Dosimetric analyses of critical organs (Kidney, Liver and Spleen) of patients with Neuroendocrine Tumors treated with $^{177}$Lu-DOTATATE

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Neuroendocrine Tumors

- Neuroendocrine tumors (NETs) constitute a heterogeneous group of tumors.

- NETs or more properly gastro-entero-pancreatic Neuroendocrine tumors (GEP-NETs), are cancers of the interface between the endocrine (hormonal) system and nervous system.

- NETs are very rare tumors (fewer than 2 cases per 100000) which accounts for only 0.5% of all malignant tumors.
Targeting NETs

- Somatostatin receptors highly expressed by NETs
- Targeting SST receptors can provide symptom and disease control

\[
\text{Ala - Gly - Cys - Lys - Asn - Phe - Phe - Trp - Lys - Thr - Phe - Thr - Ser - Cys} \\
\text{DTPA - D-Phe - Cys - Phe - D-Trp - Lys - Thr - Cys - Thr(ol)} \\
\text{DOTA - D-Phe - Cys - Tyr - D-Trp - Lys - Thr - Cys - Thr(ol)} \\
\text{DOTA - D-Phe - Cys - Tyr - D-Trp - Lys - Thr - Cys - Thr(OH)} \\
\text{DOTA - D-Phe - Cys - Nal - D-Trp - Lys - Thr - Cys - Thr(ol)} \\
\text{(Nal = 3- (1-naphtalenyl)-L-alanyl)} \\
\text{DTPA-Octreotide} \\
\text{DOTATOC} \\
\text{DOTATATE} \\
\text{DOTANOC}
\]
Aims and Objectives

➢ Bio-kinetic and dosimetric parameters for estimation of the absorbed dose to kidney, Liver, Spleen and neuroendocrine tumors were collected.

➢ Radiation absorbed dose to Kidney, Spleen, Liver and NETs were calculated with the help OLINDA/EXM1.0
Methods and Materials

Patient recruitment

➢ All the patients referred to OPD, Department of Nuclear Medicine,

Inclusion criteria

➢ Patient with positive $^{68}$Ga-DOTANOC PET-CT scan were only included

➢ Patients with appropriate volume NETs for $^{177}$Lu- DOTATATE therapy from $^{68}$Ga-DOTATATE scan.

➢ Patients already diagnosed histologically as NETs or Patients with appropriate clinical features of any Neuroendocrine tumor

EXCLUSION CRITERIA

➢ Patient with negative $^{68}$Ga-DOTANOC scan
➢ Pregnancy, Patient unwilling to continue in this project
Radiopharmaceuticals

- The somatostatin analogue DOTATATE were procured from ABX Advanced Biochemical Compounds.
- $^{177}$Lu were procured from BRIT, BARC, Mumbai, India.
- $^{177}$Lu-DOTATATE prepared according to procedures described by Das et al. Radiolabelling yield would be determined with the use of ITLC-silica chromatography.
Amino Acid Infusion

➢ All patients were infused solution of positively charged amino acids for renal protection.

➢ The concentration of L-Lysine and L-Arginine in the infusion was 19.2 mg/ml and 10.9 mg/ml respectively.

➢ The volume of infusion was determined by the patient weight and was around 15 – 18 ml/kg body weight.

➢ The amino acid infusion was started 30 min before administration of $^{177}$Lu-DOTATATE and continued up to 4 -5 hours. The flow rate was maintained at 4 – 5 ml/min.
Treatment Protocol

➢ All patients were explained the procedure of administration of drug, anticipated complications and side effects and risks associated with treatment and written consent was taken from each patient.

➢ Patients were admitted in special isolation ward for administration of treatment with radioisotopes.

➢ Ondansetron 8 mg was given orally 1 hr prior to infusion of amino acids and the same dose repeated after 4 hrs (i.e., at the end of infusion of amino acids).

➢ The amino-acid infusion was started 30–45 minutes before the administration of the radiopharmaceutical and lasted between 4 – 5 hours.

