Contents

• The use of radioiodine in thyroid cancer
• Peptides in neuroendocrine and prostate cancer

Disclosures

None

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124I-NaI PET: Building block for precision medicine in metastatic thyroid cancer

(PIs: Larson/ Humm / Tuttle)
The Concept of Maximum Tolerated Activity (MTA)


1) Blood clearance (beta dose)
2) Whole Body Clearance (gamma dose)

Bone marrow is the dose limiting for most radionuclide therapies. Blood is commonly used as a surrogate for marrow.

\[ D_T (cGy/MBq) = D_\beta (\text{blood}) + D_\gamma (\text{WB}) \]

\[ \text{MTA} (\text{MBq}) = \frac{200\text{cGy}}{D_T (cGy/MBq)} \]

Blood Thyroid lesion dosimetry (by $^{124}$I PET)

Thyroid bed
Lung mets
Neck nodes

Restoring Radioiodine Uptake in Thyroid Cancer

A Paradigm Shift

New drugs are under development, such as selumetinib and vemurafenib, that have the potential to restore the NaI symporter expression, and thus enable the radiolabels to redistribute in when patients with metastatic thyroid cancer.

Use $^{124}$I PET/CT imaging to evaluate vemurafenib impact upon radioiodine incorporation

Discontinue vemurafenib
Continue vemurafenib and treat with RAI
Measuring $^{124}$I Avidity change by PET after Vemurafenib

Peptides theranostics for neuroendocrine and prostate cancer

Comparing Antibody Against Peptide

$^{89}$Zr-anti PSMA antibody

$^{18}$F-DCFPyL PSMA binding peptide

Dosimetric Implications for diagnostic imaging and treatment follow-up

Radiolabeled Peptides in Current Use

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Applications</th>
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<tr>
<td>SSTR-targeting agents</td>
<td>Neuroendocrine Tumors</td>
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<tr>
<td>¹⁷⁷Lu-DOTATATE</td>
<td>Neuroblastoma/Pheochromocytoma</td>
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<td>Therapy</td>
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<tr>
<td>¹⁷⁷Lu-DOTATOPA</td>
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<tr>
<td>⁶⁸⁸Ga-DOTATATE</td>
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<td>PSMA-targeting agents</td>
<td>Prostate Cancer</td>
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<tr>
<td>⁶⁸⁸Ga-PSMA-11-BDC-CC</td>
<td>Vascular Tumors</td>
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<tr>
<td>Therapy</td>
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<tr>
<td>²⁰¹ THF</td>
<td></td>
</tr>
<tr>
<td>¹⁷⁷Lu-PSMA-A2 / PSMA-617</td>
<td></td>
</tr>
<tr>
<td>²²⁵Ac-PSMA-A17</td>
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</tbody>
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Theranostic Imaging Isotopes

- **68Ga** (68 min half-life)
  - 90% positron yield
  - Produced by a ⁶⁸Ge generator
- **177Lu** (6.7 day half-life)
  - Mean β⁺ ray energy of 0.159MeV (1.6mm range)
  - 10% yield of 208 keV photons for imaging
Lutathera Treatment at MSKCC

Ga-DOTATATE PET scan

Injection and volives - 2.5% Lysine and 2.5% Arginine

Ga-DOTATATE infused over 30min using Graseby pump

Ga-DOTATATE 177Lu DOTATATE QA Scan

Ant Post

68Ga / 177 Lu concordance

Improving peptide targeting

The example of JR11

- Preliminary clinical studies (Wild et al. 2014) with JR11 indicated higher tumor uptake and retention of SSTR antagonist compared to DOTATATE agonist.
- MSK Study (20 pts) imaged with 68Ga-DOTA-JR11 followed by therapy with 177Lu-DOTA-JR11.
- Dosimetry admin (50 mCi) followed by 2 x therapy admin (~200 mCi) with absorbed dose limits (23 Gy to kidney; 1.5 Gy to red marrow).


7.4 GBq

1.85 GBq
**68Ga-DOTA-JR11 Uptake and Biodistribution**

No significant uptake in any normal tissues except kidney
High uptake of 68Ga-DOTA-JR11 in liver disease
Rapid disease uptake with prolonged retention

**Determining the MTA for 177Lu-DOTA-JR11 (treatment planning)**

- Pre-Therapy Administration: 44 mCi (1.61 GBq)

**Projections for Therapy**

- Activity limits: 89 mCi (3.28 GBq) (Liver) 69 mCi (2.53 GBq) (Kidney)
- Index Lesion: 22.4 mCi

- Lesion dose @ MTA: 14.6 Gy
- Lesion dose @ 200 mCi: 44.5 Gy

**177Lu-DOTA-JR11 Toxicity after 20 patient clinical trial**

- Red marrow radiation dose vs G4 thrombocytopenia
- **Red**: G4 thrombocytopenia after two cycles (3 months apart)
- **Green**: G4 thrombocytopenia after two cycles (6 months apart)
- **Blue**: G4 thrombocytopenia after two cycles (> 3 months apart)
- **Black**: G4 thrombocytopenia after one cycle (did not have second cycle)
Combining EBRT with Targeted Radionuclide therapy

**Rationale:** Use radionuclide therapy to treat micrometastases and use EBRT to boost the dose to bulky disease inadequately treated by radionuclide therapy. Minimal overlap in dose-limiting toxicity: For targeted radionuclide therapies it is usually marrow, kidney and salivary glands.

- Radioiodine was the 1st targeted radionuclide theranostic.
- It led to the foundation of a dosimetric method with which to estimate the maximum tolerated activity (MTA) and the use of an imaging dose being used to guide the selection of a therapy dose.
- The ability of PET to quantify radioiodine uptake and the emergence of new thyroid differentiation agents offer the new potential to use imaging to select which patients benefit from radionuclide therapy.

**Summary 1**

- ImmunoPET requires long-lived radionuclides e.g. $^{89}$Zr and $^{124}$I commensurate with the slow targeting pharmacokinetics of antibodies.
- Small peptides have faster uptake and clearance kinetics relative to antibodies which allows the short half-lived radionuclides e.g. $^{68}$Ga and $^{18}$F for imaging that results in lower radiation doses.
- Two promising peptide therapies are SSTR (neuroendocrine tumors) and PSMA (prostate cancer).
- Most currently favored theranostic radionuclide $^{177}$Lu, which has a 6.7 day half-life and a low yield of photon emissions but ideal for imaging.
- Lutathera was FDA approved in 2018. PSMA theranostic agents approved in Europe and Australia and likely soon in the U.S.

**Summary 2**
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