Neuroendocrine tumors

PAST AND PRESENT DIAGNOSIS AND TREATMENT

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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

Neuroendocrine tumors: Basics

- 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

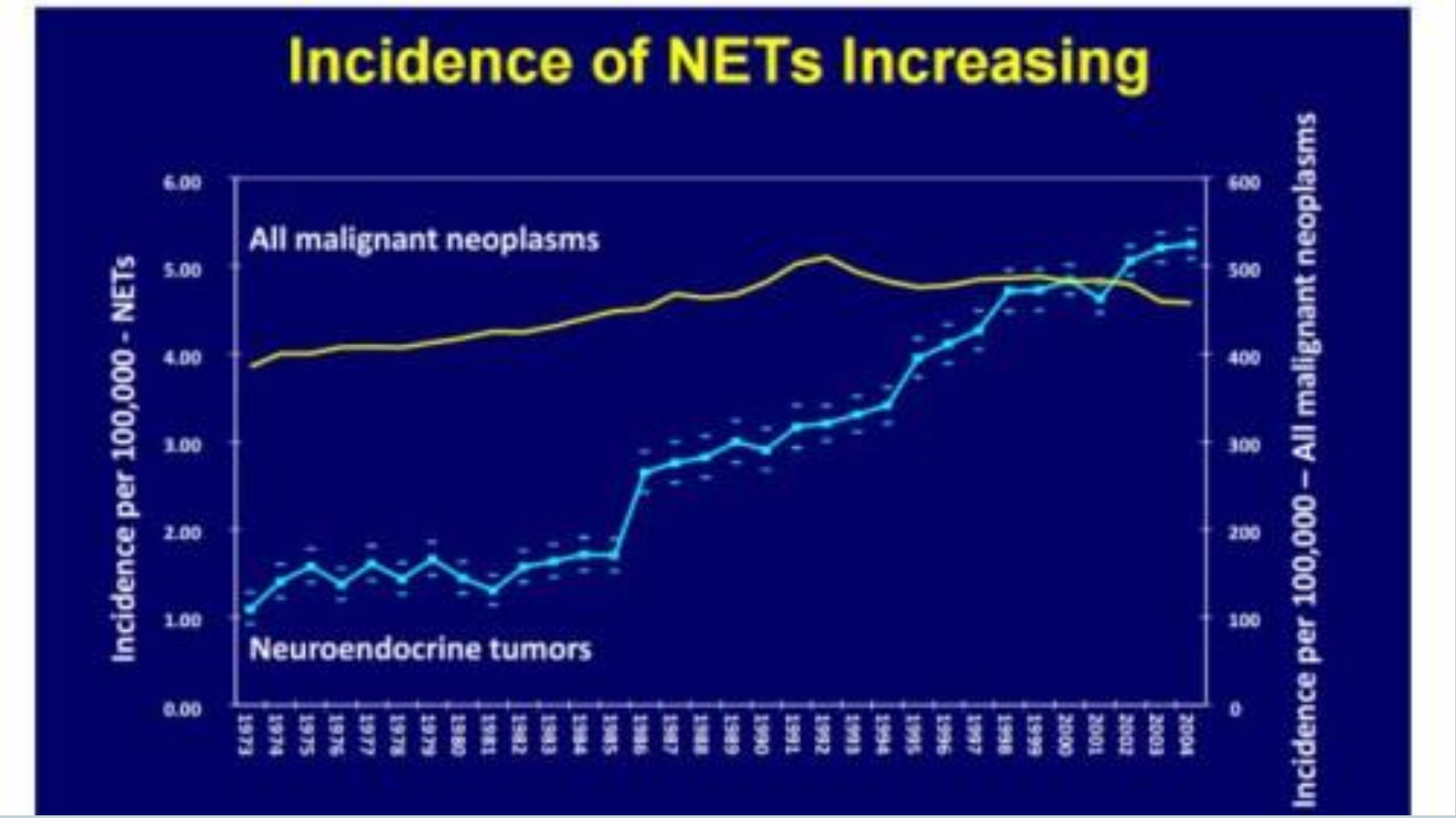
Neuroendocrine tumors: Basics

- 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

Neuroendocrine tumors: Patient presentation

- 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

Neuroendocrine tumors: Patient presentation

- 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

Neuroendocrine tumors: Patient presentation

- Several laboratory markers may be abnormal and include:
  - Chromogranin A
  - 5-hydroxyindolacetic acid (5-HIAA)
  - Synaptophysin (found in presynaptic vesicles)
  - Neuron-specific enolase

