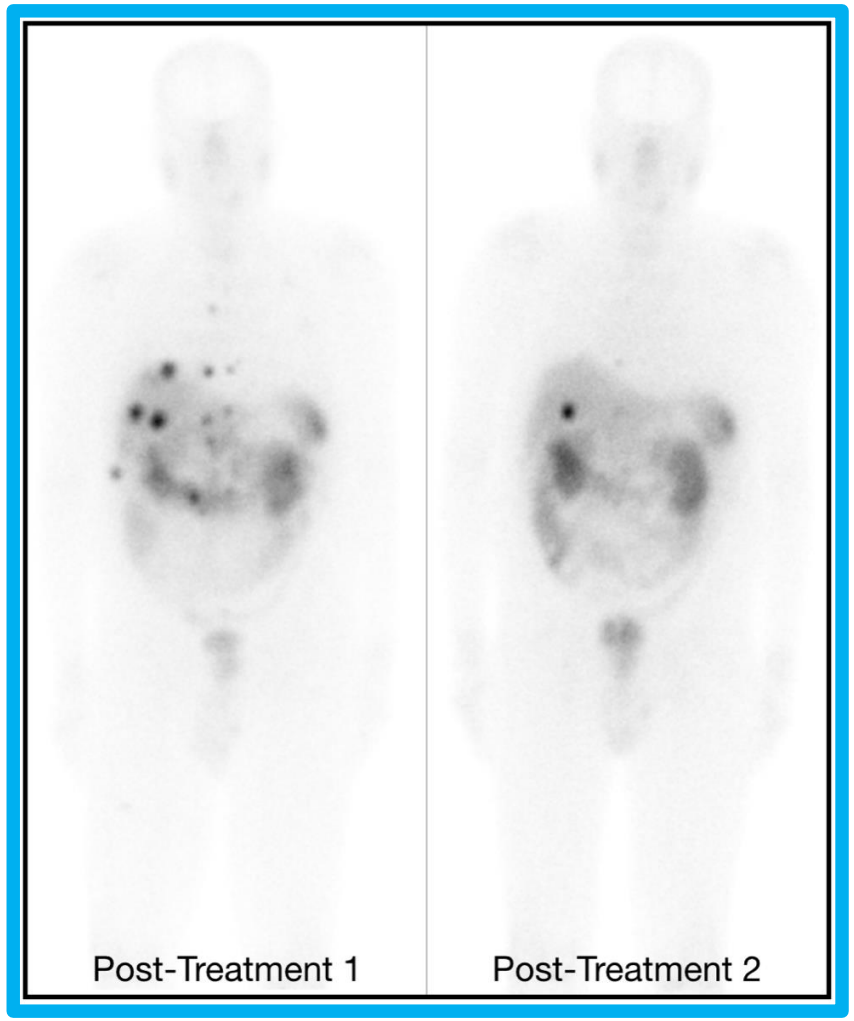


Image courtesy of Dr. Thomas Hope, UCSF Department of Radiology

Outline

Using imaging to determine the received dose to tumors and normal tissues for patients receiving TRT

- Approach
- Validation

Dose effects for tumors and normal tissues

- How do we chose to report dose?
- How do we quantify response?

Can we use imaging to quantify the tumor response?

^{177}Lu-DOTATATE Examples

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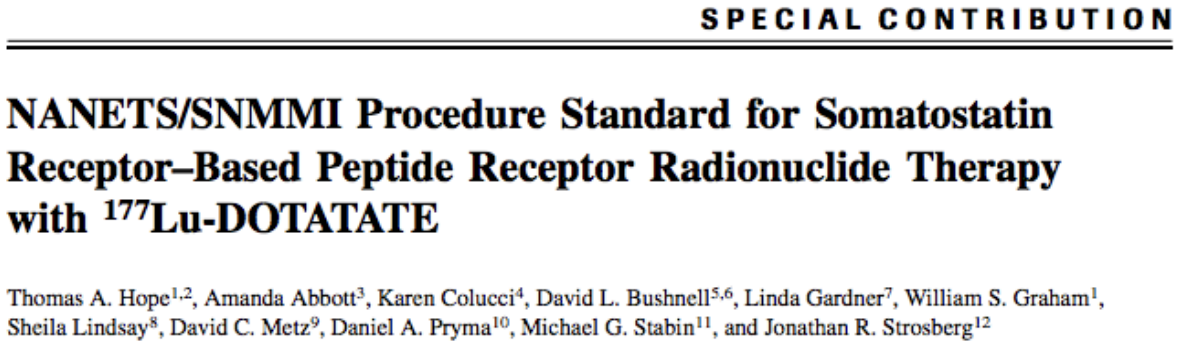
Patient Selection – The role of pretreatment imaging studies

- Patients can be imaged to see if they have tumors that the RNT is targeting
- Chemistry is identical, except for the substitution of 68Ga for 177Lu
- Examples of this are:
  - ^{68}Ga-DOTATATE
  - ^{68}Ga-PSMA PET

^{68}Ga has a 68 minute half-life. This is suitable for diagnostic imaging and patients are typically imaged ~ 1 hour post-administration.



SPECIAL CONTRIBUTION

NANETS/SNMMI Procedure Standard for Somatostatin Receptor–Based Peptide Receptor Radionuclide Therapy with ^{177}Lu-DOTATATE

Thomas A. Hope[1,2], Amanda Abbott[3], Karen Colucci[4], David L. Bushnell[5,6], Linda Gardner[7], William S. Graham[1], Sheila Lindsay[8], David C. Metz[9], Daniel A. Pryma[10], Michael G. Stabin[11], and Jonathan R. Strosberg[12]

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Pretreatment ^{68}Ga DOTATATE PET and Post-Cycle 177Lu SPECT

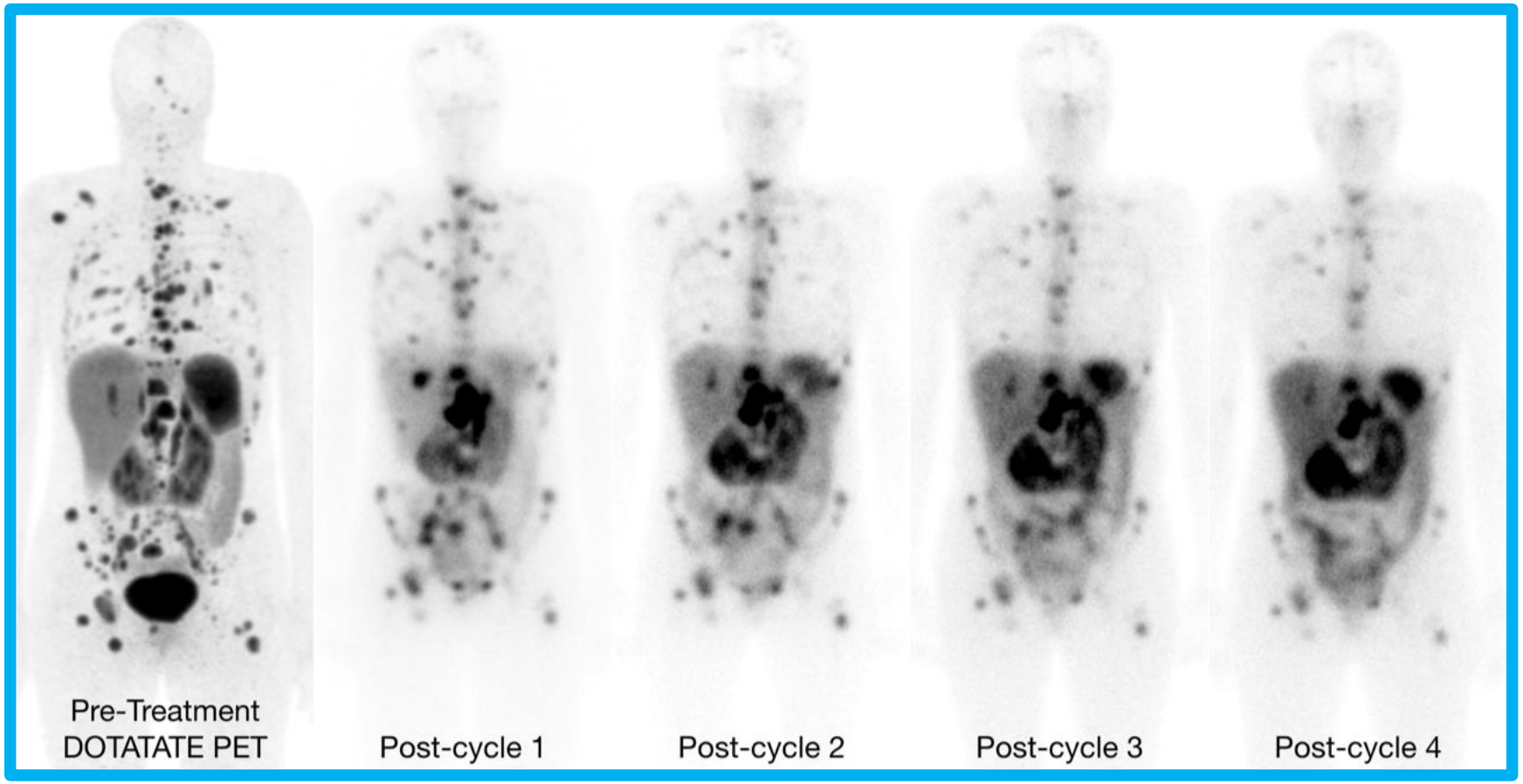


Image courtesy of Dr. Thomas Hope, UCSF Department of Radiology

Guidelines for Quantitative ^{177}Lu SPECT

MIRD Pamphlet No. 26 has recommendations regarding :

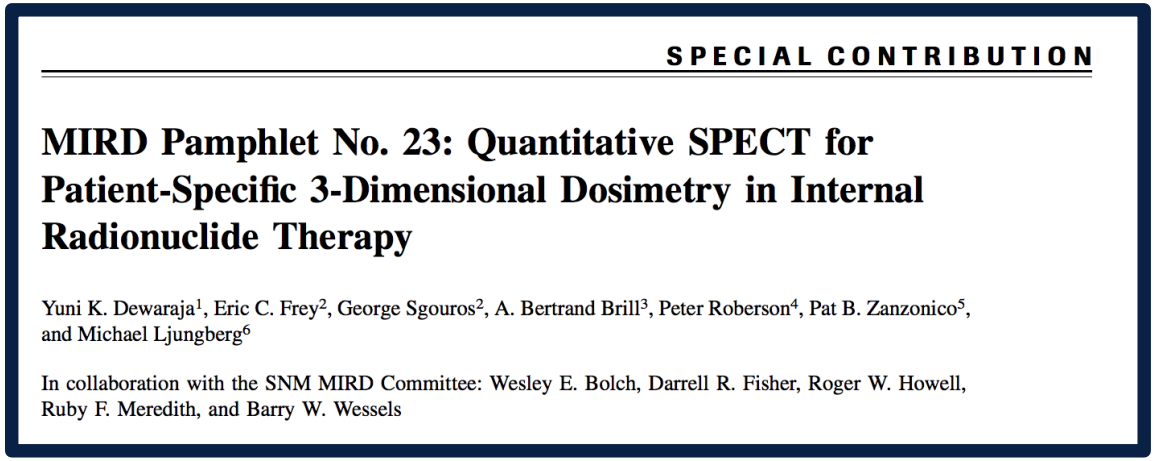
Energy window
Collimator
Reconstruction choices
…

SPECIAL CONTRIBUTIONS

MIRD Pamphlet No. 26: Joint EANM/MIRD Guidelines for Quantitative ^{177}Lu SPECT Applied for Dosimetry of Radiopharmaceutical Therapy

Michael Ljungberg[1], Anna Celler[2], Mark W. Konijnenberg[3], Keith F. Eckerman[4], Yuni K. Dewaraja[5], and Katarina Sjögreen-Gleisner[1]

In collaboration with the SNMMI MIRD Committee: Wesley E. Bolch, A. Bertrand Brill, Frederic Fahey, Darrell R. Fisher, Robert Hobbs, Roger W. Howell, Ruby F. Meredith, George Sgouros, and Pat Zanzonico, and the EANM Dosimetry Committee: Klaus Bacher, Carlo Chiesa, Glenn Flux, Michael Lassmann, Lidia Strigari, and Stephan Walrand.



