Neuroendocrine tumors
Disclosures

- Siemens
- Lucerno Dynamics
- Pharmalogic
- Spectrum Dynamics
- Ionetix
Introduction

- Definitions
- Epidemiology
- Clinical presentation
- Types
- Imaging past and state of the art
- Treatment past and current state of the art
Neuroendocrine tumors (NETs): Basics

- Arise from neuroendocrine or enterochromaffin cells (Kulchitsky) which are ubiquitous throughout the body
- Comprise a very heterogeneous group of tumors
- Historically sometimes called APUD (amine precursor uptake and decarboxylation) tumors
- These tumors produce biogenic amines which when present in abnormally high concentrations result in patient symptoms
Most lesions will arise from the GI tract including the pancreas

GI tract may be divided into foregut, midgut and hindgut

Foregut includes stomach and proximal duodenum but also pancreas, lungs and bronchi

Midgut is second portion of duodenum through the transverse colon

Hindgut is beyond the transverse colon
While GI tract origin is predominantly seen, tumors can arise from essentially anywhere in the body.

Spectrum of disease includes bronchial carcinoid and small cell lung cancer, pheochromocytoma, medullary thyroid carcinoma, neuroblastoma, Merkel cell carcinoma and many more.

NETs are part of genetic conditions including MEN1&2, NF1, VHL and others.
**Neuroendocrine tumors: Basics**

- NETs are uncommon compared to many other cancers estimated at approximately 5 per 100K (Oberg et al, Cancer and Metastasis Reviews, 2011)
- Incidence has been increasing
- Currently not clear if this is a true increase or the result of better means of detection and diagnosis
Neuroendocrine tumors: Basics

From SEER study, 2004
Because most NETs are GI/pancreatic in origin, two categories are often used.

Carcinoid generally and more accurately refers to tumors of intestinal origin.

Those arising from pancreas are considered separately as they often derive from islet cell origin and are sometimes designated PNETs.

The two categories will usually have different clinical manifestations.
Neuroendocrine tumors: Patient presentation

- Carcinoids will most commonly arise from the terminal ileum and often involve the appendix
- Most carcinoids are detected incidentally and are asymptomatic (Kimura et al, Dig Dis Sci, 1991)
- A small percentage (~10%) may be symptomatic due to excess hormone production
- Serotonin is usually implicated when symptoms are present but may be a result of substance P which has proinflammatory effects
Neuroendocrine tumors: Patient presentation

- Symptoms of hypersecretory carcinoid include flushing, diarrhea and abdominal cramping
- Long standing excess serotonin can damage the cardiac valves, particularly the TV and PV
- This can lead to heart failure
- The primary lesion as well as mesenteric desmoplastic change associated with mesenteric nodal metastasis can cause bowel obstruction
PNETs or islet cell tumors account for about 1/3 of the gastroenteropancreatic tumors.

Most are non-functional which do not secrete hormones and therefore are generally asymptomatic unless progressive enlargement causes symptoms such as from biliary obstruction.

Functioning tumors such as gastrinoma, insulinoma and glucagonoma may cause gastric ulcers, hypoglycemia or hyperglycemia respectively.
Several laboratory markers may be abnormal and include:

- Chromogranin A
- 5-hydroxyindolacetic acid (5-HIAA)
- Synaptophysin (found in presynaptic vesicles)
- Neuron-specific enolase
Historically, conventional anatomic imaging has been used to define tumor extent and location but has often been limited in tumors of small size less than 1cm (Tan et al, World J Clin Onc, 2011).

These exams lack specificity and provide no information about the tumor’s metabolism.

Molecular imaging has several distinct advantages.
There are two ways to image NETs from a molecular standpoint.

The biochemical pathways that lead to hormone production can be targeted with radiolabeled agents that become incorporated into the synthesis or taken up by transporters and stored in intracytoplasmic vesicles.
Alternatively, specific tumor receptors can be targeted which, in the case of NETs, are the somatostatin receptors (SRs).

