Calculating and Reporting Absorbed Dose from Radionuclide Therapies

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Introduction (to your speaker)

- Assistant Professor of Clinical Radiation Oncology at UCSF
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.

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?
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:
  • 68Ga-DOTATATE
  • 68Ga-PSMA PET

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

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SANFORD HEALTH 

2019 JAPAN 2019 INTERNATIONAL CONFERENCE ON RADIOISOTOPES IN MEDICINE 

FEBRUARY 27-MARCH 1, 2019 

33rd ANNUAL SUMMER TOPICS IN BIOPHYSICS 

JULY 8-12, 2019 

6TH INTERNATIONAL SYMPOSIUM ON RADIATION ONCOLOGY & MEDICAL PHYSICS IN JAPAN 

JULY 11-14, 2019 

THE 36TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF PHYSICAL THERAPISTS 

JULY 24-27, 2019
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

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

Michael Ljungberg, Anna Celleti, Mark W. Koningaen, Keith F. Eckerman, Yuni K. Dewaraja, and Katarina Sjogreen-Gleisner


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

Yuni K. Dewaraja, Eric C. Fray, George Sgouros, A. Bertrand Brill, Peter Roberson, Pat B. Zanzeonico, and Michael Ljungberg

In collaboration with the SNMMI MIRD Committee: Wesley E. Bolch, Darrell R. Fisher, Roger W. Howell, Ruby F. Meredith, and Barry W. Wexels
## Dose Calculation Methods

<table>
<thead>
<tr>
<th>Monte Carlo</th>
<th>Point Dose Kernel Convolution</th>
<th>Local Energy Deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>Kernels are generated with Monte Carlo methods and are convolved with the SPECT study</td>
<td>Most simplistic model, where all of the energy is assumed to be deposited in the voxel with activity</td>
</tr>
</tbody>
</table>

### Monte Carlo
- **GATE**

### Point Dose Kernel Convolution
- **EGSnrc**
  - Toolkit for Monte Carlo simulation of ionizing radiation transport
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.
Dose Calculation Engines (2)

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

• DICOM RTDose files are generated with GATE.
  • Can be read out by commercial and open source software.
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.
Dose from C1 + C2 + C3
Dose from C1 + C2 + C3 + C4
Example of Summed Doses for $^{177}$Lu-DOTATATE
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.
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 result 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.
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

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**TABLE 1**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
<th>96 h</th>
<th>120 h</th>
<th>144 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>0.73</td>
<td>0.84</td>
<td>0.93</td>
<td>0.98</td>
<td>0.99</td>
<td>0.98</td>
</tr>
<tr>
<td>Liver</td>
<td>0.67</td>
<td>0.84</td>
<td>0.93</td>
<td>0.98</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.55</td>
<td>0.77</td>
<td>0.89</td>
<td>0.97</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>NET</td>
<td>0.63</td>
<td>0.80</td>
<td>0.92</td>
<td>0.97</td>
<td>0.99</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Pearson correlation coefficient $r$

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

Heribert Hünscheid1, Constantin Lapa1, Andreas K. Buck1, Michael Lassmann1, and Rudolf A. Werner1,2

1Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany; and 2Division 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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2020 Joint AAPM/COMP Meeting
Imaging at one timepoint

Sample data set with added error to illustrate the role of imaging at one timepoint
Reporting Dose: Dose Volume Histograms

- Tumor 1: 50 Gy
- Tumor 2: 25 Gy
- Tumor 3: 0 Gy
- Tumor 4: 25 Gy

Graph showing dose (Gy) on the x-axis and volume (%) on the y-axis.
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)
Reporting Dose: Average dose, near minimum dose

It is important to record what dose is reported.
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.
Quantifying response

• All of the previous examples dealt with dose uncertainties ($\Delta x$)
• There are also uncertainties in how we quantify response
  • RECIST criteria?
  • At what time are we evaluating response?

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

https://xkcd.com/2110/
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).

$$\text{Response} = 1 - \frac{\text{Course 4 Uptake}}{\text{Course 1 Uptake}}$$
What can we do now that we have dose?

- 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 177Lu between Course #4 and Course #1 (tumor level).

\[
\text{Response} = 1 - \frac{\text{Course 4 Uptake}}{\text{Course 1 Uptake}}
\]
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.
Alliance A021901 (protocol in development)

- Unresectable or metastatic bronchial carcinoid
- SSTR+ on DOTATATE PET^a^
- Radiographic progression within 12 months
- No limit on prior lines of therapy

N = 108

Stratification:
- Prior/Concurrent** SSA use

1:1

177Lu-DOTATATE
- 200 mCi x 4 every 8 weeks

Imaging Q3 months

Everolimus
- 10 mg oral daily

Primary endpoint
- PFS (by RECIST)*

Secondary endpoint
- ORR
- OS
- Safety

Exploratory
- Late toxicities, QOL, Dosimetry

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

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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