SPECIAL CONTRIBUTION

MIRD Pamphlet No. 23: Quantitative SPECT for Patient-Specific 3-Dimensional Dosimetry in Internal Radionuclide Therapy

Yuni K. Dewaraja[1], Eric C. Frey[2], George Sgouros[2], A. Bertrand Brill[3], Peter Roberson[4], Pat B. Zanzonico[5], and Michael Ljungberg[6]

In collaboration with the SNM MIRD Committee: Wesley E. Bolch, Darrell R. Fisher, Roger W. Howell, Ruby F. Meredith, and Barry W. Wessels

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Dose Calculation Methods

Monte Carlo	Point Dose Kernel Convolution	Local Energy Deposition
Monte Carlo is the 'gold standard' in dosimetry Accounts for tissue heterogeneities and composition differences Post-treatment SPECT is used to localize the radionuclide The CT component is used for radiation transport	Kernels are generated with Monte Carlo methods and are convolved with the SPECT study	Most simplistic model, where all of the energy is assumed to be deposited in the voxel with activity

GEANT4
A SIMULATION TOOLKIT

GATE

EGSnrc

Toolkit for Monte Carlo simulation of ionizing radiation transport

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Dose Calculation Engines

The purpose of the dose calculation engine is to take the acquired SPECT and arrive at an estimate of dose (Gy) per voxel in the patient.

Monte Carlo

Dose kernel convolution

Local Energy Deposition

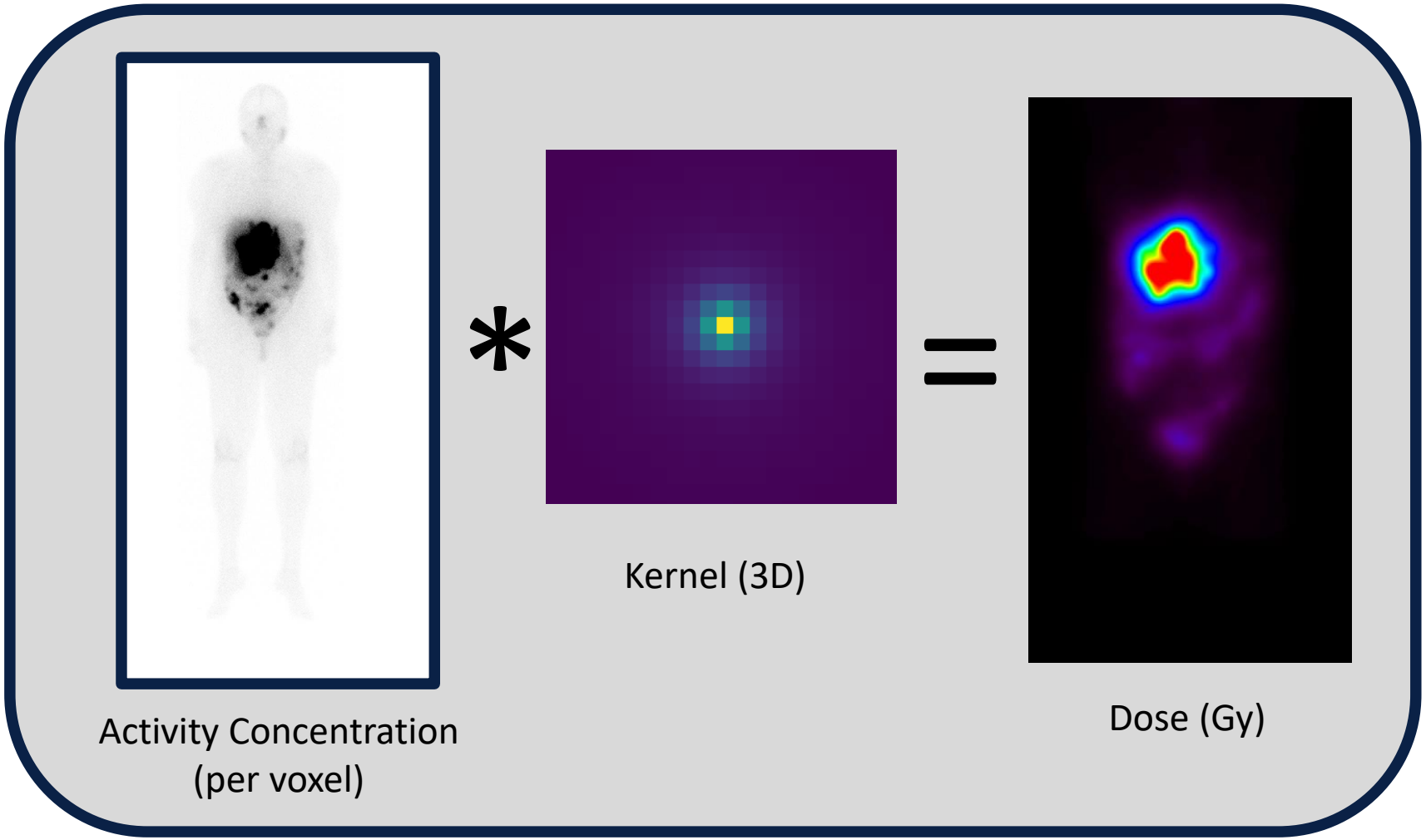
Commercial Programs

In-house Programs

Dose Calculation Engines (2)

At UCSF – we use an in-house (python based) dose calculation, based on Monte Carlo kernels generated with GATE.

- DICOM RTDose files are created for reporting volumetric dose
- Can be read out by commercial and open source software.



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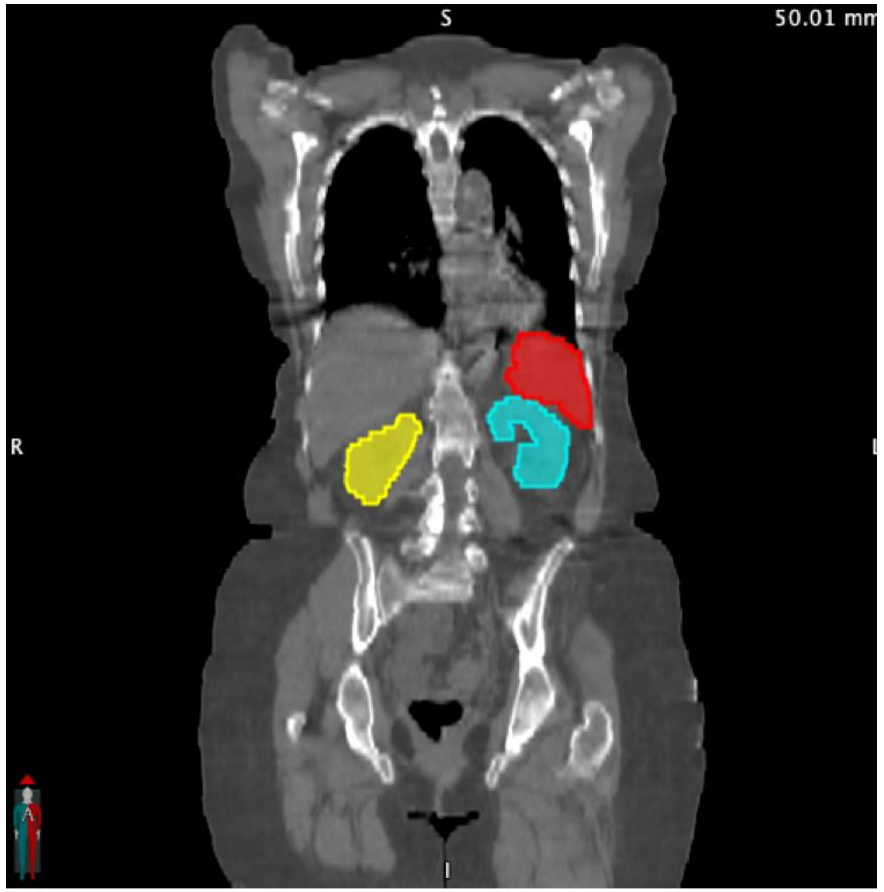
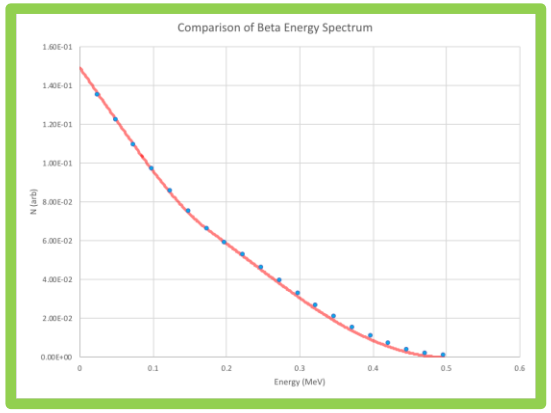
Reporting dose to targets and normal structures

- To report the received dose to targets and normal structures, one needs to know where they are
- Contour the kidney, spleen and lesions

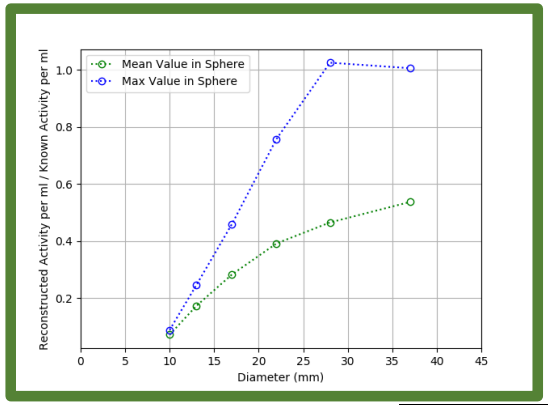


Validation

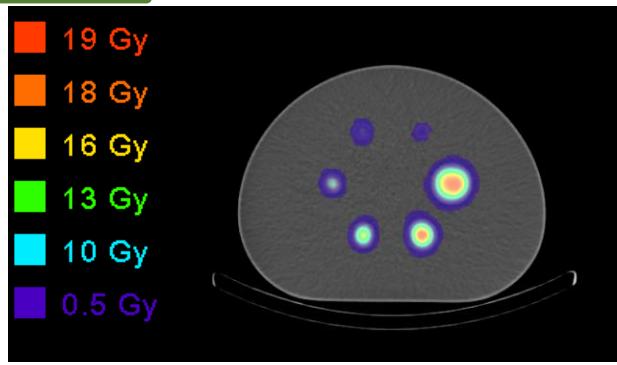
Energy spectra compared against NIST data



Phantom measurements with ^{177}Lu to ensure accuracy of SPECT calibration & spatial resolution effects



Analytic dose calculation compared with dose calculation for uniform sphere.