➢ The radiopharmaceutical ($^{177}$Lu-DOTATATE) was administered at the same time via a peristaltic infusion pump through another venflow on the other limb slowly over a period of 30 minutes.
Whole Body Scanning Protocol after Infusion of $^{177}$Lu-DOTATATE

- WBS was acquired on a dedicated Dual Head Gamma Camera (ECAM Dual Head Siemens gamma camera: LEAP collimator, dual energy window, peak at 208 keV; 15% energy window & 110 KeV; 15% energy window; 15 cm/minute) equipped with NaI(Tl) crystal in tandem with a dual slice CT gantry.

- Each patient was injected with 3700-7400 MBq (100 - 200 mCi) of $^{177}$Lu-DOTATATE with the help of infusion pump.

- Nine series of whole-Body Scan (WBS) were acquired after 30 min (pre-void), 4 h, 8 h, 12 h, 24 h, 48 h, 96 h, 144 h, 168 h (post-void) infusion of $^{177}$Lu-DOTATATE. Image was acquired using a matrix of 1024 X 1024 matrix size.
The geometric mean of the measured anterior-posterior image was calculated on a pixel-by-pixel basis.

The first WBS (with full bladder) followed immediately after the administration of Lu-177 DOTATATE, whereas subsequent WBS (with empty bladder) was acquired at 4, 8, 12, 24, 48, 96, 144 and 168 hours.

The whole body counts of first WBS with full bladder were defined to be 100% activity of the administered activity. All other activities were expressed as the percent of administered activity (%IA).

These percentages, at different time points of WBS, were used to describe the uptakes of the radioactivity in the body. The ROIs were drawn over kidneys, liver, spleen, pituitary gland, and NETs.

A narrow background ROI was defined on non-vascular region on thigh. ROI data were quantified by using geometric mean of anterior and posterior WBS with geometric based background subtraction method.
Method of Dosimetry

- The radiation absorbed dose estimations of kidney, liver and spleen were determined according to the MIRD scheme.

- The % IA obtained from whole body scintigraphic images were then fitted depending on the degree of correlation to a mono- or bi-exponential function with the help of OLINDA/EXM software.

- The total number of disintegrations for kidney, liver and spleen were obtained from Kinetic input from option of OLINDA/EXM which were equivalent to the cumulated activity and S-values for the Lu-177.

- Radiation absorbed dose of kidney, liver and spleen in the unit of mGy/MBq was calculated.
<table>
<thead>
<tr>
<th>Frame: Anterior</th>
<th>Number of Pixels: 993</th>
<th>ROI:</th>
<th>Average Counts: 99.70</th>
<th>Minimum: 22.00</th>
<th>Standard Deviation: 28.72</th>
<th>Size (mm²): 5708.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior 3161K Duration: 876 sec</td>
<td>Total Counts: 99000.00</td>
<td>Max: 194.00</td>
<td>Variance: 824.60</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frame: Anterior</th>
<th>Number of Pixels: 993</th>
<th>ROI:</th>
<th>Average Counts: 57.09</th>
<th>Minimum: 57.00</th>
<th>Standard Deviation: 57.00</th>
<th>Size (mm²): 5700.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior 1454K Duration: 860 sec</td>
<td>Total Counts: 5688</td>
<td>Max: 102.00</td>
<td>Variance: 163.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

30 min post Images

4 hr post Images
Lutetium WB Scan 11/3/2010

24 hr post Images

Anterior 610K Duration: 816 sec
Posterior 600K Duration: 816 sec

Lutetium WB Scan 11/6/2010

6th day min post Images

Anterior 180K Duration: 776 sec
Posterior 180K Duration: 776 sec
Select the radionuclide

To see a listing of the decay data for any element, go to http://www.ornl.gov/public/health/nucl_decaydata.cfm

Select the body model

- Adult Male
- Adult Female
- 15-year-old
- 10-year-old
- 5-year-old
- Newborn
- 1-year-old
- 3 month pregnant woman
- 6 month pregnant woman
- 9 month pregnant woman
The previously used quantity of residence time was confusing to many users. This was only a measure of the number of disintegrations occurring in a source organ. This code works with the number of disintegrations per unit activity administered (μCi-in/hr or Bq-in/hr), either entered directly, or as calculated from formulas. This is mathematically equivalent to residence times, but is perhaps easier to understand. You may also enter data from a kinetic model, involving values of activity and half-lives, and fit them to a function.