- There are 5 subtypes of SRs.
- Most tumors have the type II subtype which is usually in highest abundance.
- May also have affinity for the type V subtype.
Metaiodobenzylguanidine (MIBG) is an agent that is taken up by NE transporter and subsequently into vesicles.

- Labeled with I-123 or I-131
- Largely limited to the detection of pheochromocytoma, paraganglioma and neuroblastoma
- Sensitivity of 77-95% with nearly 100% specificity (Shapiro et al, JNM 1985)
Molecular Imaging: MIBG

- The accuracy for detecting pheochromocytoma decreases when location is extra-adrenal or when malignant with poor differentiation
- Rule of 10 for pheo: 10% bilateral, 10% extra-adrenal and 10% malignant
- MIBG also with limited sensitivity in the detection of other NETs such as carcinoid which is far more common than pheo
MIBG is a challenging exam to perform and interpret
Patients generally receive SSKI to block thyroid uptake of the radioiodine
Exam requires several days in order to complete
Usually expensive and not readily available in nuclear pharmacies
Poor count rates, particularly with the higher energy I-131, result in limited image quality

Interpretation and sensitivity helped with SPECT and SPECT-CT

Many drugs can interfere with target uptake of the radiotracer
### EANM guidelines

**Molecular Imaging: MIBG**

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Approved name</th>
<th>Recommended withdrawal time</th>
<th>Mechanism of interaction *</th>
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<tbody>
<tr>
<td>CARDIOVASCULAR AND SYMPATHOMIMETIC DRUGS</td>
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<tr>
<td>Anti-arrhythmics for ventricular arrhythmias</td>
<td>Amiodarone</td>
<td>Not practical to withdraw</td>
<td>1,3</td>
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<tr>
<td>Combined β-blocker</td>
<td>Labetalol</td>
<td>72 hours</td>
<td>1,3</td>
</tr>
<tr>
<td>Adrenergic neuron blockers</td>
<td>Brethuxium</td>
<td>48 hours</td>
<td>2,3</td>
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<tr>
<td></td>
<td>Guanethidene</td>
<td>48 hours</td>
<td>2,3</td>
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<tr>
<td></td>
<td>Reserpine</td>
<td>48 hours</td>
<td>2</td>
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<tr>
<td>β-blockers</td>
<td>Phenoxbenzamine</td>
<td>15 days</td>
<td>5</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Amiodipine</td>
<td>48 hours</td>
<td>4,5</td>
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<td>Diltiazem</td>
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<td>Lercanidipine</td>
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<td>Nicardipine</td>
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<td>Nifedipine</td>
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<td>Nimodipine</td>
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<td>Nisoldipine</td>
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<td></td>
<td>Verapamil</td>
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<td>4,5</td>
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<td>INOTROPIC sympath-mimetics</td>
<td>Dobutamine</td>
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<td></td>
<td>Dopamine</td>
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<td></td>
<td>Doxepamine</td>
<td>24 hours</td>
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<tr>
<td>Vasconstrictor sympathomimetics</td>
<td>Ephedrine</td>
<td>24 hours</td>
<td>1</td>
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<tr>
<td></td>
<td>Metaraminol</td>
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<tr>
<td></td>
<td>Norepinephrine</td>
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<td></td>
<td>Phenylephrine</td>
<td>24 hours</td>
<td>3</td>
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<tr>
<td>β2 stimulants (sympathomimetics)</td>
<td>Salbutamol</td>
<td>24 hours</td>
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<td></td>
<td>Terbutaline</td>
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<td>Efrornetol</td>
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<td>Bambuterol</td>
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<td>Fenoterol</td>
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<td></td>
<td>Salmeterol</td>
<td>24 hours</td>
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**Other drugs**