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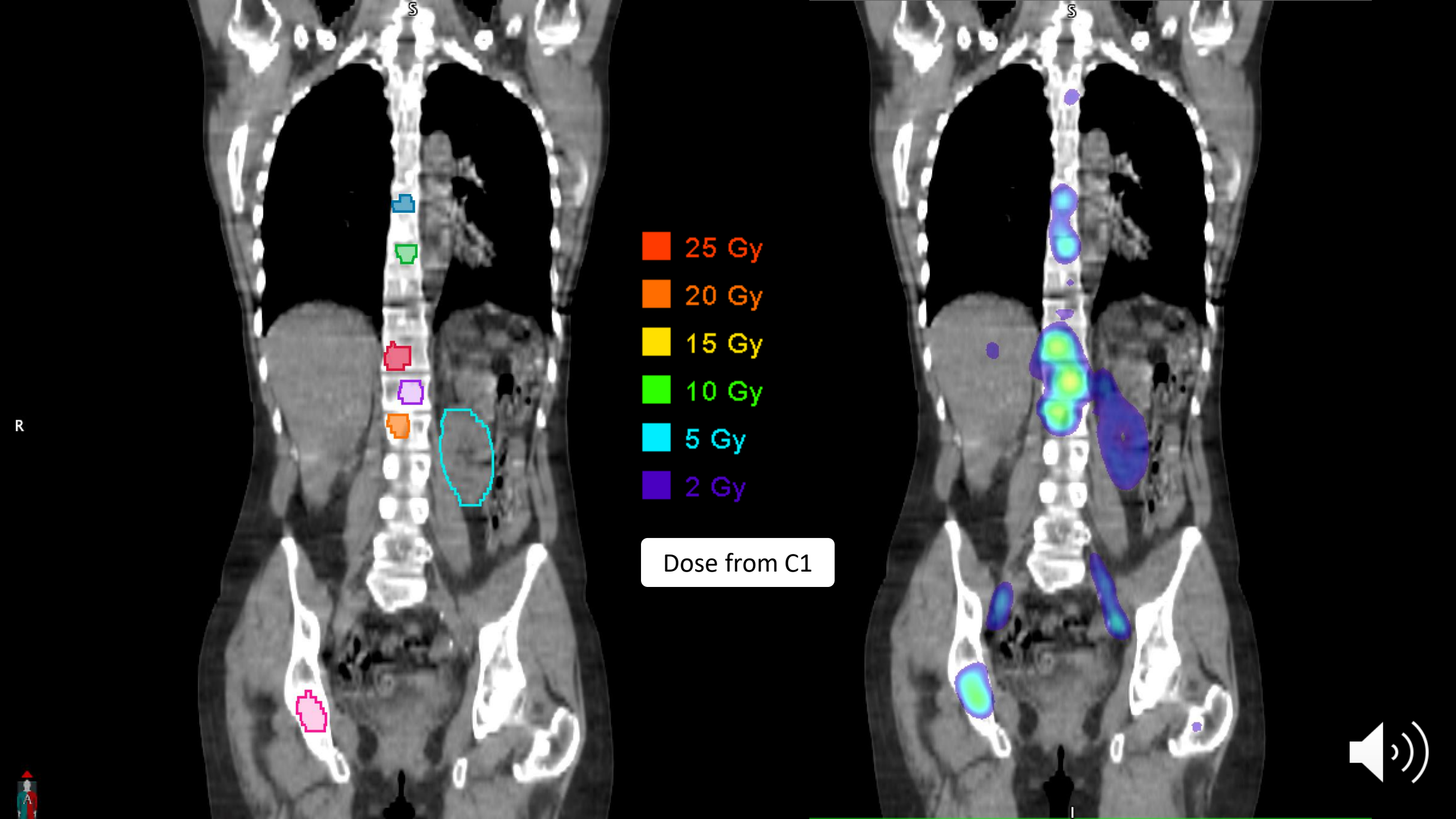
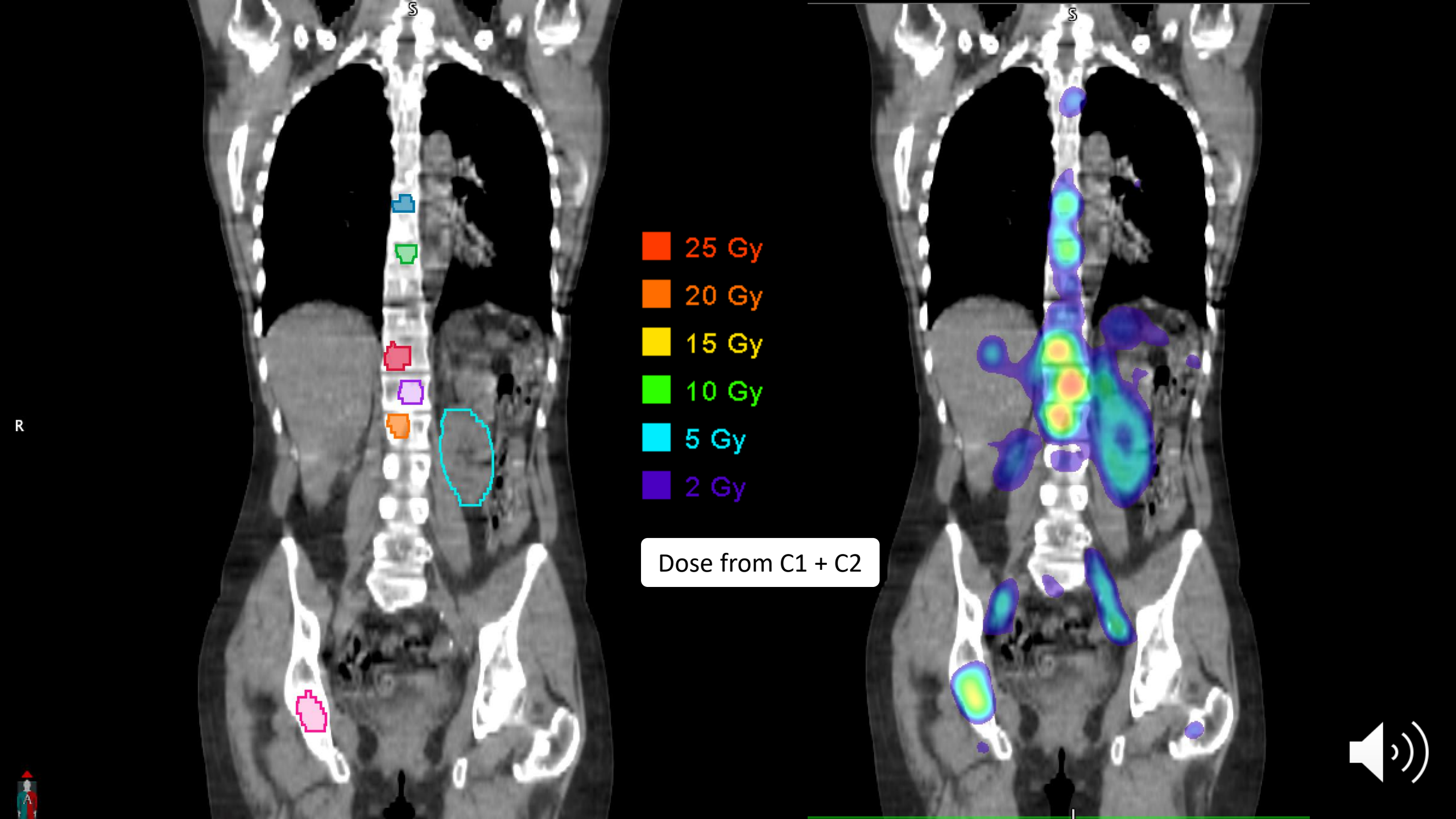
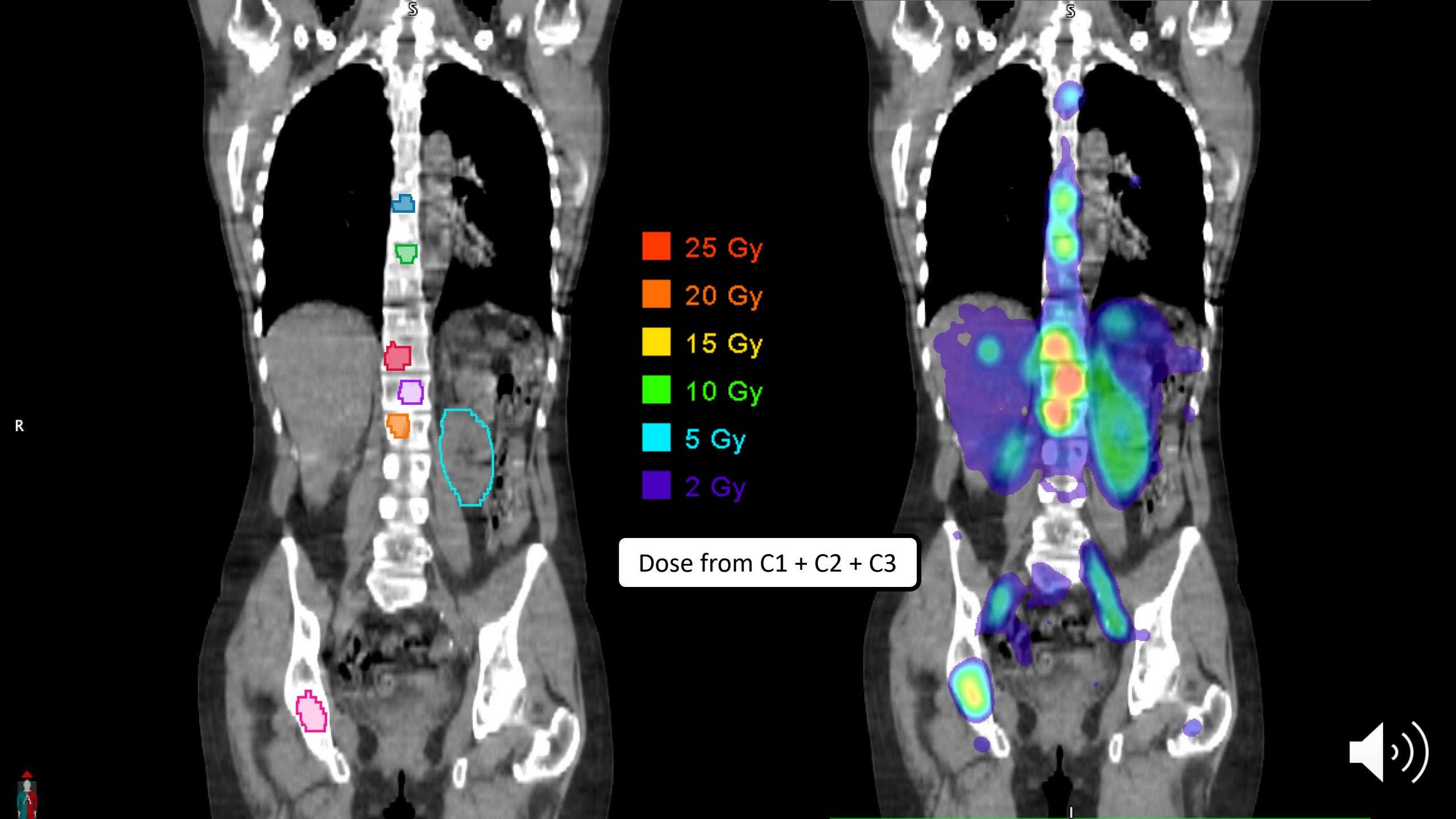
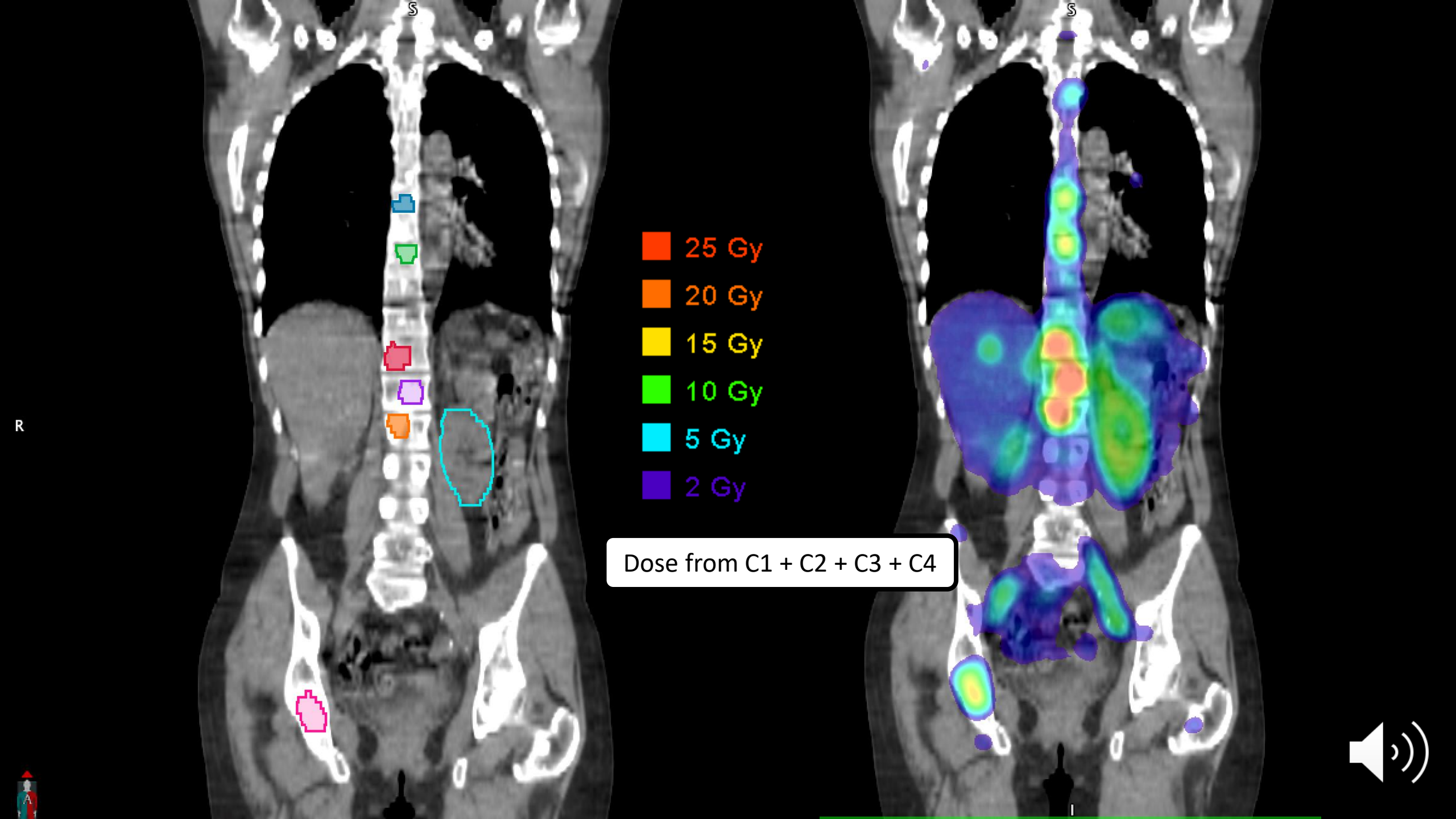
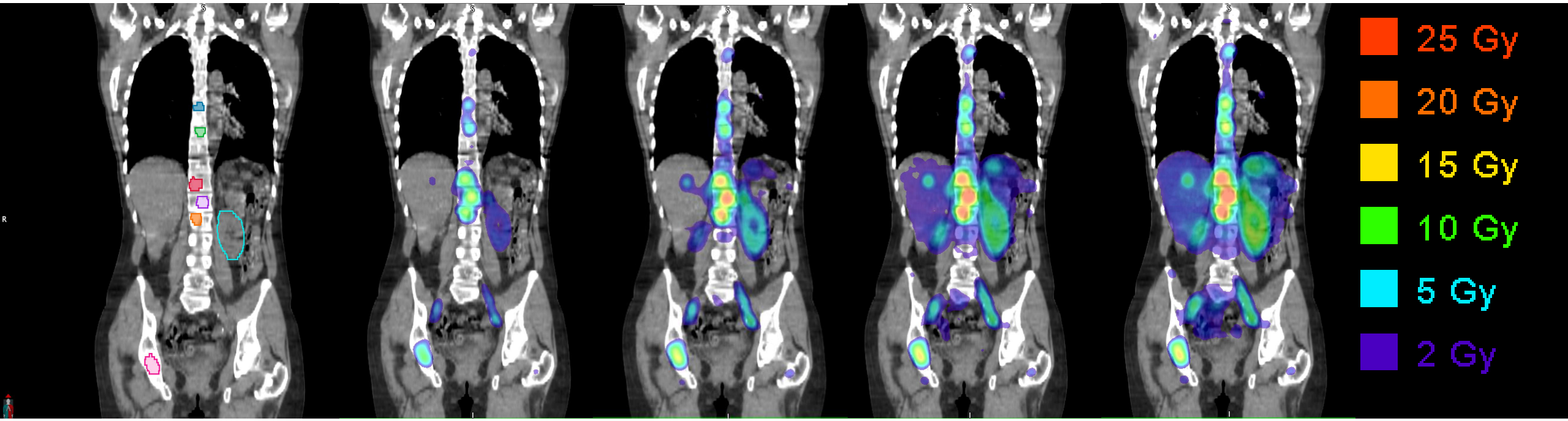