Neuroendocrine tumors: Molecular Imaging

- 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

Neuroendocrine tumors: Molecular Imaging

- 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

Neuroendocrine tumors: Molecular Imaging

- 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

Molecular Imaging: MIBG

- 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

Molecular Imaging: MIBG

- 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

Molecular Imaging: MIBG

- 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

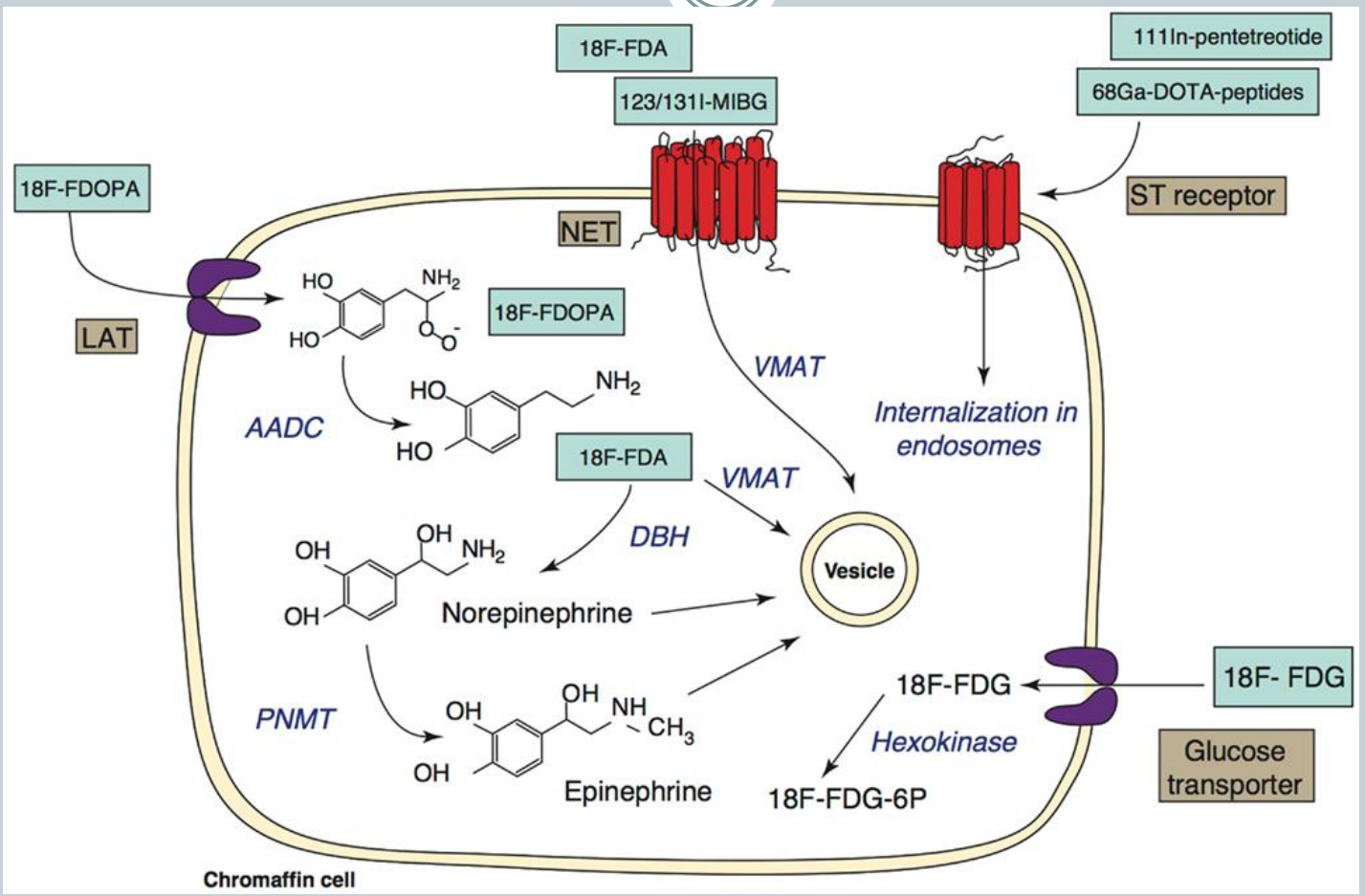
Molecular Imaging: MIBG

Other adrenoreceptor stimulants	Orciprenaline	24 hours	*3*
Systemic and local nasal decongestants, compound cough and cold preparations	Pseudoephedrine	48 hours	**3**
	Phenylephrine	48 hours	**3**
	Ephedrine	24 hours	**1**
	Xylometazoline	24 hours	**3**
	Oxymetazoline	24 hours	**3**
Sympathomimetics for Glaucoma	Brimonidine	48 hours	*3*
	Dipivefrine	48 hours	*3*
NEUROLOGICAL DRUGS			
Antipsychotics (neuroleptics)	Chlorpromazine	24 hours	*1*
	Benperidol	48 hours	*1*
	Flupentixol	48 hours, or 1 month for depot	*1*
	Fluphenazine	24 hours, or 1 month for depot	*1*
	Haloperidol	48 or 1 month for depot	*1*
	Levomepromazine	72 hours	*1*
	Pericyazine	48 hours	*1*
	Perphenazine	24 hours	*1*
	Pimozide	72 hours	*1*
	Pipotiazine	1 month for depot	*1*
	Prochlorperazine	24 hours	*1*
	Promazine	24 hours	*1*
	Sulpiride	48 hours	*1*
	Thioridazine	24 hours	*1*
	Trifluoperazine	48 hours	*1*
	Zuclopenthixol	48 hours, or 1 month for depot	*1*
	Amisulpride	72 hours	*1*
	Clozapine	7 days	*1*
	Olanzapine	7 – 10 days	*1*
	Quetiapine	48 hours	*1*
	Risperidone	5 days or 1 month for depot	*1*
	Sertindole	15 days	*1*
	Zotepine	5 days	*1*
Sedating antihistamines	Promethazine	24 hours	*1*
Opioid analgesics	Tramadol	24 hours	**1**
Tricyclic anti-depressants	Amitriptyline	48 hours	**1**
	Amoxapine	48 hours	1
	Clomipramine	24 hours	**1**
	Dosulepin (Dothiepin)	24 hours	**1**
	Doxepin	24 hours	1
	Imipramine	24 hours	**1**
	Lofepramine	48 hours	**1**
	Nortriptyline	24 hours	1
	Trimipramine	48 hours	**1**
Tricyclic-related anti-depressants	Maprotiline	48 hours	*1*
	Mianserin	48 hours	*1*
	Trazolone	48 hours	*1*
	Venlaflaxine	48 hours	*1*
	Mirtazepine	8 days	*1*
	Reboxetine	3 days	*1*
CNS Stimulants	Amphetamines eg Dexamfetamine	48 hours	*3*
	Atomoxetine	5 days	*1*
	Methylphenidate	48 hours	*5*
	Modafinil	72 hours	*5*
	Cocaine	24 hours	**1**
	Caffeine	24 hours	*5*

Drug Group	Approved name	Recommended withdrawal time	Mechanism of interaction *
CARDIOVASCULAR AND SYMPATHOMIMETIC DRUGS			
Anti-arrhythmics for ventricular arrhythmias	Amiodarone	Not practical to withdraw	**1,3**
Combined □□ blocker	Labetalol	72 hours	**1,3**
Adrenergic neurone blockers	Brethylium	48 hours	*2,3*
	Guanethidine	48 hours	*2,3*
	Reserpine	48 hours	2,3
□- blockers	Phenoxybenzamine (IV doses only)	15 days	**5**
Calcium channel blockers	Amlodipine	48 hours	*4,5*
	Diltiazem	24 hours	4,5
	Felodipine	48 hours	*4,5*
	Isradipine	48 hours	*4,5*
	Lacidipine	48 hours	*4,5*
	Lercanidipine	48 hours	*4,5*
	Nicardipine	48 hours	4,5
	Nifedipine	24 hours	4,5
	Nimodipine	24 hours	4,5
	Nisoldipine	48 hours	*4,5*
	Verapamil	48 hours	**4,5**
Inotropic sympatho-mimetics	Dobutamine	24 hours	*3*
	Dopamine	24 hours	*3*
	Dopexamine	24 hours	*3*
Vasoconstrictor sympathomimetics	Ephedrine	24 hours	1
	Metaraminol	24 hours	3
	Norepinephrine	24 hours	3
	Phenylephrine	24 hours	3
□2 stimulants (sympathomimetics)	Salbutamol	24 hours	*3*
	Terbutaline	24 hours	*3*
	Eformoterol	24 hours	*3*
	Bambuterol	24 hours	*3*
	Fenoterol	24 hours	*3*
	Salmeterol	24 hours	*3*