| Antipsychotics (nerveleptics)                  |               |                             |                           |
| Clomipramine                                   | 48 hours      | 3                           |                           |
| Mirtazapine                                    | 48 hours      | 3                           |                           |
| Doxepin (Doxepin)                              | 24 hours      | 3                           |                           |
| Donazepil                                     | 24 hours      | 3                           |                           |
| Zopiclone                                     | 24 hours      | 3                           |                           |
| Zopiclone                                     | 7 days        | 3                           |                           |
| Zopiclone                                     | 7-10 days     | 3                           |                           |
| Zopiclone                                     | 5 days        | 3                           |                           |
| Zopiclone                                     | 3 days        | 3                           |                           |
| | Sedating antihistamines                       |               |                             |                           |
| |                           |               |                             |                           |
| | Tricyclic anti-depressis                      |               |                             |                           |
| |                           |               |                             |                           |
| | Tricyclic-related anti-depressants            |               |                             |                           |
| |                           |               |                             |                           |
| | CNS stimulants                               |               |                             |                           |
| |                           |               |                             |                           |
Proposed pathway for MIBG into chromaffin cell
Molecular Imaging: MIBG

Adrenal pheochromocytoma
Dihydroxyphenylalanine (L-DOPA) is another agent that is taken up into the biochemical pathway of NETs. Currently not FDA approved. PET agent and may be labeled with F-18 or C-11. L-DOPA enters neuroendocrine cells by the large neutral amino acid transporter and is decarboxylated to become a biogenic amine.
L-DOPA metabolism pathway to a biogenic amine
Molecular Imaging: L-DOPA

- Has some utility in finding primary disease in patients with metastases of unknown origin
- Study by Imperiale et al (JNM 2014) showed L-DOPA to identify primary lesion in 44% who had previously had negative somatostatin receptor imaging, US, CT and MRI
- Another study by Montravers et al (J Clin Endocrinol Metab, 2009) showed 38% detection rate of unknown primary in patients with abdominal metastases
Molecular Imaging: L-DOPA

- L-DOPA has better detection of certain NETs over other radiotracers particularly medullary thyroid cancer, non-aggressive catecholamine tumors and well differentiated carcinoid (Balogova et al, Eur J Nucl Med Mol Imaging, 2013)

- In tumors with low Ki-67 index as well as with high serotonin, urinary 5-HIAA, catecholamine metabolites or calcitonin, F18-DOPA is an excellent agent for imaging and detection of primary lesions (Lin et al, Appl Immunohistochem Mol Morphol, 2007)
Molecular Imaging: L-DOPA

Patient with recurrent MTC, F-18 DOPA vs F-18 FDG
Pt with metastatic carcinoid. Both scans show a similar distribution of disease but DOPA reveals two myocardial metastases.

Helle-Brit et al, Circulation, 2008
In-111 Octreotide is a somatostatin analog and has affinity to the type II somatostatin receptor.

Somatostatin is a 14 amino acid peptide that inhibits release of certain intestinal and pancreatic peptides such as insulin, secretin, motolin etc...

Octreotide is an 8 amino acid peptide that has a longer plasma half-life and is better suited for imaging.
Molecular Imaging: Octreoscan

- Imaging may be done as planar or SPECT or SPECT-CT
- Images are acquired at 4 and 24 hours after injection and frequently at 48 or even 72 hours after imaging
- Our protocol is to perform planar imaging at 4, 24 and 48 hours with SPECT-CT also at 48 hours usually of the abdomen and pelvis depending on planar findings
Octreotide imaging has an 80-90% sensitivity for the detection of carcinoid (Kronenberg et al, Williams textbook of endocrinology, 2003) compared to MIBG which has a 55-70% sensitivity (van der Lely et al, Arq Bras Endocrinol Metab, 2005).

- Octreotide has sensitivity for gastrinoma of 75-93% (Krenning et al, Nuclear Med Ann, 1995).
- Limited sensitivity for poorly differentiated tumors (high Ki-67) due to paucity of receptors.
- F-18 FDG preferred for poorly differentiated tumors.
In pheochromocytoma, there is poor sensitivity with octreotide for well differentiated adrenal lesions with a false negative rate up to 75% (van der Harst et al, J Clin Endocrinol Metab, 2001).

Sensitivity increases with extra-adrenal tumors and there is 87% sensitivity for malignant pheo (van der Harst et al, J Clin Endocrinol Metab, 2001).