S
S
R
25 Gy
20 Gy
15 Gy
10 Gy
5 Gy
2 Gy
Dose from C1


S
S
R
25 Gy
20 Gy
15 Gy
10 Gy
5 Gy
2 Gy
Dose from C1 + C2


S
S
R
25 Gy
20 Gy
15 Gy
10 Gy
5 Gy
2 Gy
Dose from C1 + C2 + C3


S
S
R
25 Gy
20 Gy
15 Gy
10 Gy
5 Gy
2 Gy
Dose from C1 + C2 + C3 + C4



Example of Summed Doses for ^{177}Lu-DOTATATE

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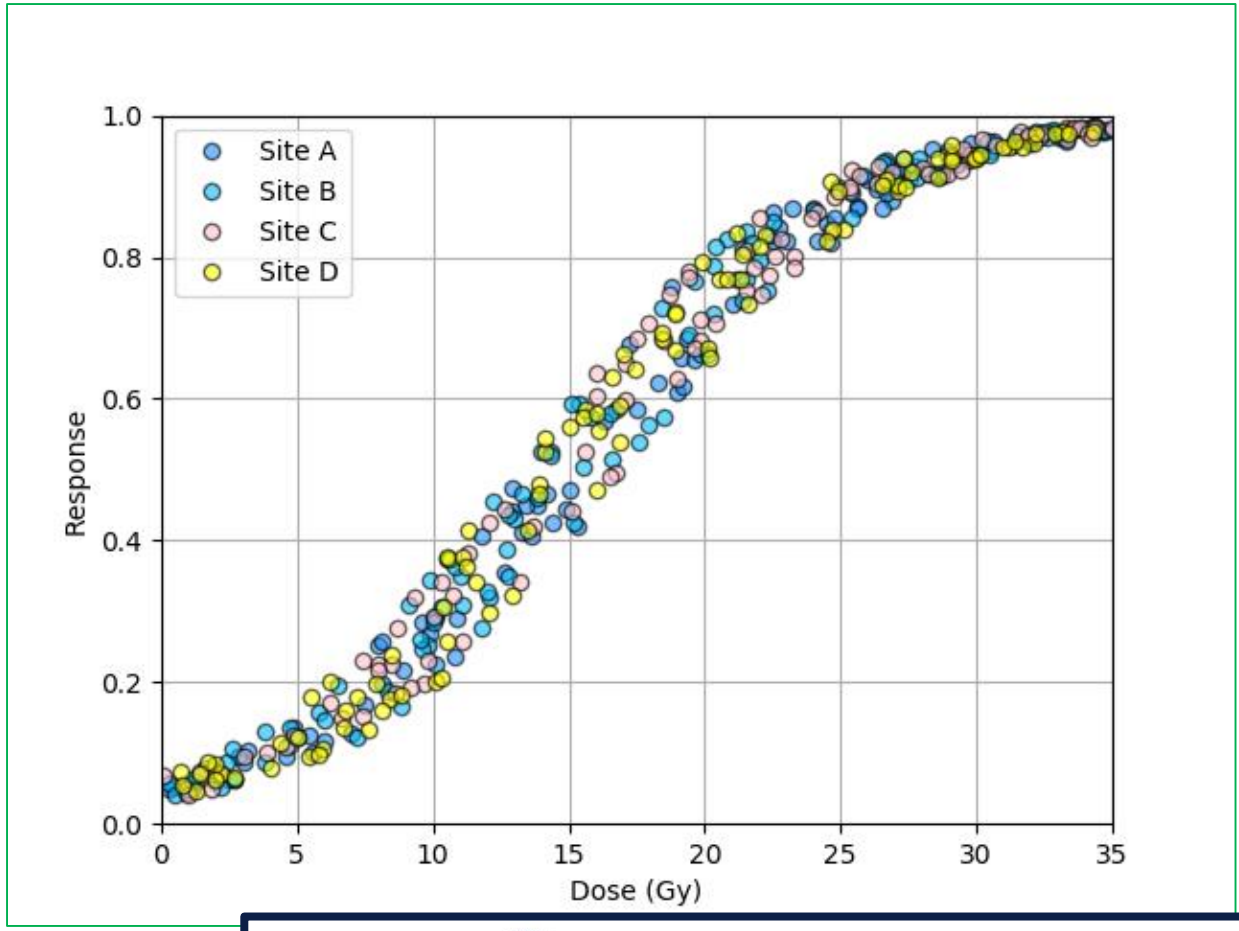
Other Commercial and In-house Methods

There are many vendors and other groups that are doing work on dose calculations for TRTs.

There will be many solutions for how dose is calculated and reported for our patients.

The need for harmonized reporting of dose

In a dose response model, a response is seen between the absorbed dose and the response.