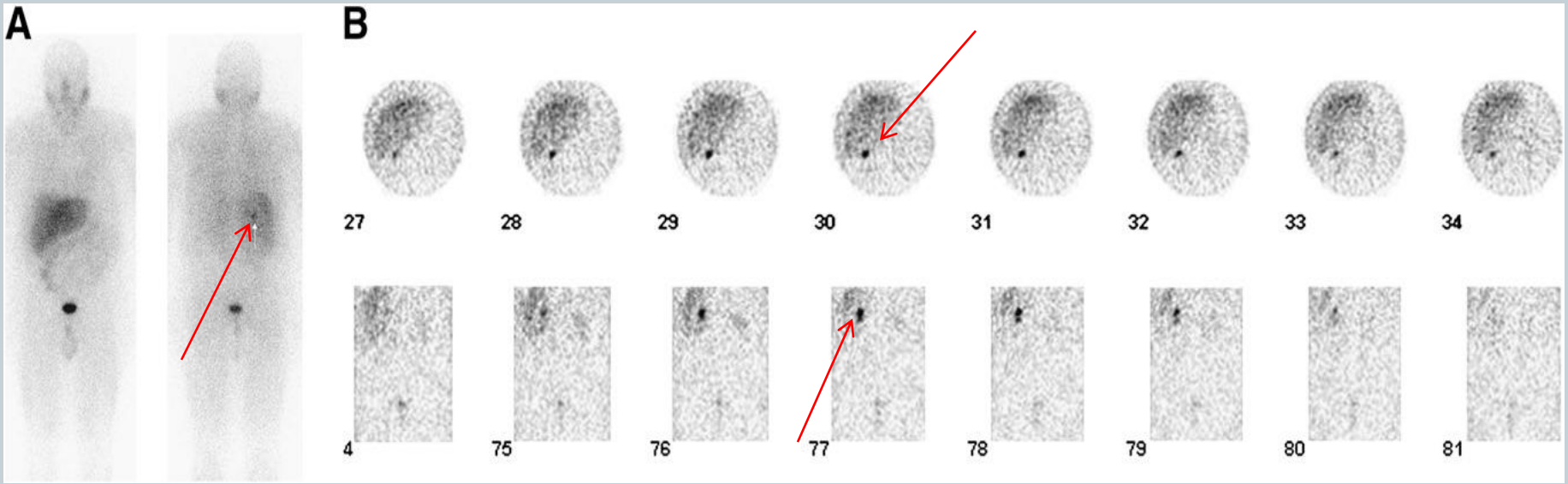
EANM guidelines

Molecular Imaging: MIBG



Proposed pathway for MIBG into chromaffin cell

Molecular Imaging: MIBG



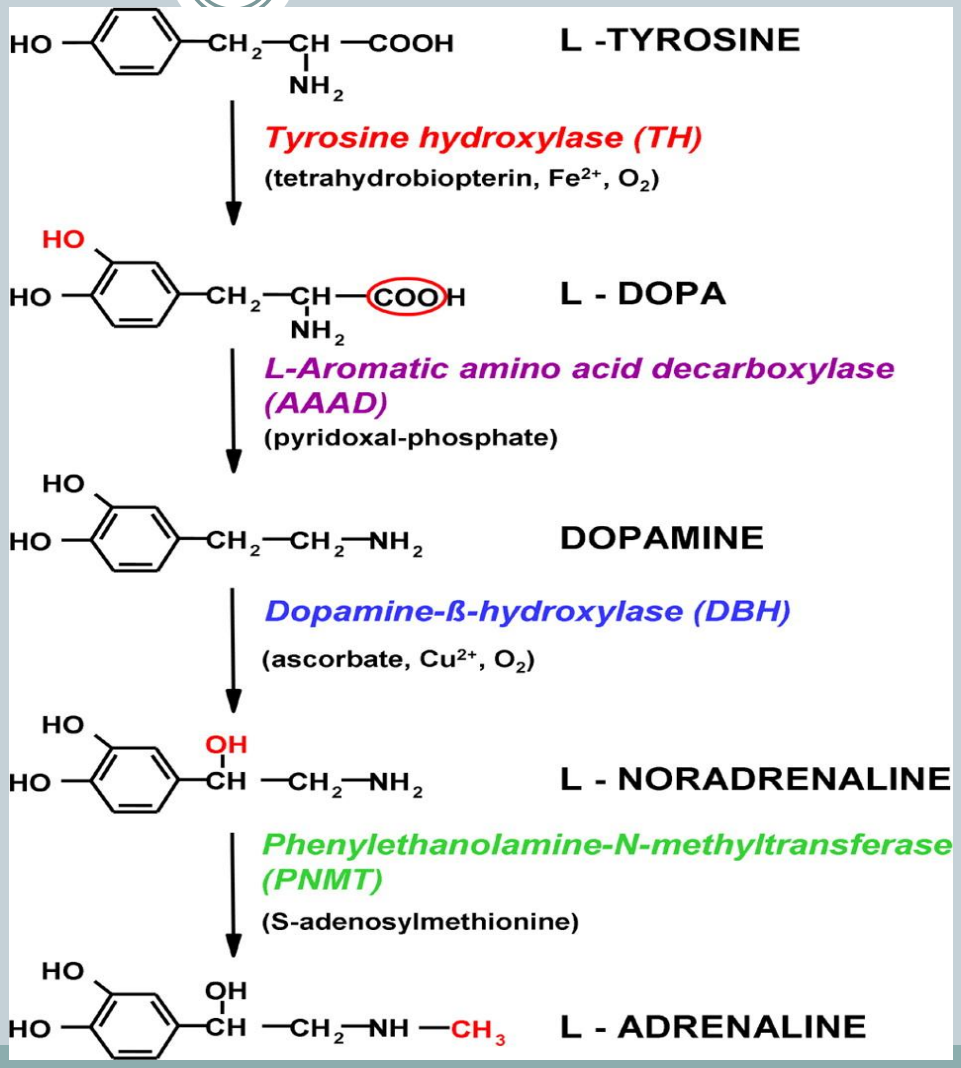
Adrenal pheochromocytoma

Molecular Imaging: L-DOPA

- 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

Molecular Imaging: L-DOPA

L-DOPA metabolism pathway to a biogenic amine



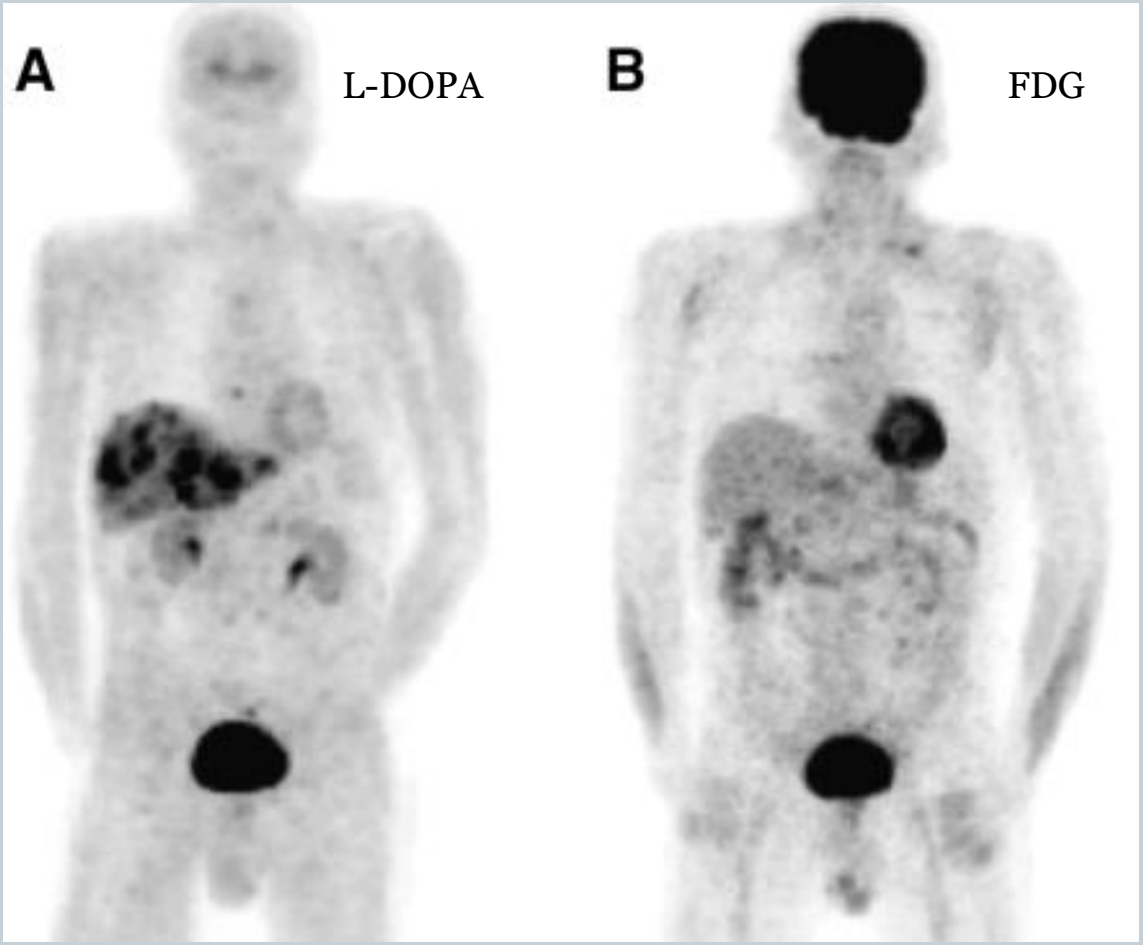
Molecular Imaging: L-DOPA

- 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

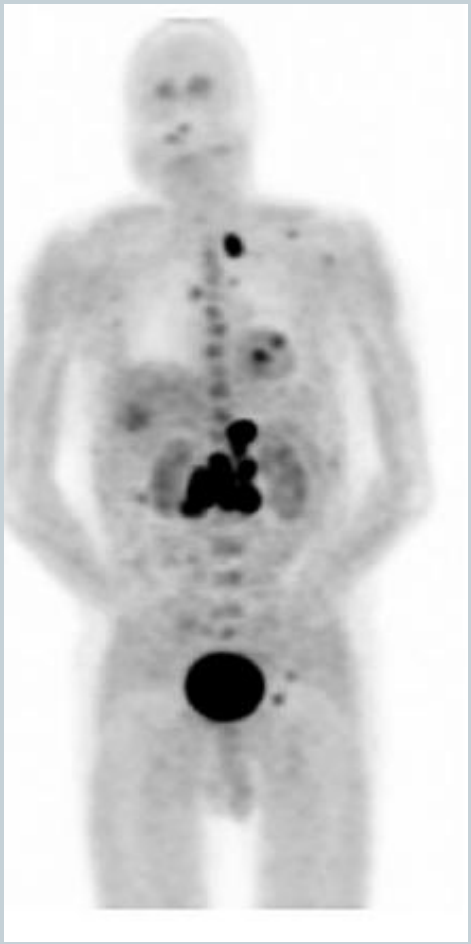
- L-DOPA has better detection of certain NETs over other radiotracers particularly medullary thyroid cancer, non-aggressive catecholamine tumors and well differentiated carcinoid(Balogova *et al*, Eur J Nucl Med Mol Imaging, 2013)
- In tumors with low Ki-67 index as well as with high serotonin, urinary 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



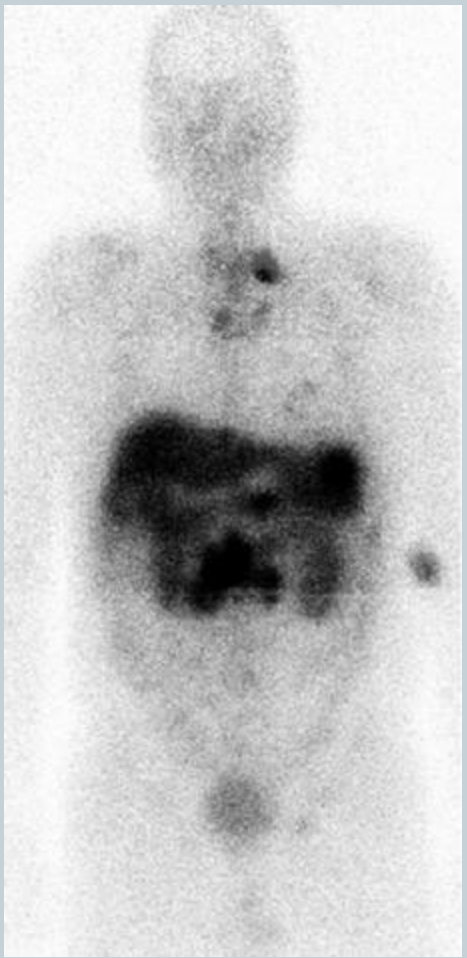
Patient with recurrent MTC, F-18 DOPA vs F-18 FDG