MIBG is preferred for well differentiated adrenal tumors.
Molecular Imaging: Octreoscan

Planar In-111 octreotide of malignant carcinoid with ileal (arrow) primary and metastases to liver, lung and left supraclavicular lymph node (arrowhead)
Molecular Imaging: Octreoscan

CT and In-111 octreotide SPECT of pancreatic glucagonoma
In-111 octreotide fused SPECT-CT glucagonoma
Molecular Imaging: Octreoscan

4 hour whole body planar octreotide scan for metastatic insulinoma (arrow)
The newest agents available for somatostatin receptor imaging are the DOTA based agents. PET agents labeled with Ga-68. There are three different agents available: DOTATATE, DOTATOC and DOTANOC. All three agents are very similar but with some important differences. Currently only DOTATATE is commercially available in the US.
Neuroendocrine tumors: The DOTAs

(27) $[^{68}\text{Ga}]\text{Ga-DOTA-TOC}$

(28) $[^{68}\text{Ga}]\text{Ga-DOTA-TATE}$

(29) $[^{68}\text{Ga}]\text{Ga-DOTA-NOC}$
As mentioned earlier, there are 5 subtypes of somatostatin receptors

Somatoreceptor subtypes (ssts) that are present in 70-100% of gastroenteropancreatic NETs are sst-2 and sst-5 (Reubi et al, Eur J Nucl Med Mol Imaging, 2003)

However, different tumors may show variable sst distribution and density causing such tumors with paucity of these receptors not to be detected with the DOTA agents
DOTATATE and DOTATOC both target the sst-2 receptor.
The binding potential of DOTATATE is 10 times greater than that of DOTATOC.
Study by Poeppel et al (JNM, 2011) looked at 40 patients with NETs comparing DOTATATE and DOTATOC.
DOTATATE detected 78 lesions while DOTATOC detected 79.
Study concluded that the two radiotracers are comparable with a slight edge to DOTATOC even though the sst affinity is 10 fold less.

It was also noted unexpectedly that the SUVmax of DOTATOC was generally higher.
Neuroendocrine tumors: The DOTAs

Same pt with ileal carcinoid-SUVmax for TOC 21 and for TATE 8.2
Because some tumors such as gastrinomas, ileal carcinoids and VIPomas also have a high density of somatostatin sst-5 as well as sst-2, agents targeting other receptors in addition to sst-2 have been developed (Poeppel et al, JNM, 2011)

- DOTANOC targets not only sst-2 but also sst-3 and sst-5
Wild *et al* conducted a study comparing DOTATATE and DOTANOC.

18 patients with gastroenteropancreatic NETs were enrolled.

Both radiotracers had only one false negative.

DOTATNOC had a sensitivity of 93.5% and DOTATATE 85.5%.

The greater detection with DOTATNOC was related to better visualization of liver metastases.
Neuroendocrine tumors: The DOTAs

Comparison of DOTATATE and DOTANOC showing better detection of hepatic metastases of NOC
DOTANOC scan shows right lobe liver metastasis not seen on DOTATATE. Left renal metastasis also with greater uptake on NOC compared to TATE.
The DOTAs show tremendous benefit in sensitivity over octreotid imaging.

- PET-CT vs. SPECT/SPECT-CT offers higher resolution, 2-3mm vs 6-8mm.
- Ga-68 DOTATATE gives a lower dose to the patient (Walker RC et al, JNM, 2013).
- DOTA only requires about 2 hours to complete the exam compared to 2 days for octreotide.
- DOTA PET allows for quantification of uptake with SUV measurements.
There are few prospective studies comparing DOTATATE against octreotide.

Study by Kumar et al. (JNM supplement, 5/2014) compared DOTA and octreotide in 37 patients.

DOTA showed higher detection rates for organs, bones and combined organ, lymph node and bone lesions.