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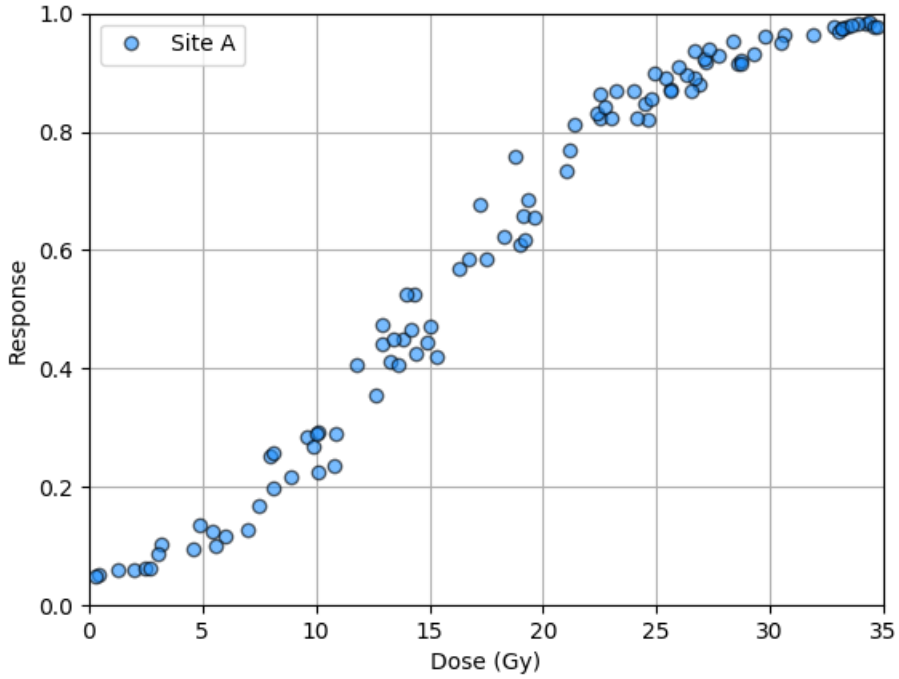
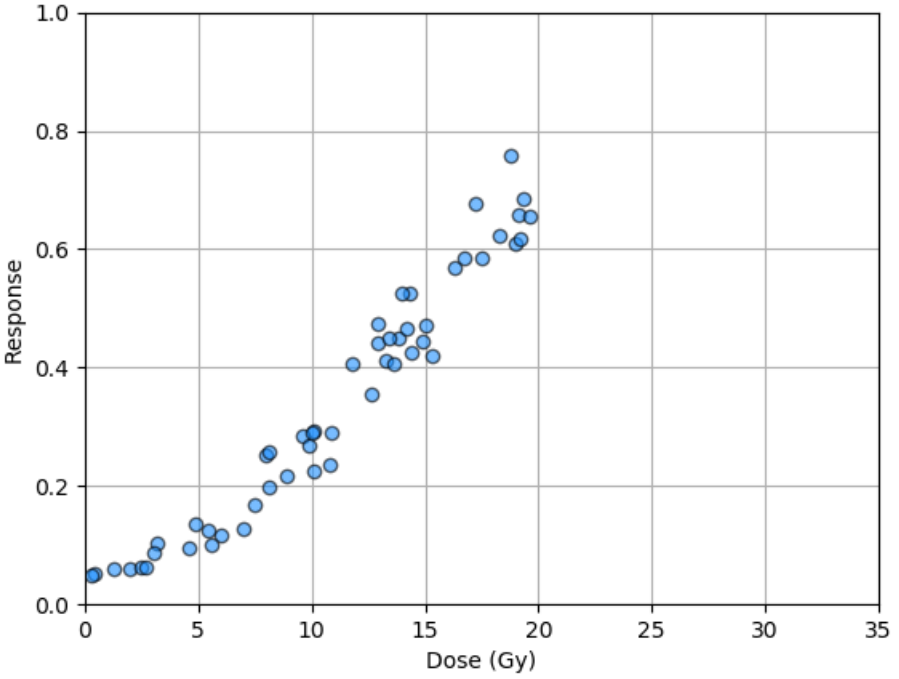
In TRT, the dose delivered is modulated by the administered activity



Complete response is not often seen in the patient data – Tumor response curves truncated to reflect that



In TRT, there are many additional sources of uncertainty in reported dose …

The impact of tumor size

Below a certain threshold, the reconstructed activity in the SPECT study is inaccurate and may results in gross errors in dose calculation

In this example, the authors excluded tumors of diameter < 2.2 cm (based on measurements) and then applied a secondary cut of 4 cm.

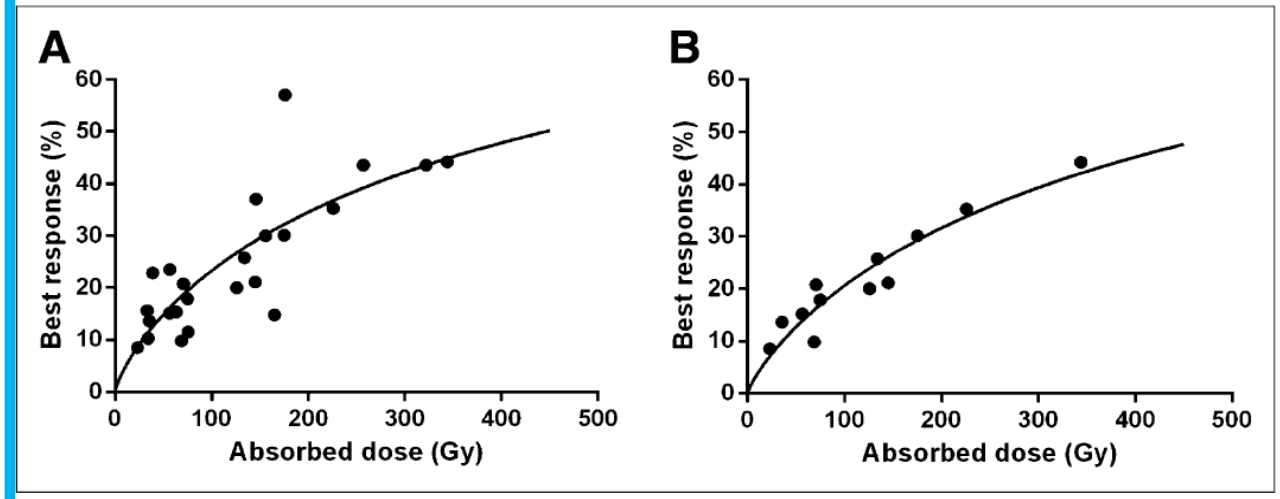


FIGURE 5. Tumor dose–response relationship for patients with PNETs treated with PRRT using ^{177}Lu-DOTATATE, including tumors larger than 2.2 cm (A) and only tumors larger than 4 cm (B). Solid lines represent 2-parameter sigmoid fits ($y = 100/(1+ (\alpha/x)^{\beta})$), where α and β are fitting parameters. Parameters α and β were 445 and 0.79, with SEs of 104 and 0.14, respectively, for tumors larger than 2.2 cm and 504 and 0.84, with SEs of 83 and 0.1, respectively, for tumors larger than 4 cm. Pearson correlation coefficients (R^2) were 0.64 (A) and 0.91 (B).

Dose Response of Pancreatic Neuroendocrine Tumors Treated with Peptide Receptor Radionuclide Therapy Using ^{177}Lu-DOTATATE

Ezgi Ilan[1,2], Mattias Sandström[1,2], Cecilia Wassberg[1,3], Anders Sundin[1,3], Ulrike Garske–Román[1,3], Barbro Eriksson[4], Dan Granberg[4], and Mark Lubberink[1,2]

[1]Nuclear Medicine and PET, Department of Radiology, Oncology, and Radiation Science, Uppsala University, Uppsala, Sweden; [2]Medical Physics, Uppsala University Hospital, Uppsala, Sweden; [3]Molecular Imaging, Medical Imaging Centre, Uppsala University Hospital, Uppsala, Sweden; and [4]Section of Endocrine Oncology, Department of Medical Science, Uppsala University Hospital, Uppsala, Sweden

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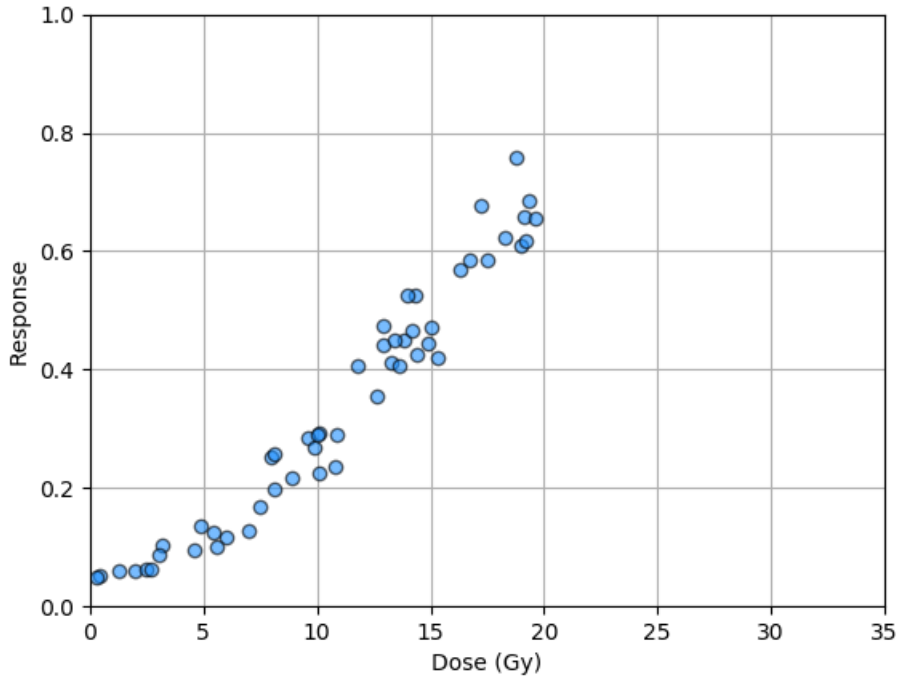
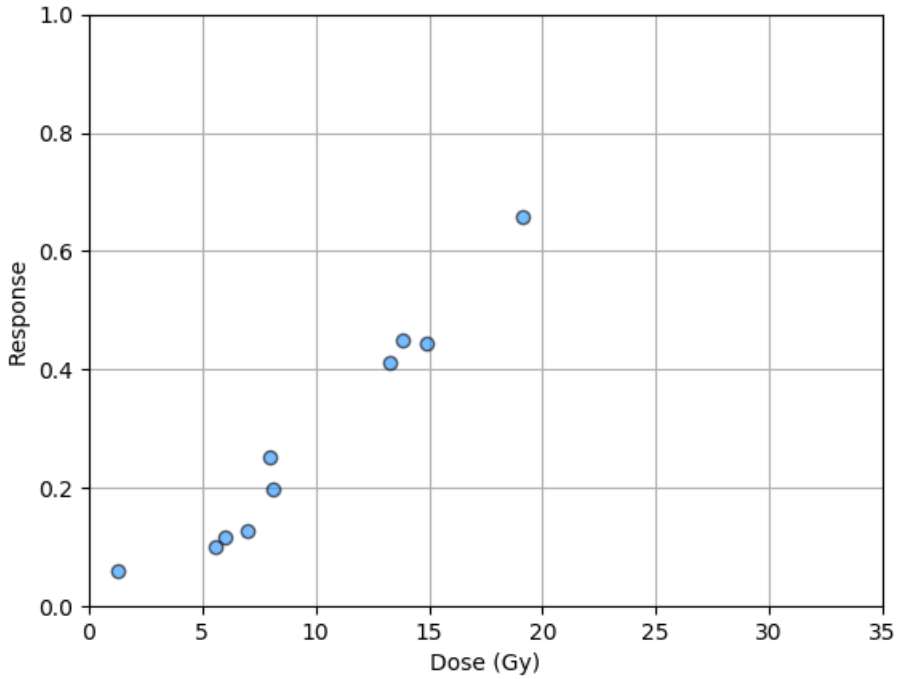
The impact of tumor size : impact on dose response models



Sample data set truncated to illustrate role of eliminating all tumors below diameter ~ 4 cm



Imaging at one timepoint

It may not be feasible to acquire many patient images – assumptions about physical and effective half life may or may not be included in dose calculations.