Molecular Imaging: L-DOPA



F-18 DOPA

Pt with metastatic carcinoid. Both scans show a similar distribution of disease but DOPA reveals two myocardial metastases



In-111 Octreotide

Helle-Brit *et al*, Circulation, 2008

Molecular Imaging: Octreoscan

- 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

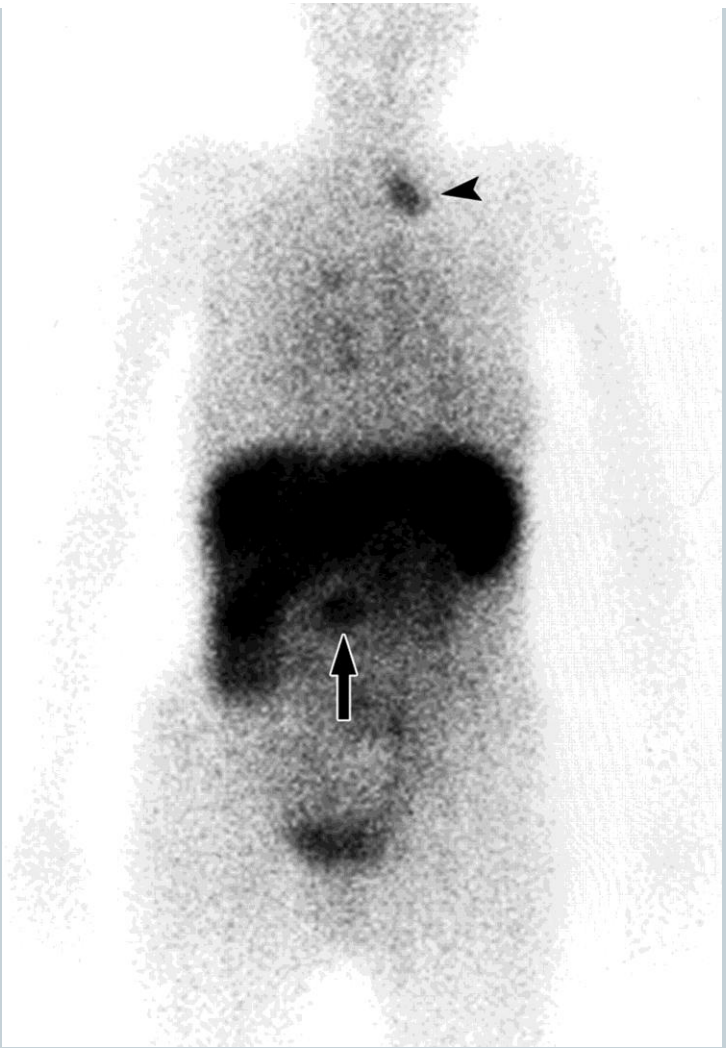
Molecular Imaging: Octreoscan

- 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

Molecular Imaging: Octreoscan

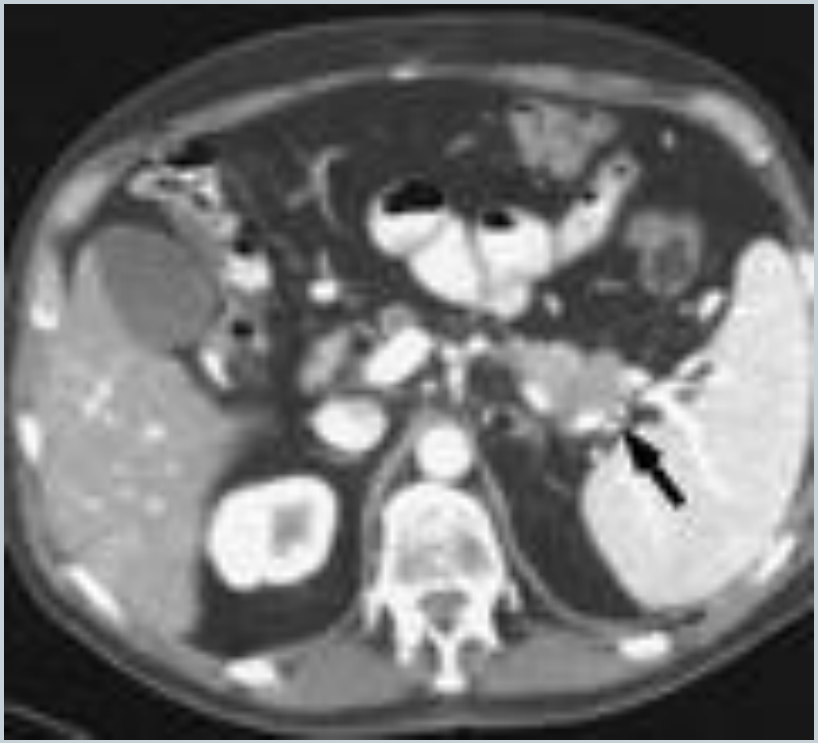
- In pheochromocytoma, there is poor sensitivity with octreotide for well differentiated adrenal lesions with a false negative rate up to 75%(van der Harst *et al*, J Clin Endocrinol Metab, 2001)
- Sensitivity increases with extra-adrenal tumors and there is 87% sensitivity for malignant pheo (van der Harst *et al*, J Clin Endocrinol Metab, 2001)
- MIBG is preferred for well differentiated adrenal tumors