No significant difference was seen between the two with regard to lymph nodes only.
Neuroendocrine tumors: The DOTAs

- There have been several studies comparing DOTATOC to octreotide all of which have shown the superiority of DOTATOC.
- Study by Gabriel et al (JNM, 2007) compared DOTANOC, octreotide and CT.
- DOTATOC had sensitivity and specificity of 97% and 92% respectively compared to octreotide with 52% and 92% respectively.
Neuroendocrine tumors: The DOTAs

Octreoscan

DOTATOC
DOTA vs MIBG in pheochromocytoma/paraganglioma

Maurice et al (Eur J Nucl Med Mol Imaging, 2012) performed a retrospective analysis of 15 patients with pheo or paraganglioma

Concluded that DOTATATE should be used as first line for imaging in patients with familial paraganglioma syndromes
Also, in patients with negative MIBG scan, DOTATATE should be considered when there is still high clinical suspicion.

DOTATATE also recommended when there is concern of metastatic disease.
In our practice, when searching for primary adrenal lesion in patients with spontaneous, non-familial disease, MIBG is used first after anatomic imaging has been performed (CT, MRI, US).

In patients with familial syndromes, extra-adrenal lesions on anatomic imaging or metastatic disease in the setting of a suspicious clinical setting, we image initially with DOTATATE.
When imaging GEP-NETs when there is a histologic diagnosis, we first consider the Ki-67 index.

Table 2: Histologic classification of pancreatic neuroendocrine tumors

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Mitotic count (per 2 mm²)</th>
<th>Ki-67 Index (%)</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated</td>
<td>Low grade (G1)</td>
<td>&lt;2</td>
<td>≤2</td>
<td>NET, Grade 1</td>
</tr>
<tr>
<td>Well-differentated</td>
<td>Intermediate grade (G2)</td>
<td>2-20</td>
<td>3-20</td>
<td>NET, Grade 2</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High grade (G3)</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>NET, Grade 3</td>
</tr>
</tbody>
</table>
Neuroendocrine tumors: The DOTAs

- If tumor is low or intermediate grade (G1 or G2), patient will be imaged with Ga-68 DOTATATE PET-CT
- Grade 3 tumors will usually have F-18 FDG PET-CT
- Demonstrating somatostatin receptor density and avidity to DOTA in grades 1 and 2 tumors can have important implications for therapy
- FDG does not provide any information on receptor status
Neuroendocrine tumors: The DOTAs

Possible imaging scheme for GEP-NETs
There is no particular prep for the patients, however, Sandostatin must be discontinued.

In patients receiving long acting Sandostatin as a monthly injectable, PET scan is scheduled to take place at a time just before the next dose is to be given.

Patients may be placed on short-acting Sandostatin temporarily if there are excessive symptoms which should be discontinued 24 hours before the scan is to take place.
Neuroendocrine tumors: The DOTAs

Axial PET and fused PET-CT Ga-68 DOTATATE
Neuroendocrine tumors: The DOTAs

Axial PET and fused PET-CT in patient with metastatic NET of unknown origin
Axial PET and fused images in same patient shows uptake in terminal ileum. Primary lesion confirmed at surgery.
Theranostics is the evolving discipline in molecular imaging where the agent used to image tumor receptors can also be used to treat the patient.

In the case of NETs, Ga-68 can be substituted with Lu-177, a beta emitter, in the DOTATATE complex.

In order to treat patients, a Ga-68 DOTA scan is done first to stage the patient as well as to confirm sst receptor avidity.
Neuroendocrine tumors: Theranostics

Ga-68 and Lu-177 DOTATATE
NETTER-1 phase III trial studied the results of patients treated with Lu-177 DOTA

- 230 patients enrolled
- Compared Lu-177 DOTA 200mCi q 8 weeks against long-acting Octreotide 60mg given every 4 weeks
- Showed significantly better progression free survival, overall survival and overall response rate
Lu-177 DOTA currently not FDA approved but available through an expanded access protocol through clinicaltrials.gov

Initial indication was for midgut neuroendocrine tumors but has recently expanded to include all neuroendocrine tumors

Inclusion criteria include pts with metastatic, locally advanced or inoperable disease

For G1 and G2 tumors that must have presence of somatostatin receptors with diagnostic imaging (Ki-67 <20%)

Pts should have documented progression of disease while on standard therapy (Octreotide LAR)
The treatment protocol lasts about 4 hours.