* Results based on planar (not volumetric) estimates of activity

TABLE 1

Correlation Between Approximation $\tilde{u}_l(r_S, t_l) = u(r_S, t_l) \times 2 \times t_l/\ln(2)$ Deduced from Single Measurement After 24, 48, 72, 96, 120, and 144 Hours and Actual Time Integral $\tilde{u}(r_S)$

	Pearson correlation coefficient *r*					
Tissue	24 h	48 h	72 h	96 h	120 h	144 h
Kidneys	0.73	0.84	0.93	0.98	0.99	0.98
Liver	0.67	0.84	0.93	0.98	0.99	0.99
Spleen	0.55	0.77	0.89	0.97	0.99	0.99
NET	0.63	0.80	0.92	0.97	0.99	0.99

Dose Mapping After Endoradiotherapy with ^{177}Lu-DOTATATE/DOTATOC by a Single Measurement After 4 Days

Heribert Hänscheid[1], Constantin Lapa[1], Andreas K. Buck[1], Michael Lassmann[1], and Rudolf A. Werner[1,2]

[1]Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany; and [2]Division of Nuclear Medicine and Molecular Imaging, The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins School of Medicine, Baltimore, Maryland

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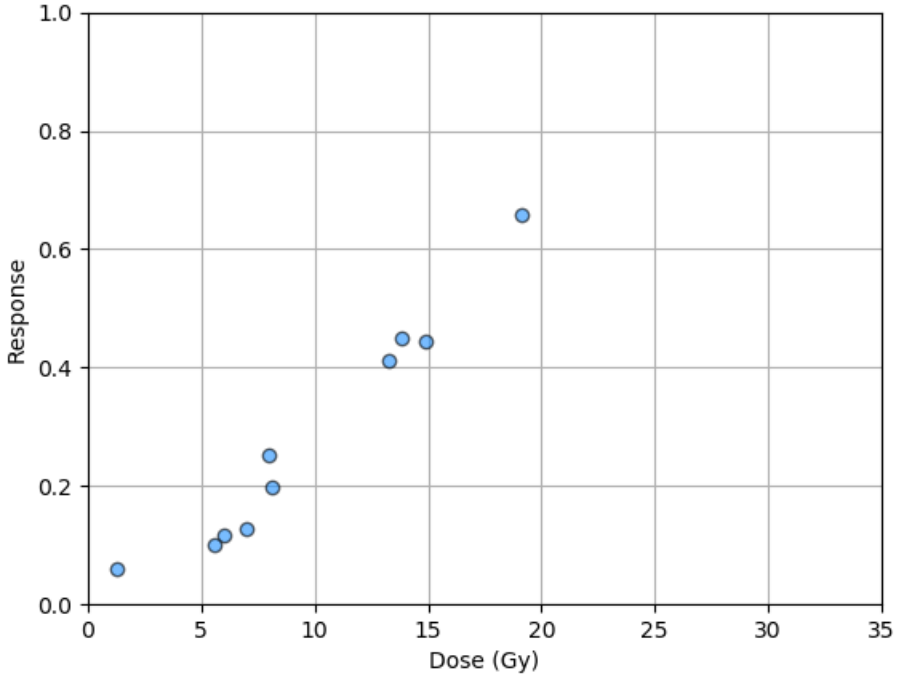
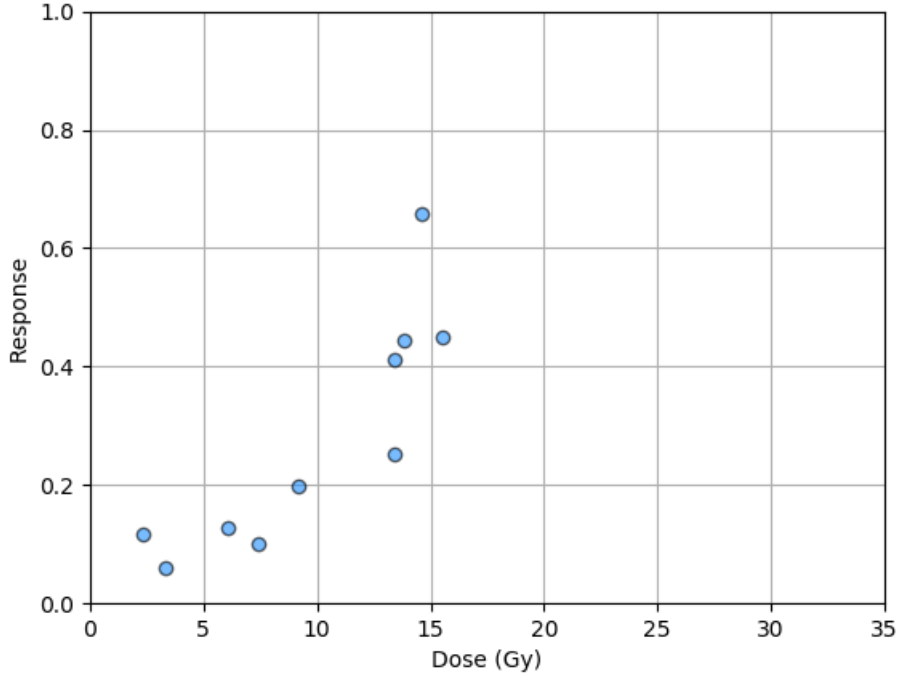
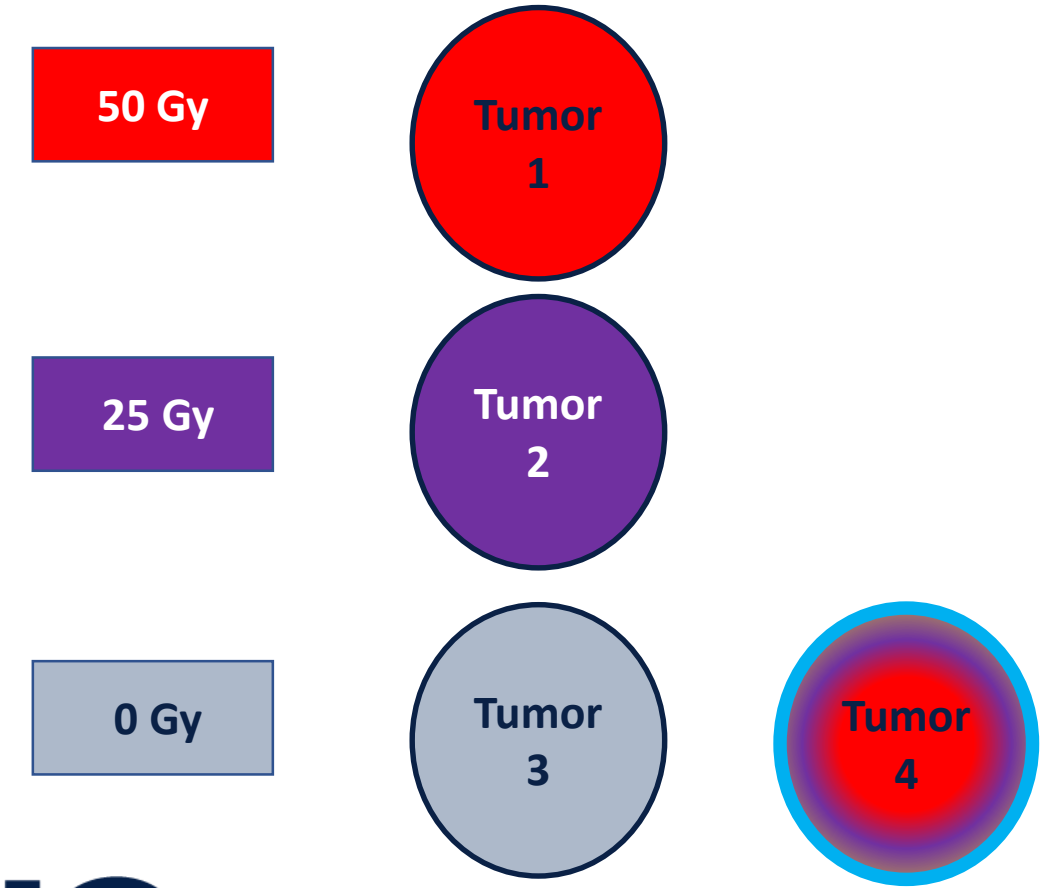
Imaging at one timepoint

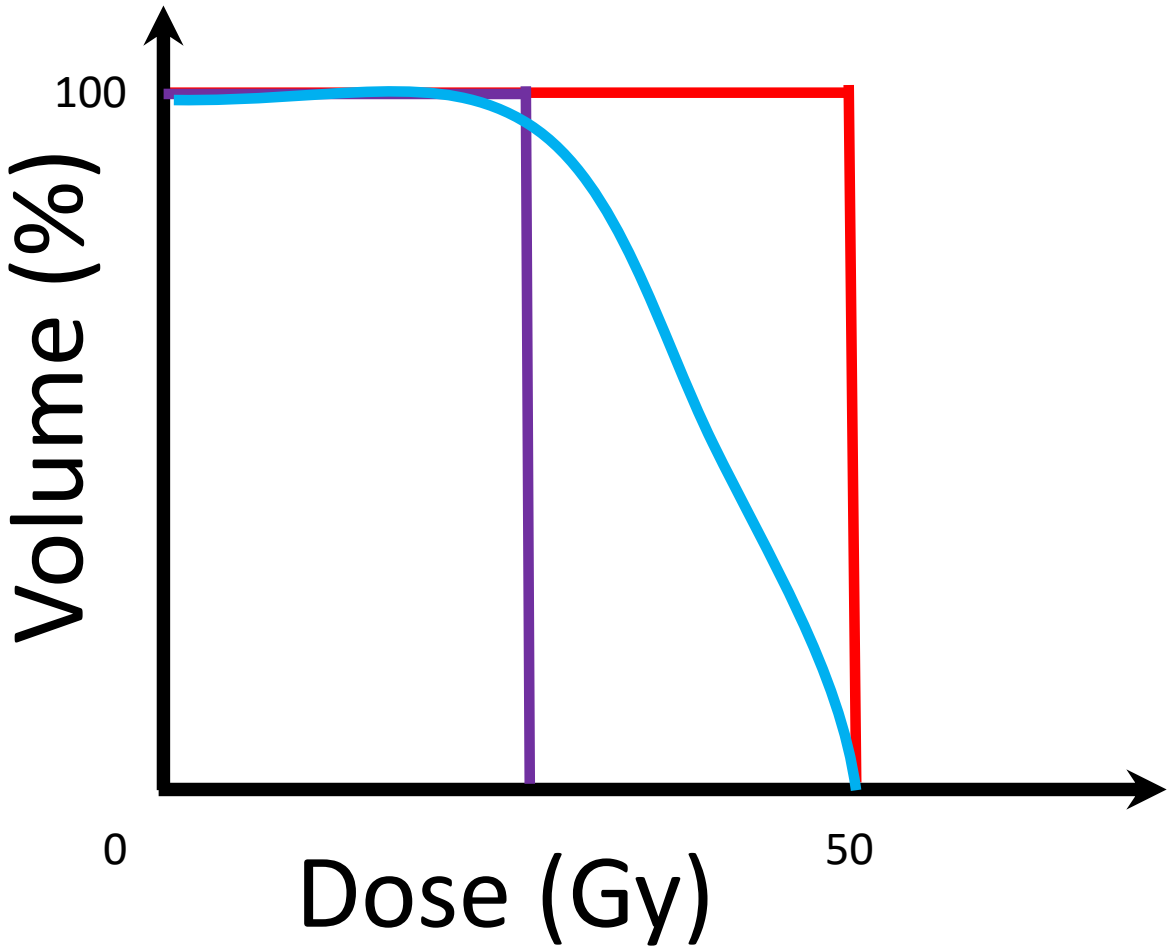


Sample data set with added error to illustrate the role of imaging at one timepoint



Reporting Dose : Dose Volume Histograms





Reporting Dose : Dose Volume Histograms

The dose to different tumors in the same patient is variable.