Enter the number of disintegrations for the source organs, or use some of the special options below.

Note: for the Tct Body/Rem. Body field - enter value for Rem. Body if any other organ has been chosen.
## Organ Doses: \( \text{mSv/MBq} \)

**Nuclide: Lu-177 (6.73E00 day), Adult Male**

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Alpha</th>
<th>Beta</th>
<th>Photon</th>
<th>Total</th>
<th>EDE Cont.</th>
<th>ED Cont.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>5.43E-03</td>
<td>5.43E-03</td>
<td>3.26E-04</td>
<td>1.36E-05</td>
</tr>
<tr>
<td>Brain</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>7.36E-06</td>
<td>7.36E-06</td>
<td>0.00E00</td>
<td>1.64E-08</td>
</tr>
<tr>
<td>Breasts</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>4.84E-04</td>
<td>4.84E-04</td>
<td>7.26E-05</td>
<td>2.42E-05</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>4.36E-03</td>
<td>4.36E-03</td>
<td>0.00E00</td>
<td>0.00E00</td>
</tr>
<tr>
<td>LIL Wall</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>3.97E-04</td>
<td>3.97E-04</td>
<td>0.00E00</td>
<td>4.77E-05</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>1.36E-03</td>
<td>1.36E-03</td>
<td>0.00E00</td>
<td>3.41E-06</td>
</tr>
<tr>
<td>Stomach Wall</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>4.71E-03</td>
<td>4.71E-03</td>
<td>0.00E00</td>
<td>5.65E-04</td>
</tr>
<tr>
<td>ULI Wall</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>1.60E-03</td>
<td>1.60E-03</td>
<td>0.00E00</td>
<td>2.52E-06</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>1.68E-03</td>
<td>1.68E-03</td>
<td>0.00E00</td>
<td>0.00E00</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.00E00</td>
<td>7.47E-01</td>
<td>1.73E-02</td>
<td>7.64E-01</td>
<td>4.58E-02</td>
<td>1.91E-03</td>
</tr>
<tr>
<td>Liver</td>
<td>0.00E00</td>
<td>1.41E-01</td>
<td>7.05E-03</td>
<td>1.46E-01</td>
<td>7.40E-03</td>
<td>3.74E-03</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>1.53E-03</td>
<td>1.53E-03</td>
<td>1.91E-04</td>
<td>1.91E-04</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>9.83E-04</td>
<td>9.83E-04</td>
<td>0.00E00</td>
<td>2.46E-06</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>4.75E-04</td>
<td>4.75E-04</td>
<td>1.19E-04</td>
<td>9.51E-05</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>3.64E-03</td>
<td>3.64E-03</td>
<td>5.18E-04</td>
<td>2.16E-05</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>1.11E-03</td>
<td>1.11E-03</td>
<td>1.33E-04</td>
<td>1.33E-04</td>
</tr>
<tr>
<td>Osteogenic Cells</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>1.27E-03</td>
<td>1.27E-03</td>
<td>3.06E-05</td>
<td>1.27E-05</td>
</tr>
<tr>
<td>Skin</td>
<td>0.00E00</td>
<td>0.00E00</td>
<td>3.92E-04</td>
<td>3.92E-04</td>
<td>0.00E00</td>
<td>3.92E-06</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.00E00</td>
<td>2.16E00</td>
<td>4.08E-02</td>
<td>2.22E00</td>
<td>1.33E-01</td>
<td>5.66E-02</td>
</tr>
</tbody>
</table>

**Note:** you must enter MBq or convert mCi to MBq BEFORE multiplying.

**mCi to MBq calculator**

<<<Convert:
Biodistribution

➢ There was a single case of primary NET of brain and another case of pituitary macro-adenoma with increased radiotracer uptake of Ga-68 DOTANOC PET study.

➢ Also, two cases of somatostatin receptor expressing carotid body tumors and single case of medullary carcinoma thyroid with skull base metastases were present in study cohort.

➢ These five patients with radiotracer avid intracranial tumors or extension of head and neck tumors into the cranial cavity were not included in pituitary gland dose estimation.