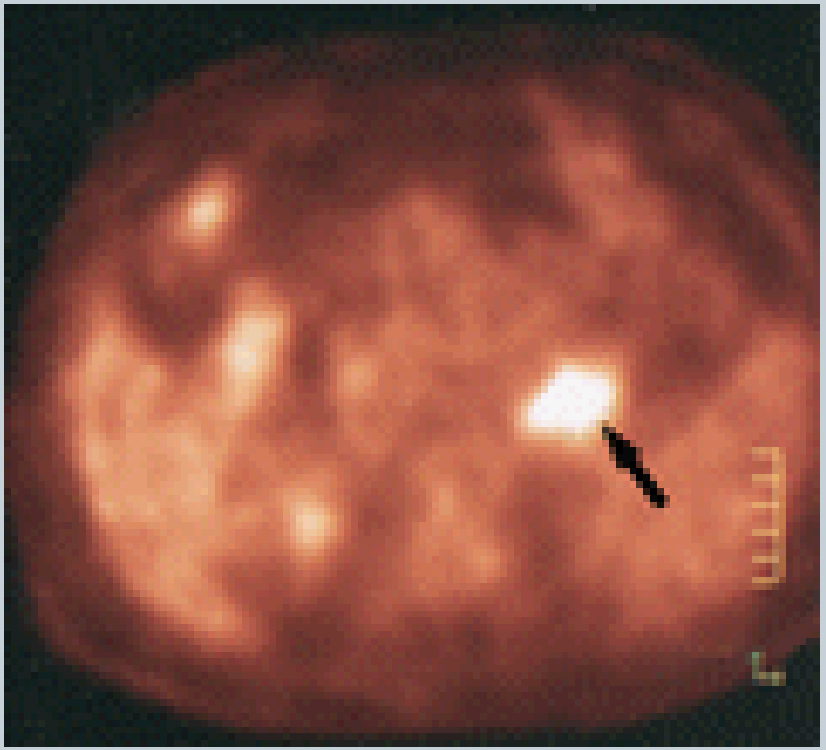
Molecular Imaging: Octreoscan



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

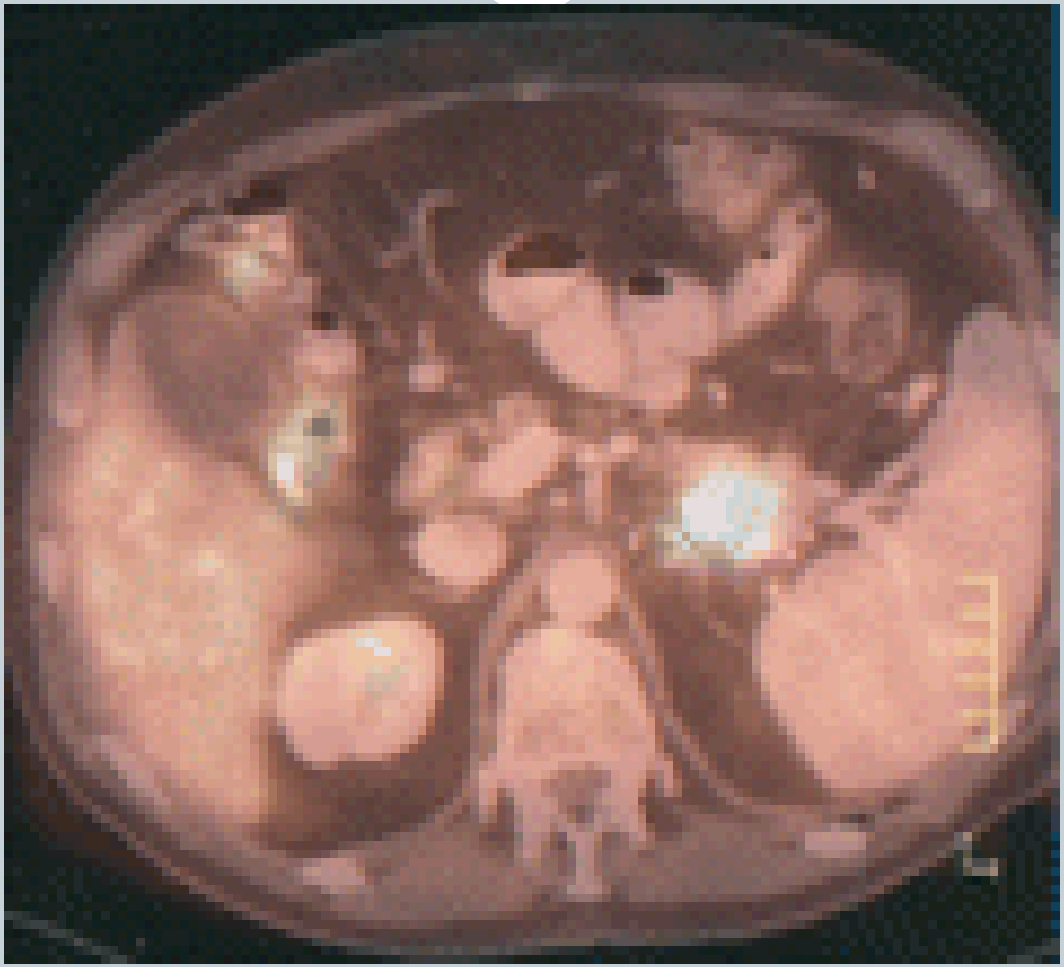
Molecular Imaging: Octreoscan





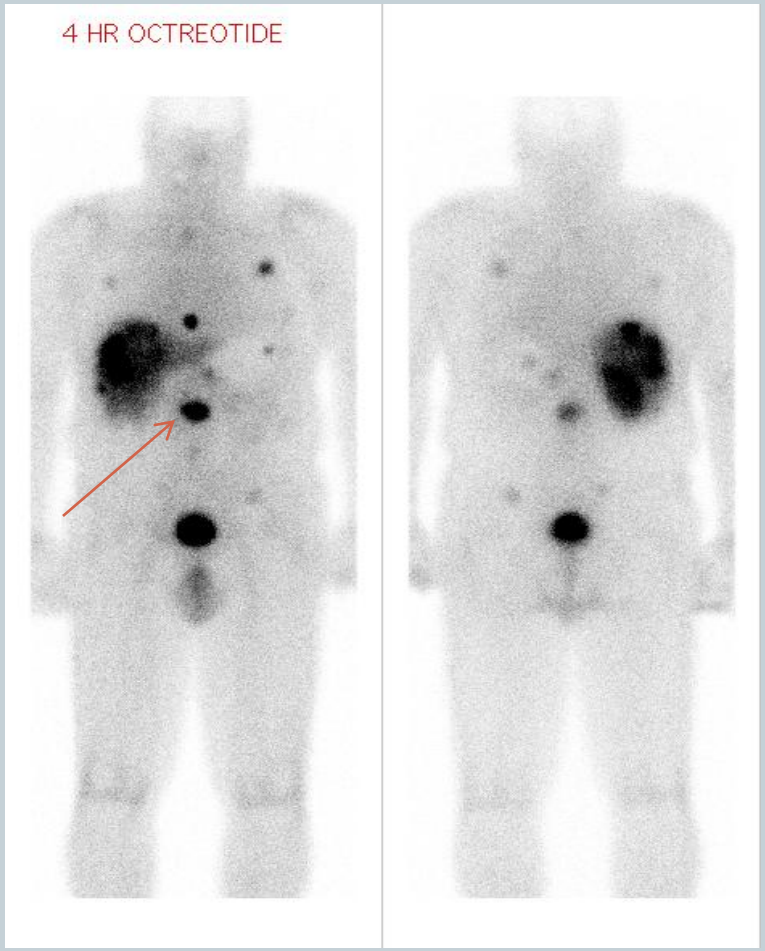
CT and In-111 octreotide SPECT of pancreatic glucagonoma

Molecular Imaging: Octreoscan



In-111 octreotide fused SPECT-CT glucagonoma

Molecular Imaging: Octreoscan

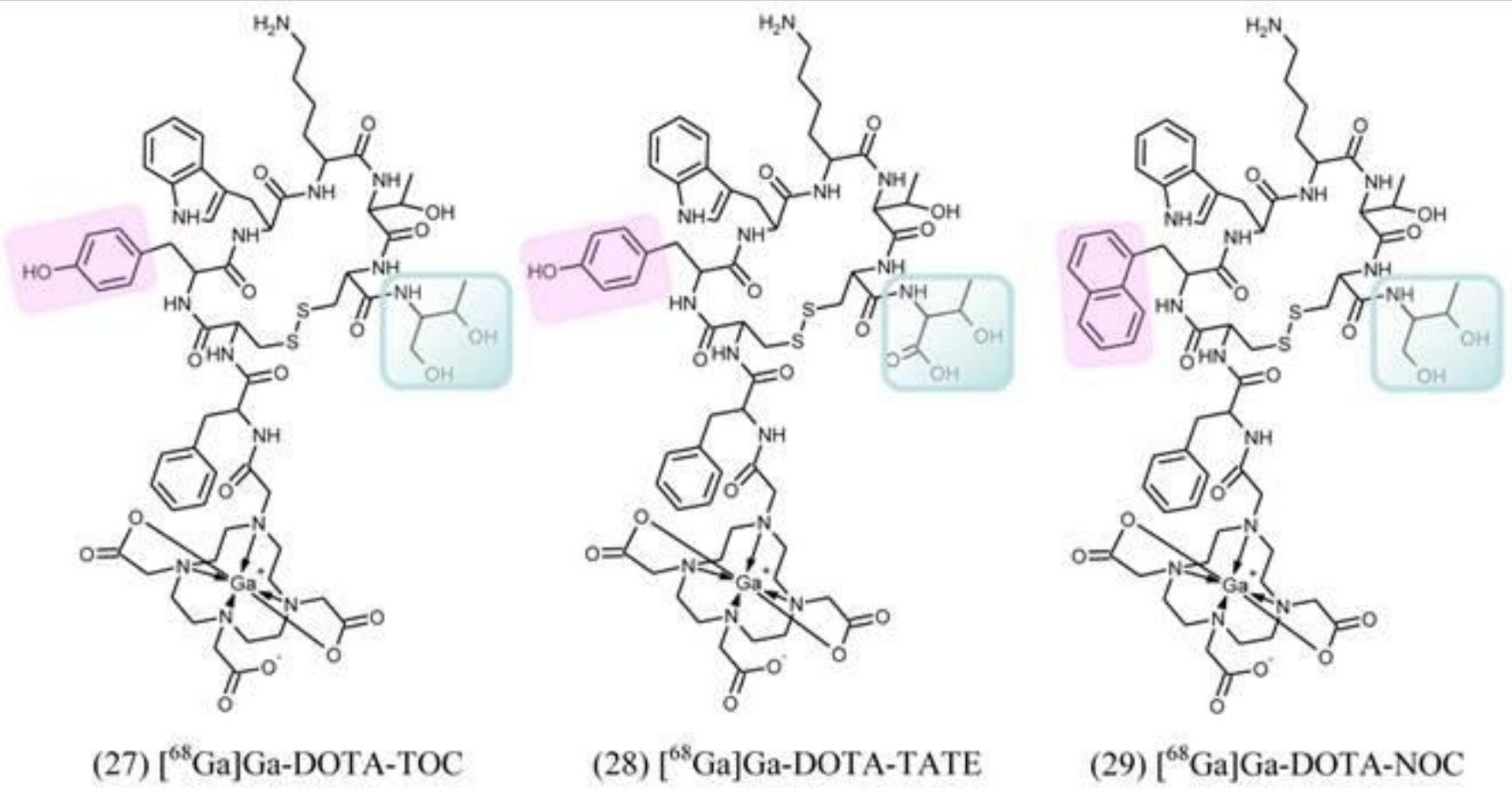


4 hour whole body planar octreotide scan for metastatic insulinoma (arrow)