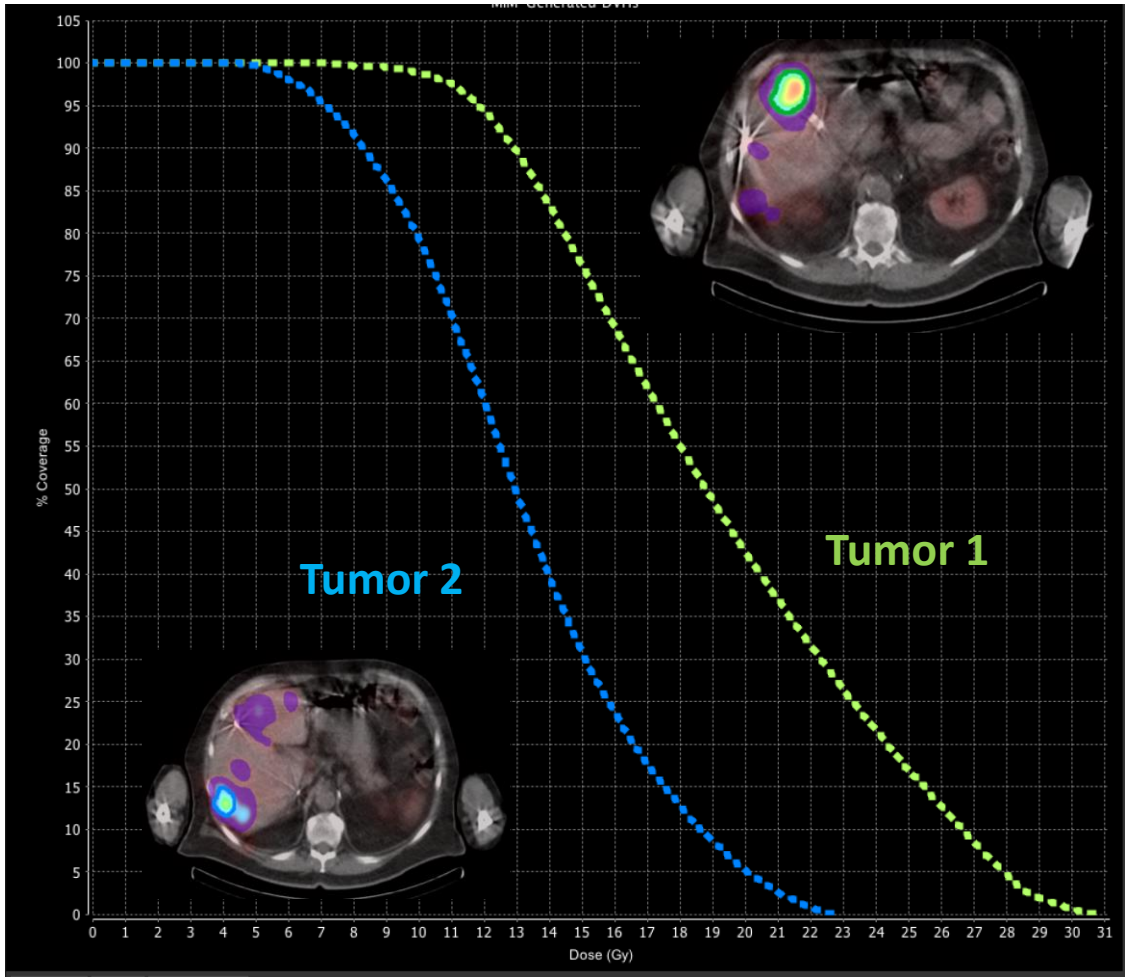
The reporting of the received dose depends on what metric is chosen:

-Average dose

-Near minimum dose

-Maximum dose

In addition, this will depend on how the tumor volume is defined (contoured)



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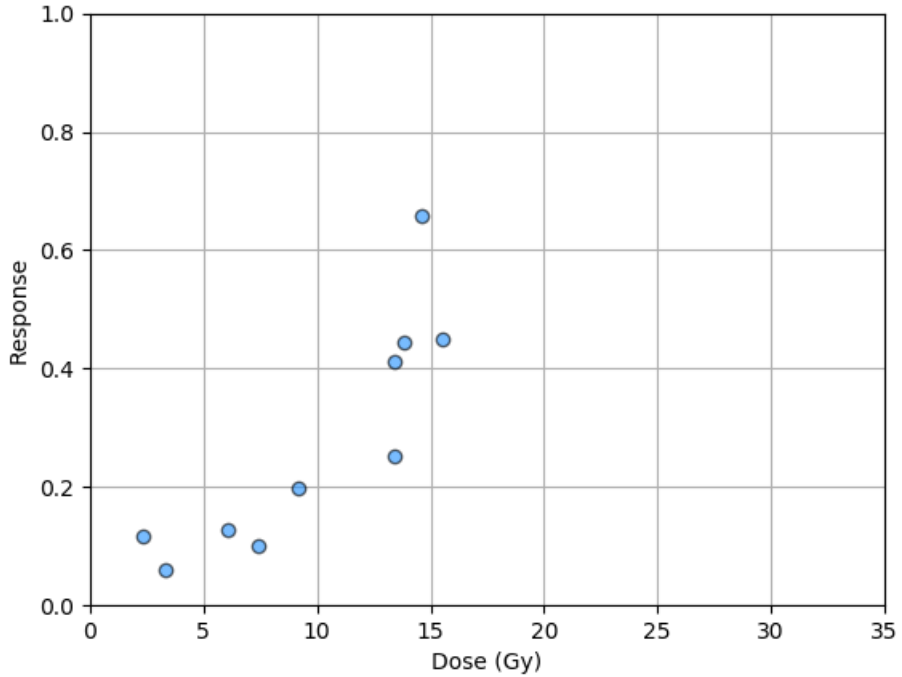
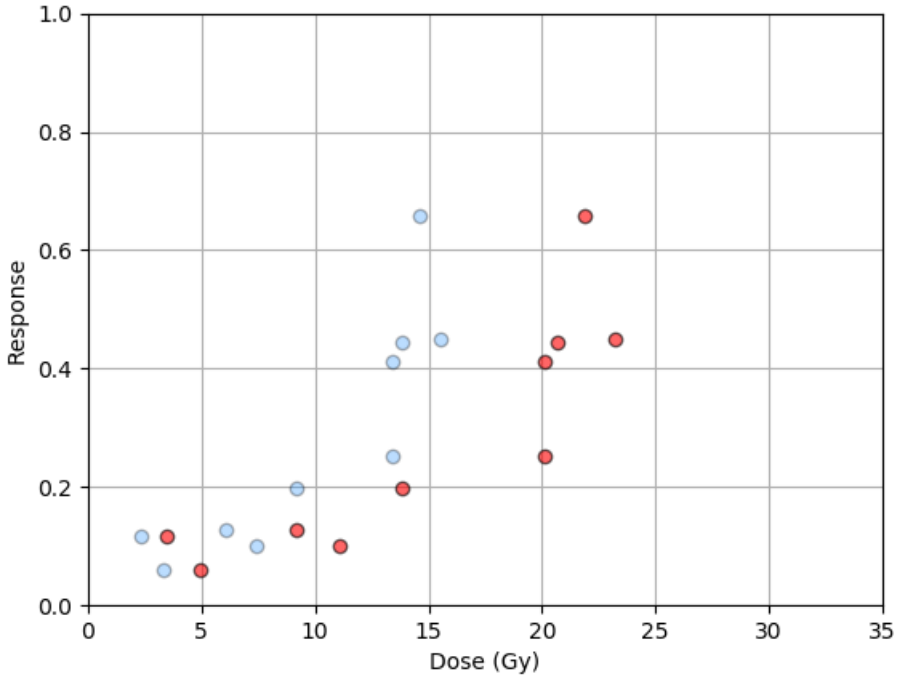
Reporting Dose : Average dose, near minimum dose



It is important to record what dose is reported



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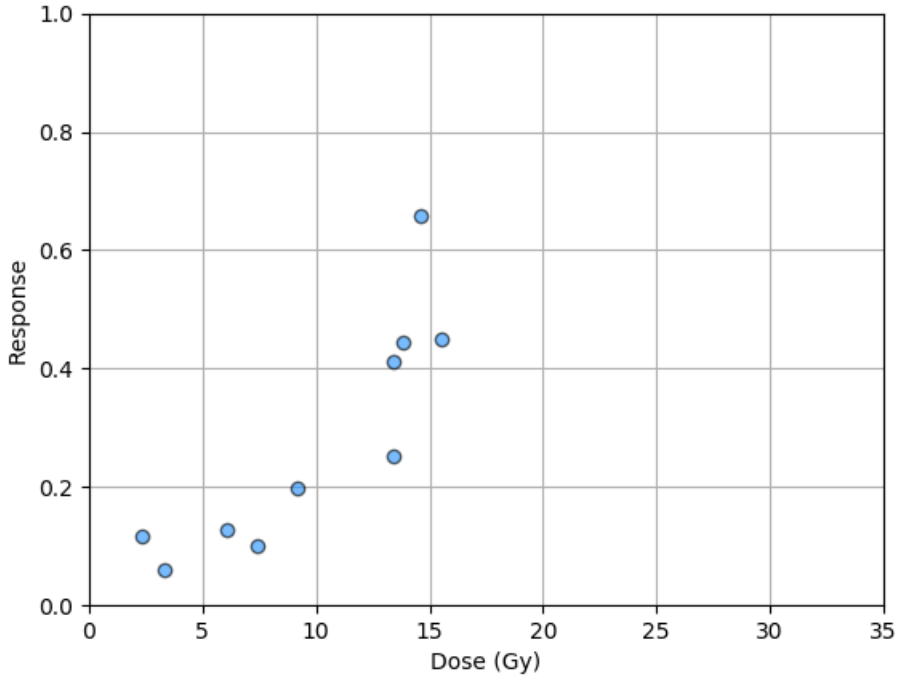
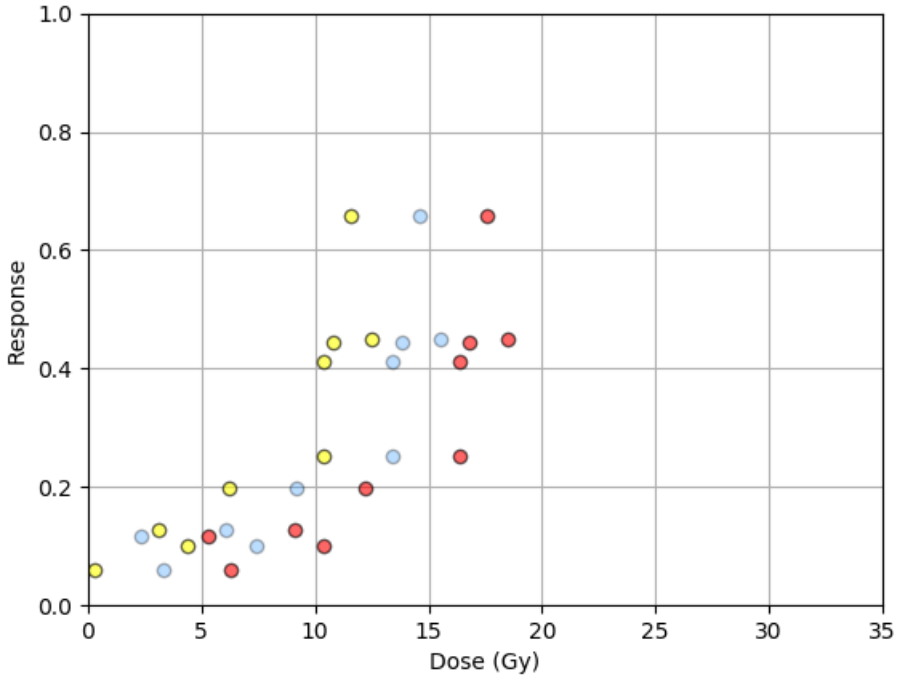
Scanner Calibration: Accuracy of the dose calculation relies on the accuracy of the imaging study that it is based upon.