Patients receive an infusion of amino acids throughout the protocol which begins 30 minutes before infusion of Lu-177 DOTA.

Amino acids are for renal protection.

Most common side effect of therapy is nausea which is a result of the amino acids rather than the Lu-177 DOTA so generous administration of anti-emetics is given.
Premedication: May include odansetron, dexamethasone, famotidine for nausea and gastric protection
Our premedication regimen is:

- Fosaprepitant 150mg IV over 30 minutes
- Kytril 1mg IV push 30 minutes before Lutathera

Breakthrough anti-emetics are:

- Odansetron 8mg po q8 prn(1st)
- Compazine 10mg po q6 prn(2nd)
- Ativan 1mg IV q4 prn(3rd)
- Zyprexa 5mg x 1(4th)*

* Caution advised due to possible sedation
Neuroendocrine tumors: Theranostics

- In the expanded access program, doses are made in Italy and sent to the US for distribution to the facility.
- The day of treatment, one or two IVs may be placed for infusion of the Lutathera and the amino acids.
- The Lutathera is delivered in a protected vial.
- To deliver therapy, a short needle is inserted into the vial to infuse saline.
- Short needle should be positioned above the fluid in the vial.
Neuroendocrine tumors: Theranostics

- A second long needle is inserted into the vial which extend to the bottom
- The second needle infuses toward the patient to deliver the dose

Long needle

Short needle

Fluid interface
Through the expanded access protocol, pts will receive infusions every 8 weeks x 4

Should be off somatostatin before therapy administered but may resume afterwards

We perform a Bremsstrahlung scan after the treatment to document delivery to targets

Bremsstrahlung scan should mirror the pre-treatment Ga-68 DOTATATE PET scan
Neuroendocrine tumors: Theranostics

Ga-68 DOTATATE PET-CT

Lu-177 DOTATATE SPECT-CT
Neuroendocrine tumors: Theranostics

Ga-68 DOTATATE PET-CT

Lu-177 DOTATATE SPECT-CT
We were frustrated with the difficulty using the 2 needle method and decided there should be a better way. To determine delivery of the Lu-177, the line exiting the vial to the patient had to be surveyed until the dpm’s decreased to a constant value. Dose monitoring was difficult and time consuming and also exposed the staff to excess radiation. Treated patients receive a large volume of fluid and frequently need to void. The initial infusion method made this very difficult.
Our Solution
Carilion Infusion Device and Method
Carilion Infusion Device and Method

Lutetium in pig
Carilion Infusion Device and Method

Received dose in dose calibrator
Carilion Infusion Device and Method

Removing 30cc of volume from 50cc bag
Carilion Infusion Device and Method

Lutetium vial behind L-block with short vent needle in place
Carilion Infusion Device and Method

Withdrawing Lu-177 from vial with long spinal needle that reaches bottom of the vial
Carilion Infusion Device and Method

Residual in vial after withdrawal of dose
Carilion Infusion Device and Method

Injecting Lu-177 into 50cc saline bag
Carilion Infusion Device and Method

Residual in syringe after delivery into saline bag
Dose in saline bag with bag in dose calibrator. Geometry issues apply regarding the measurement in the vial versus in the pliable bag.
Carilion Infusion Device and Method
Carilion Infusion Device and Method

Infusion device loaded into delivery box for transport to patient room
Carilion Infusion Device and Method

Adding saline to the syringe used to remove the Lu-177 from vial to capture the residual
Infusion device and syringe loaded into the delivery box for transport to the patient’s room.
Carilion Infusion Device and Method

Device on IV pole with amino acids
Carilion Infusion Device and Method

Flushing saline bag with syringe containing residual dose and infusing remainder into patient
Conclusion

- The theranostic approach presented is the cornerstone of future treatment options for numerous malignancies.
- Next in line in the US is most likely PSMA for imaging and therapy.
- Wherever tumor targets/receptors are identified in various cancers, these represent a possible way to image a tumor, define its presence or absence of certain receptors and then target these for therapy.
- Multiple tracers may be necessary in heterogeneous tumors which can potentially be used as a “non-invasive biopsy.”