Neuroendocrine tumors: The DOTAs

- 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}Ga]Ga-DOTA-TOC

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

(29) [^{68}Ga]Ga-DOTA-NOC

Neuroendocrine tumors: The DOTAs

- 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

Neuroendocrine tumors: The DOTAs

- 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

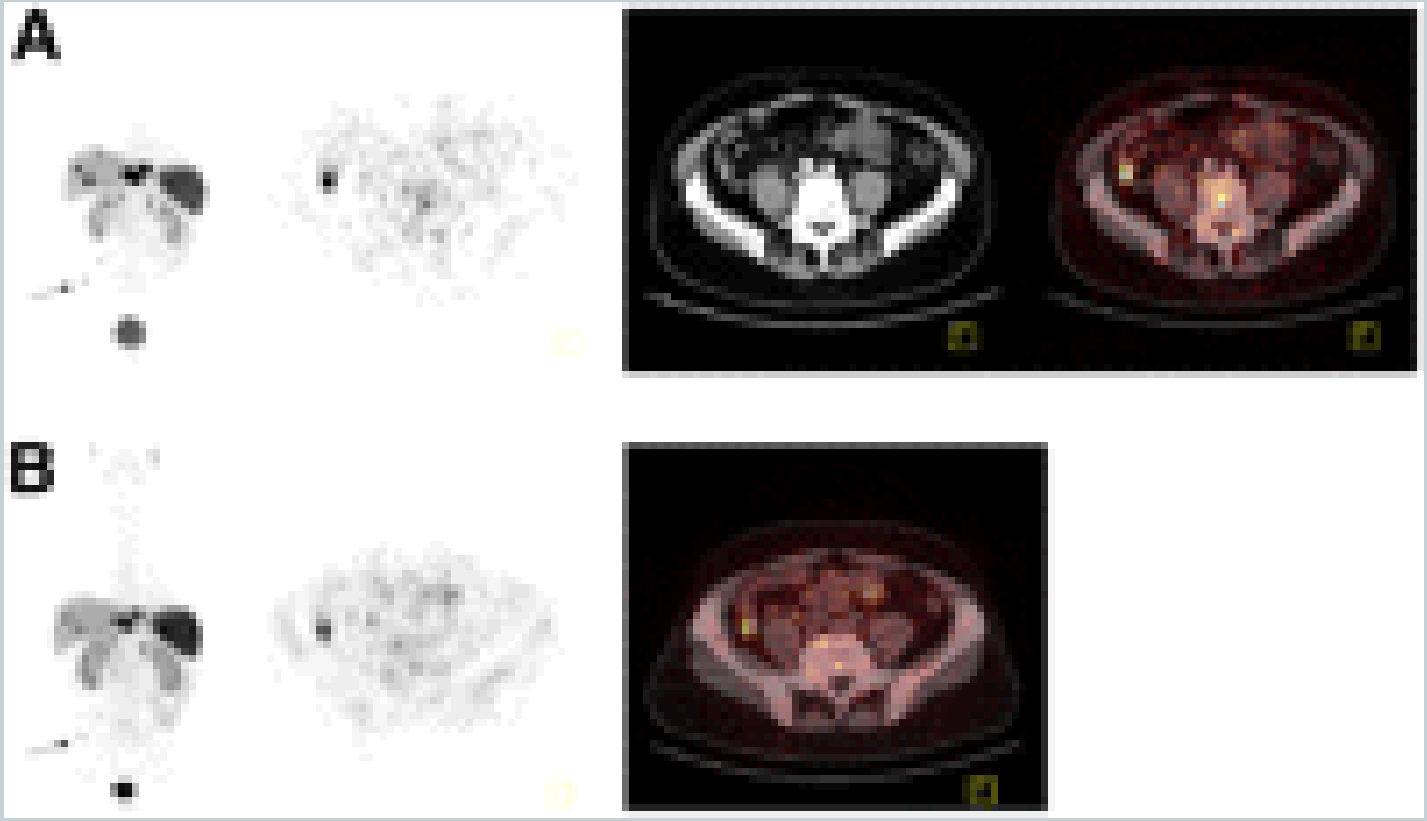
Neuroendocrine tumors: The DOTAs

- 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

TOC

TATE



Same pt with ileal carcinoid-SUVmax for TOC 21 and for TATE 8.2

Neuroendocrine tumors: The DOTAs

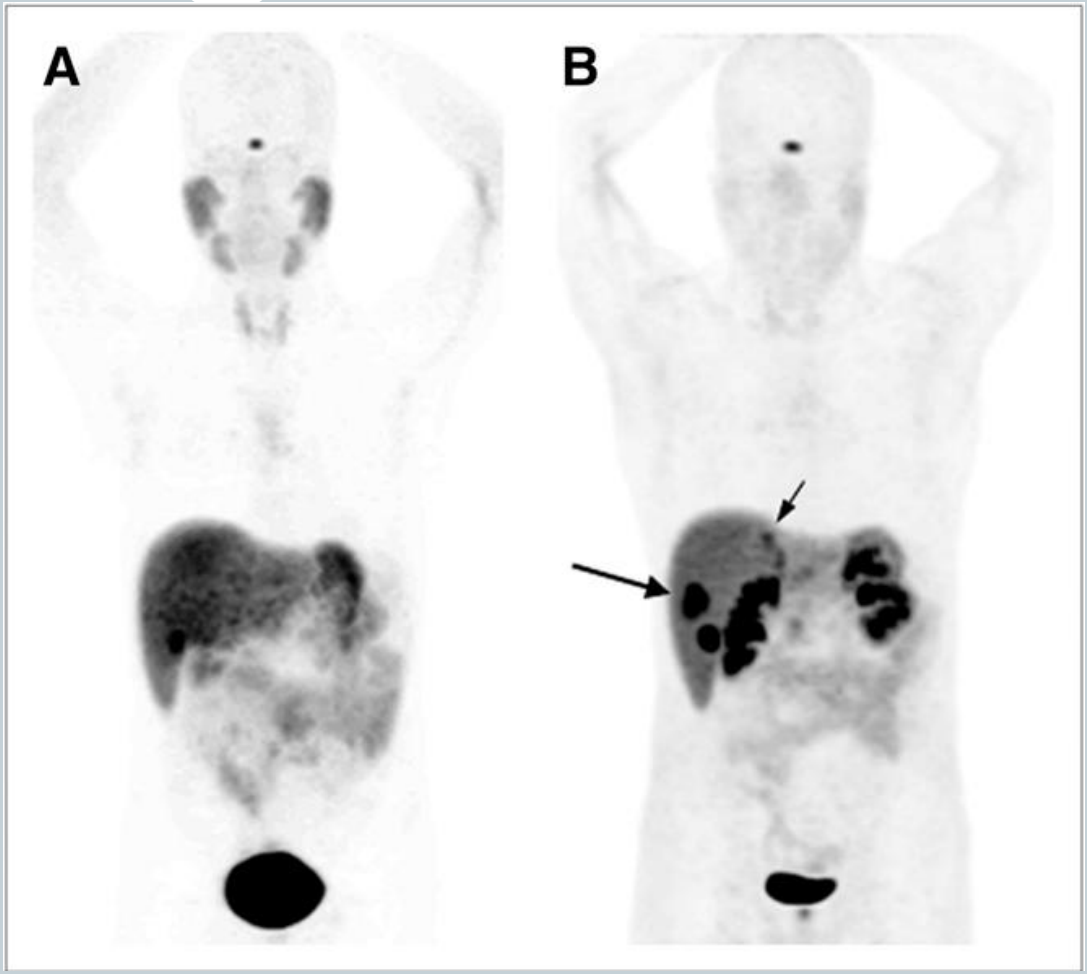
- Because some tumors such as gastrinomas, ileal carcinoids and VIPomas also have a high density of somatostatin sst-5 as well as sst-2, agents targeting other receptors in addition to sst-2 have been developed(Poeppel *et al*, JNM, 2011)
- DOTANOC targets not only sst-2 but also sst-3 and sst-5