➢ The dose calculations of kidneys, Spleen and Liver were performed for all the 81 patients.
<table>
<thead>
<tr>
<th>Time</th>
<th>Kidney</th>
<th>Liver</th>
<th>Spleen</th>
<th>Pituitary gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 hr</td>
<td>2.7 ± 0.2</td>
<td>2.2 - 3.2</td>
<td>1.2 ± 0.7</td>
<td>0.6 - 4.2</td>
</tr>
<tr>
<td>4 hr</td>
<td>3.9 ± 0.5</td>
<td>2.9 - 5.1</td>
<td>1.1 ± 0.7</td>
<td>0.6 - 4.1</td>
</tr>
<tr>
<td>8 hr</td>
<td>2.9 ± 0.3</td>
<td>2.3 - 3.9</td>
<td>1.0 ± 0.6</td>
<td>0.5 - 3.6</td>
</tr>
<tr>
<td>12 hr</td>
<td>2.3 ± 0.3</td>
<td>1.7 - 2.9</td>
<td>0.9 ± 0.5</td>
<td>0.5 - 3.0</td>
</tr>
<tr>
<td>24 hr</td>
<td>1.8 ± 0.3</td>
<td>0.9 - 2.2</td>
<td>0.8 ± 0.4</td>
<td>0.4 - 2.6</td>
</tr>
<tr>
<td>48 hr</td>
<td>1.3 ± 0.3</td>
<td>0.7 - 1.9</td>
<td>0.7 ± 0.3</td>
<td>0.4 - 2.2</td>
</tr>
<tr>
<td>96 hr</td>
<td>1.0 ± 0.2</td>
<td>0.6 - 1.4</td>
<td>0.7 ± 0.3</td>
<td>0.4 - 1.8</td>
</tr>
<tr>
<td>144 hr</td>
<td>0.8 ± 0.2</td>
<td>0.5 - 1.1</td>
<td>0.6 ± 0.2</td>
<td>0.3 - 1.6</td>
</tr>
<tr>
<td>168 hr</td>
<td>0.7 ± 0.1</td>
<td>0.4 - 0.9</td>
<td>0.5 ± 0.2</td>
<td>0.3 - 1.4</td>
</tr>
</tbody>
</table>

**Percentage injected activity of Lu-177 DOTATATE in organs**
Dosimetry

➢ We analyzed the images of all the patients for the calculation of radiation absorbed dose of kidneys.

➢ The pattern of biodistribution of RP was that of rapid uptake over 4 hours followed by a slower decrease.

➢ The peak uptake of Lu-177 DOTATATE measured as % IA in kidneys was 3.9±0.5, which was observed at 4 h after infusion of radiopharmaceutical.

➢ The uptake of radiopharmaceutical in kidneys was fitted to bi-exponential function.
Mean % IA for kidneys, liver, spleen, and pituitary derived from scintigraphic images at different time points (0.5, 4, 8, 12, 24, 48, 96, 144, and 168 hours).
<table>
<thead>
<tr>
<th>Organ</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>0.23 ± 0.05</td>
<td>0.17 - 0.36</td>
</tr>
<tr>
<td>Renal</td>
<td>0.54 ± 0.1</td>
<td>0.36 - 0.78</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.27 ± 0.14</td>
<td>0.85 - 1.41</td>
</tr>
<tr>
<td>Pituitary gland</td>
<td>0.058 ± 0.011</td>
<td>0.052 - 0.063</td>
</tr>
<tr>
<td>Tumour</td>
<td>3.41 ± 0.68</td>
<td>1.30 - 4.80</td>
</tr>
</tbody>
</table>

Absorbed dose in mGy/MBq of normal organs and tumor.
Lu-177 DOTATATE showed favourable biodistribution, as well as high affinity to tumors expressing somatostatin receptors.

Therapy with Lu-177 DOTATATE would deliver the highest doses to kidneys and spleen as well as some doses to liver and pituitary gland.

Spleen received the highest dose and that therapeutic administrations could result in doses near thresholds albeit with no serious clinical consequences.

Although the radiation absorbed dose in pituitary gland was lower than threshold dose, toxicity needs to be assessed in long term follow-up with hormonal measurements.
Thank you