Neuroendocrine Tumors
Positron Emission Tomography (PET) Imaging and Peptide Receptor Radionuclide Therapy

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SOMATOSTATIN RECEPTOR SCINTIGRAPHY WITH SPECT

Normal Octreoscan In-111

AP 4 H PA

AP 24 H PA
SOMATOSTATIN RECEPTOR IMAGING: OCTREOSCAN (IN-111 PENTETREOTIDE)

In-111

Somatostatin Analog

In-111

Peptide (stabilized)

Cyclic Octapeptide

Radionuclide
SOMATOSTATIN RECEPTOR SCINTIGRAPHY WITH SPECT

- Octreoscan (In-111 pentetreotide)
- Somatostatin analog with affinity for SSTR2
- Patient convenience and throughput:
  - Two image acquisitions required post injection
  - Two-day procedure
- Lower spatial resolution compared with newer PET techniques
SOMATOSTATIN RECEPTOR IMAGING: NETSPOT (GA-68 DOTATATE)
Octreoscan and NETSPOT scans have similar biodistributions.
PET imaging with NETSPOT has 2 to 3 times higher spatial resolution than somatostatin receptor scintigraphy with Octreoscan.

Imaging capabilities of PET with Ga 68 dotatate are above 90% for the key measures of sensitivity, specificity, and accuracy.

NETSPOT (PET) allows up to 30% more lesion detection than Octreoscan.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ga-68 dotatate PET/CT</th>
<th>In-111 Pentetreotide</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96%</td>
<td>72%</td>
</tr>
<tr>
<td>Specificity</td>
<td>93%</td>
<td>93%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>94%</td>
<td>82%</td>
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</tbody>
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Octreoscan

NETSPOT
IMPACT ON DISEASE MANAGEMENT

- Studies demonstrate the potential of NETSPOT PET/CT to impact disease management
- 71% of patients who had previously undergone SRS with Octreoscan experienced a change in clinical management after PET scan with NETSPOT
- NETSPOT altered management in 60% of patients
- 23% of patients were switched to different treatment regimens
PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (LU-177 DOTATATE)
LUTATHERA (LUTETIUM LU 177 DOTATATE)

LUTATHERA is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults.
LUTATHERA: MECHANISM OF ACTION

1. Infusion
2. Concentration in GEP-NET sites
3. Binding to somatostatin receptors (highest affinity for subtype 2 receptors)
4. Internalization into tumor cell
5. Irradiation of tumor cell
6. Radiation causes tumor cell death
Lutathera is administered as an intravenous infusion over 30-40 minutes every 8 weeks for a total of 4 doses.
Pre-Treatment Antiemetic: To help address treatment-related nausea and vomiting, an antiemetic drug is given 30 minutes before the amino acid infusion. Nausea is minimized at YNHH by our specially formulated amino acid solution containing only lysine and arginine.

Concomitant Amino Acid Infusion: An amino acid solution containing sufficient amounts of L-lysine and L-arginine is required for renal protection. This infusion must begin 30 minutes before the start of LUTATHERA infusion and must be continued during, and for at least 3 hours after LUTATHERA infusion.

LUTATHERA: Administer as an intravenous infusion over 30-40 minutes. 50 mL/hour to 100 mL/hour for 5 to 10 mins; 200 mL/hour to 300 mL/hour for the following 25 to 30 mins.
NETTER-1: INTERNATIONAL MULTICENTER RANDOMIZED CONTROLLED PHASE III STUDY

**LUTATHERA®**

- n=116
- 7.4 GBq (200 mCi) of LUTATHERA® every 8 weeks for a total of 4 doses + long-acting octreotide 30 mg¹
- Safety assessments every 2–12 weeks²
- Tumor assessment every 12 weeks per RECIST criteria²

**Control**

- n=113
- Control: long-acting octreotide 60 mg every 4 weeks¹

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NETTER-1: INCLUSION AND EXCLUSION CRITERIA

### Inclusion criteria

- Patients with midgut NET that had metastasized or were locally advanced, that were inoperable, and had progressed during treatment with octreotide LAR
- Karnofsky score ≥60
- Tumor with well-differentiated histologic features, as defined by the Ki67 index
- Somatostatin receptors present on all target lesions

### Exclusion criteria

- Serum creatinine level ≥150 μmol/L or creatinine clearance of <50 mL/min
- Hemoglobin level <8.0 g/dL
- White-cell count <2000/mm³
- Platelet count <75,000/mm³
- Total bilirubin level >3x the upper limit of normal range
- Serum albumin >3.0/dL, unless the prothrombin time value was within normal range
- Treatment with >30 mg octreotide LAR within 12 weeks before randomization
- Peptide receptor radionuclide therapy (PRRT) at any time before randomization
- Any surgery, liver-directed transarterial therapy, or chemotherapy within 12 weeks before randomization

LUTATHERA (LUTETIUM LU 177 DOTATATE)

- 79% reduced risk for disease progression
- 3x greater overall response rate compared with long-acting octreotide

LUTATHERA SIDE EFFECTS

• Majority of patients tolerate treatments well
• Nausea/vomiting: minimized with specially formulated amino acid infusion
• Hyperglycemia
• Myelosuppression:
  • anemia, thrombocytopenia, neutropenia
*Blood cell counts are monitored before, during and after treatment
LUTATHERA SIDE EFFECTS

• Renal toxicity: exposure to kidneys is reduced by concurrent infusion of amino acids during Lutathera administration
• Hepatotoxicity: *liver function monitored during treatment
• Neuroendocrine tumor-related hormonal release:
  • flushing, diarrhea, low BP
  *typically occurs within 24 hours following the initial dose - intravenous somatostatin analogs administered as needed
Patient radiation exposure:
• Treatment with Lutathera contributes to overall long-term radiation exposure – theoretical risk
• Benefit of desired therapeutic effect
• Small long-term (10-20 years) risk - similar to conventional radiation therapy
• Patients should drink and urinate frequently following administration to reduce radiation exposure
LUTATHERA RADIATION EXPOSURE

Family, friends and public radiation exposure:
• Patients and family members counseled by YNHH radiation safety personnel to minimize exposure during and after treatment
• External radiation exposure is extremely low
• By discharge from the infusion center, radiation levels are near background levels
• Not a significant risk
Neuroendocrine Tumors
Positron Emission Tomography (PET) Imaging and Peptide Receptor Radionuclide Therapy (PRRT)