Neuroendocrine tumors: The DOTAs

- 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

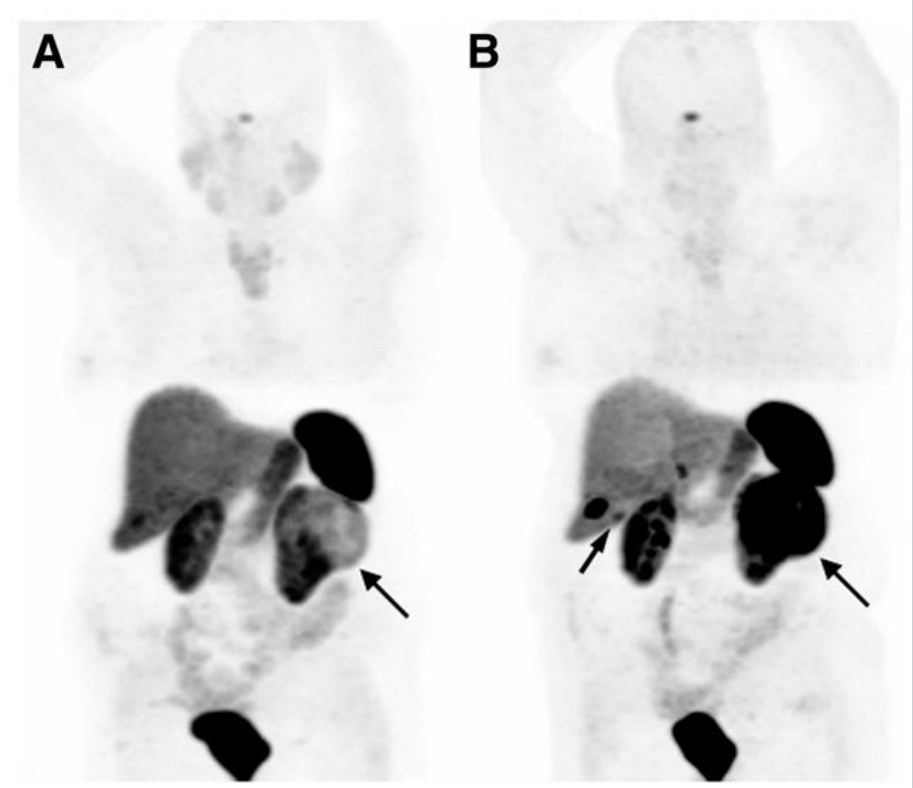
Comparison of DOTATATE and DOTANOC showing better detection of hepatic metastases of NOC



TATE NOC

Neuroendocrine tumors: The DOTAs

TATE NOC



DOTANOC scan shows right lobe liver metastasis not seen on DOTATATE. Left renal metastasis also with greater uptake on NOC compared to TATE

Neuroendocrine tumors: The DOTAs

- The DOTAs show tremendous benefit in sensitivity over octreotide 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

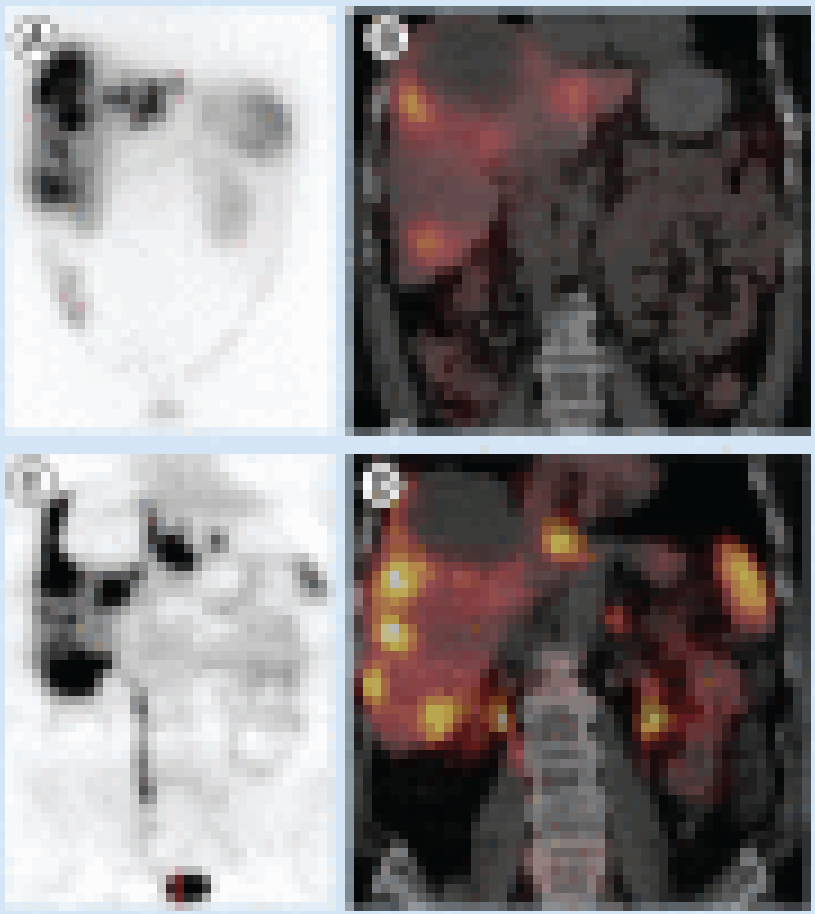
Neuroendocrine tumors: The DOTAs

- 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

Neuroendocrine tumors: The DOTAs

- 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

Neuroendocrine tumors: The DOTAs

- 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

Neuroendocrine tumors: The DOTAs

- 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

Neuroendocrine tumors: The DOTAs

- When imaging GEP-NETs when there is a histologic diagnosis, we first consider the Ki-67 index

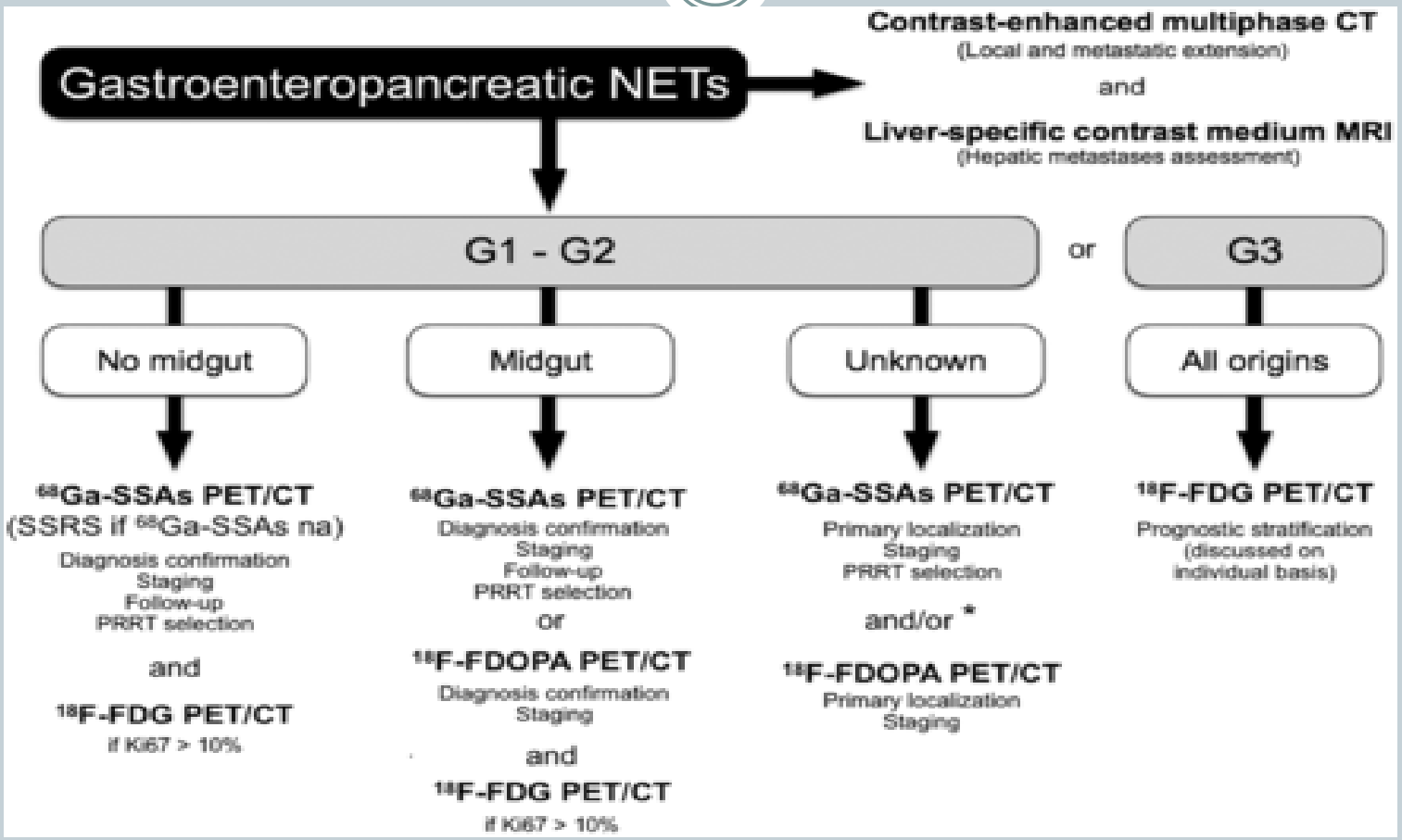
Table 2 Histologic classification of pancreatic neuroendocrine tumors