Uncertainties in Reported Dose and the need for harmonization, external validation methods

These sources of uncertainty in reporting the received dose need to be addressed consistently if the goal is to compare results between institutions

There may be a role for external validation (phantom) to credential sites to participate when reporting the received radiation dose

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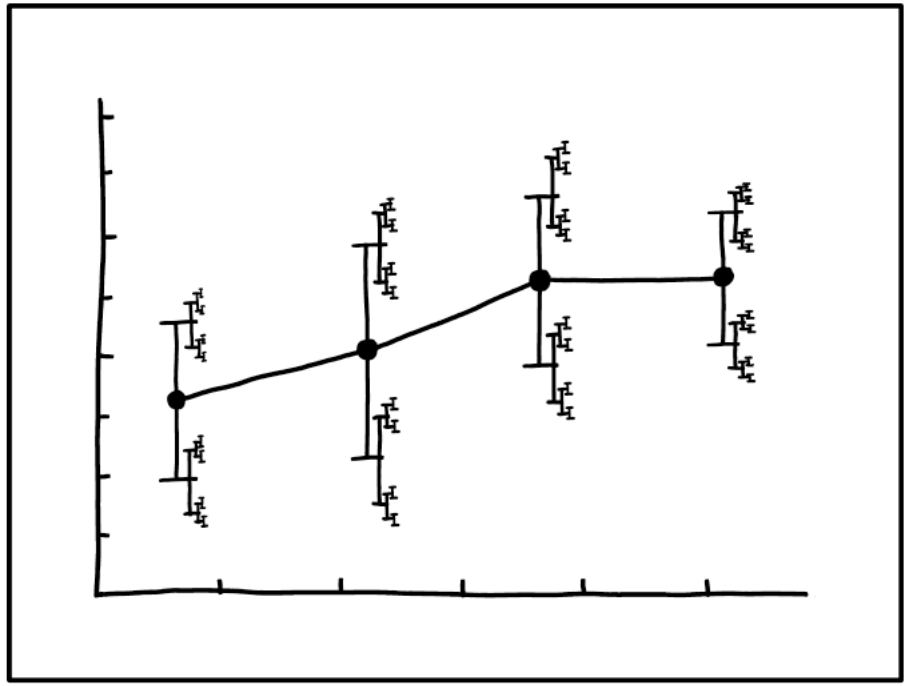
Quantifying response

- All of the previous examples dealt with dose uncertainties (Δx)
- There are also uncertainties in how we quantify response
  - RECIST criteria?
  - At what time are we evaluating response?



I DON'T KNOW HOW TO PROPAGATE ERROR CORRECTLY, SO I JUST PUT ERROR BARS ON ALL MY ERROR BARS.

https://xkcd.com/2110/

Can imaging of ^{177}Lu-DOTATATE inform response?

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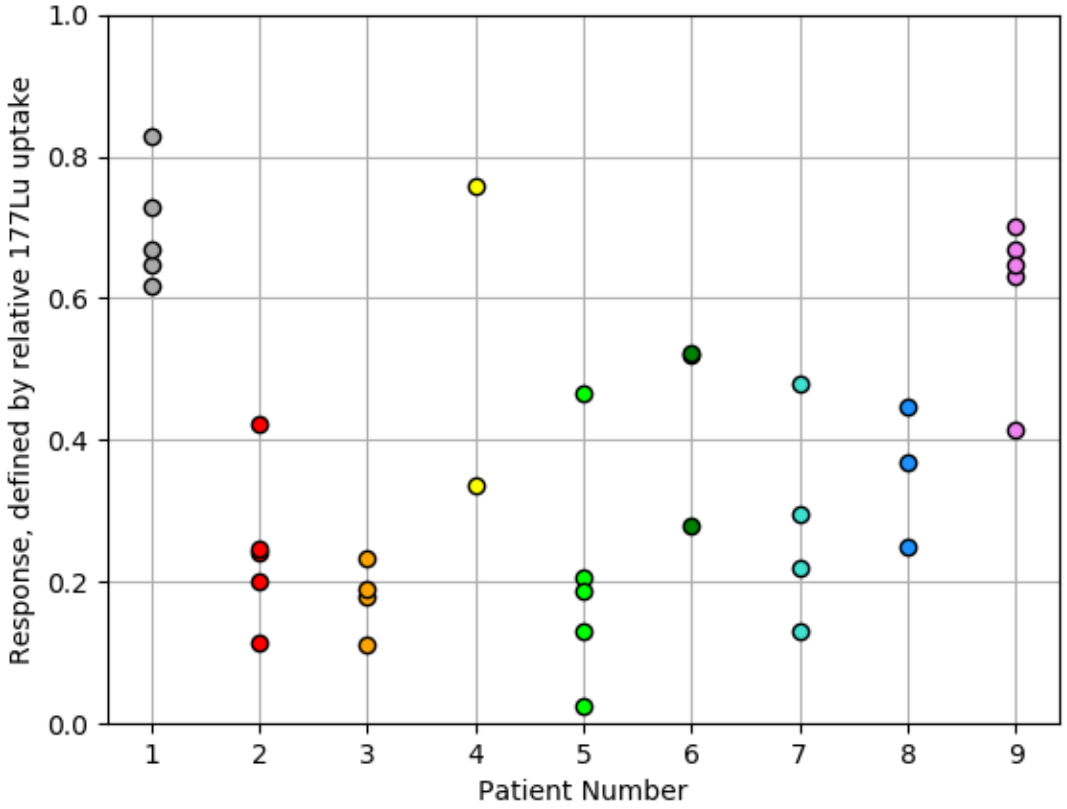
What can we do now that we have imaging?

- We can start to look at our patient data and try to understand why some patients respond to treatment, while others do not

- Started to evaluate response by looking at the relative uptake of ^{177}Lu between Course #4 and Course #1 (tumor level)

$$Response = 1 - \frac{Course\ 4\ Uptake}{Course\ 1\ Uptake}$$



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What can we do now that we have dose?

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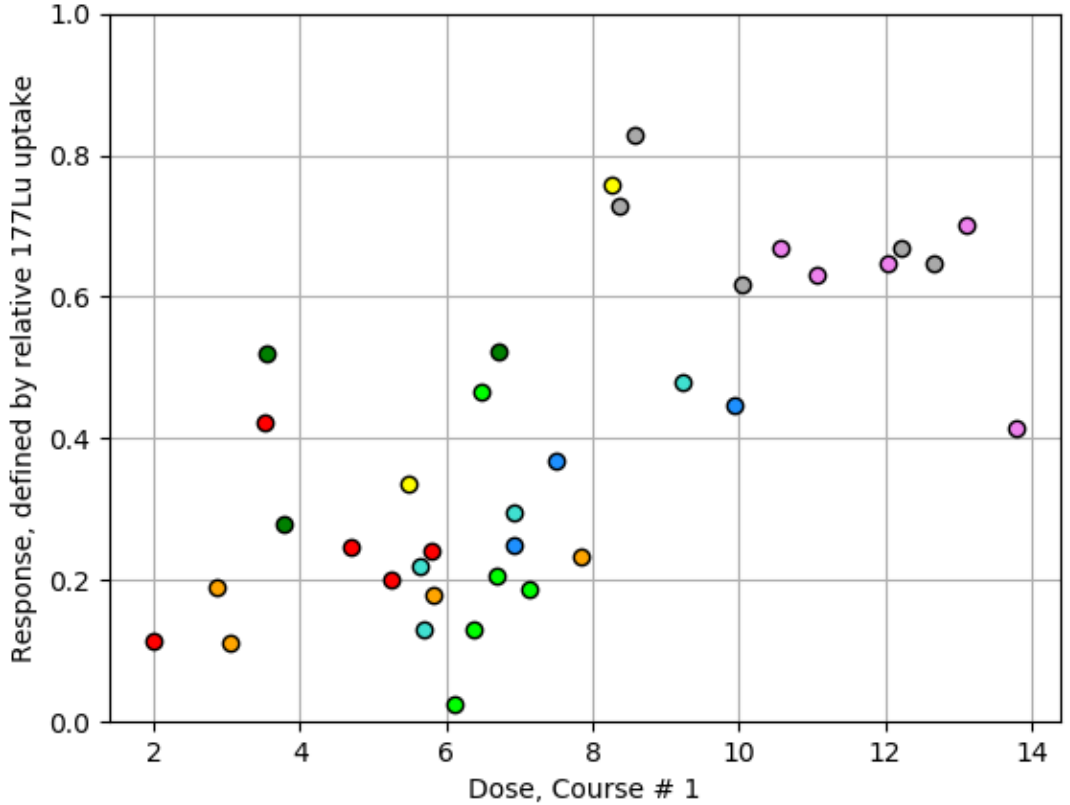

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How do we know that what we are reporting is accurate?

- Every site uses different scanners, protocols and there are starting to be many software solutions to calculate dose

- We performed phantom studies, and compared the results of our “inhouse” dose calculation method with analytic methods

- To compare results across institutions, we need to have harmonized approaches and ideally ways to validate the accuracy of the reported dose.

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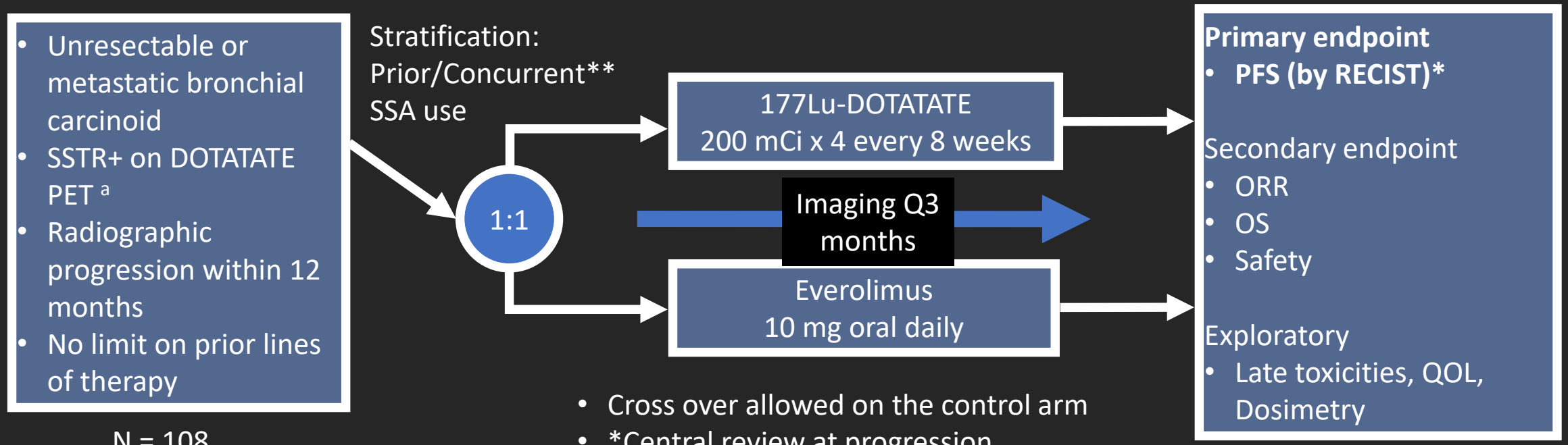
Alliance A021901 (protocol in development)



- Cross over allowed on the control arm
- *Central review at progression
- **Concurrent SSA use allowed for patients with functional tumors if on stable dose for 3 months and previous radiographic progression on SSA

Before this trial starts, we can start to plan for what reporting dose to tumors would require

co-PIs:
Thomas Hope Suki Padd

SSTR=somatostatin receptor

a=100% of typical carcinoids are SSTR+, while 50% of atypical carcinoids are SSTR+

Outlook

- Calculating received radiation dose to tumors and healthy structures is achievable.
- Agreeing on how to report doses to tumors and healthy structures will make comparing results across institutions feasible (harmonization)
- External validation has the potential to fast-track the comparison of reported doses across institutions

Acknowledgments

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UCSF Radiation Oncology Team

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