Differentiation	Grade	Mitotic count (per 2 mm^2)	Ki-67 Index (%)	WHO
Well-differentiated	Low grade (G1)	<2	≤2	NET, Grade 1
Well-differentiated	Intermediate grade (G2)	2-20	3-20	NET, Grade 2
Poorly differentiated	High grade (G3)	>20	>20	NET, Grade 3

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

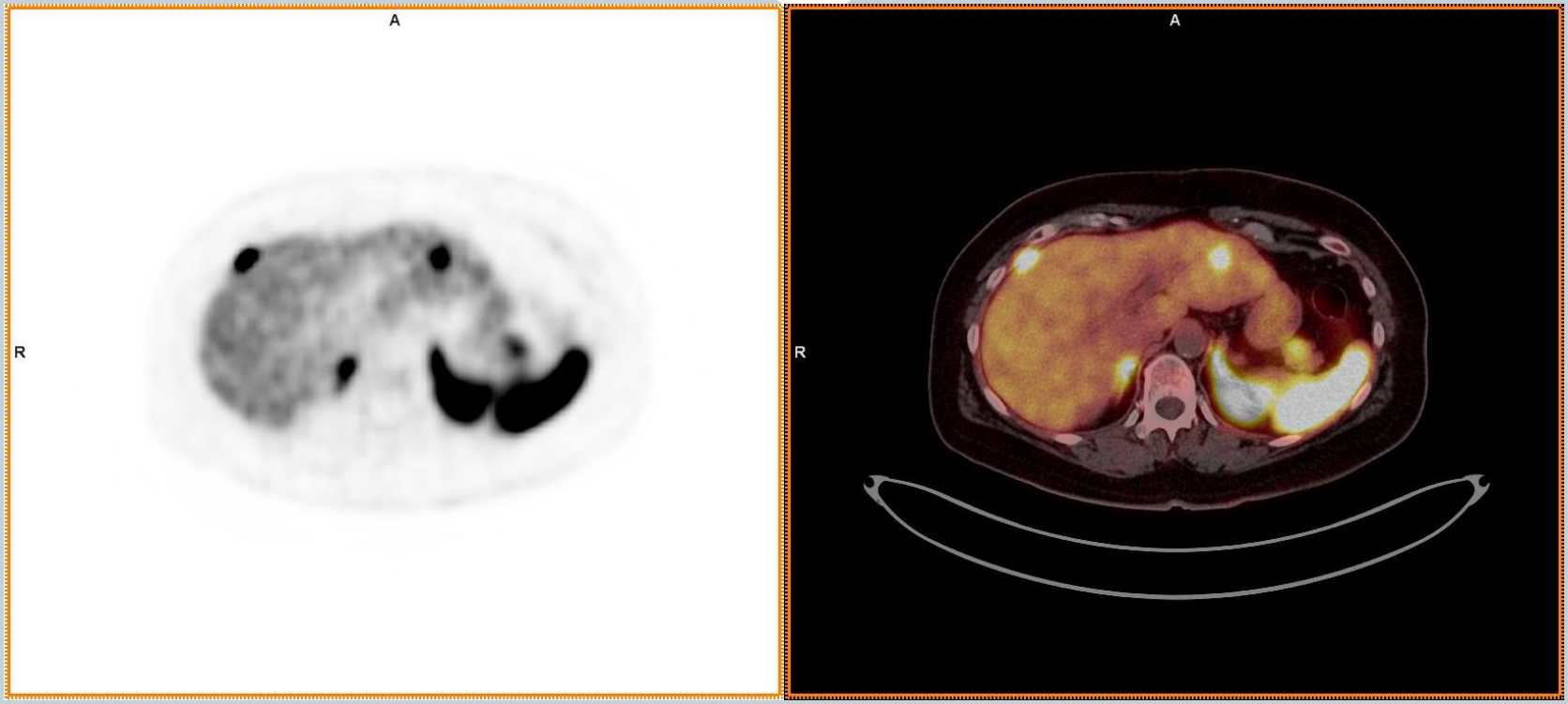


Possible imaging scheme for GEP-NETs

Neuroendocrine tumors: The DOTAs

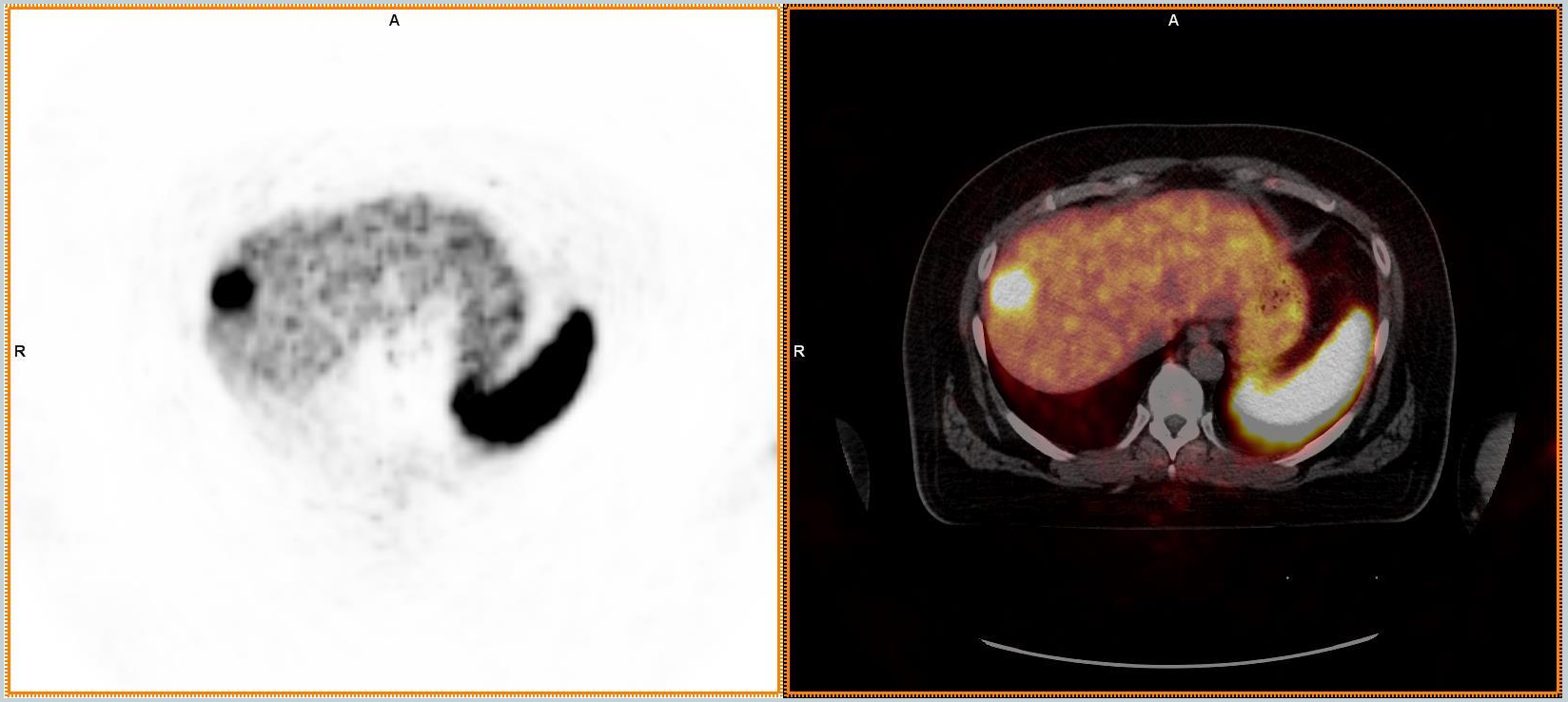
- There is no particular prep for the patients, however, Sandostatin must be discontinued
- In patients receiving long acting Sandostatin as a monthly injectable, PET scan is scheduled to take place at a time just before the next dose is to be given
- Patients may be placed on short-acting Sandostatin temporarily if there are excessive symptoms which should be discontinued 24 hours before the scan is to take place

Neuroendocrine tumors: The DOTAs



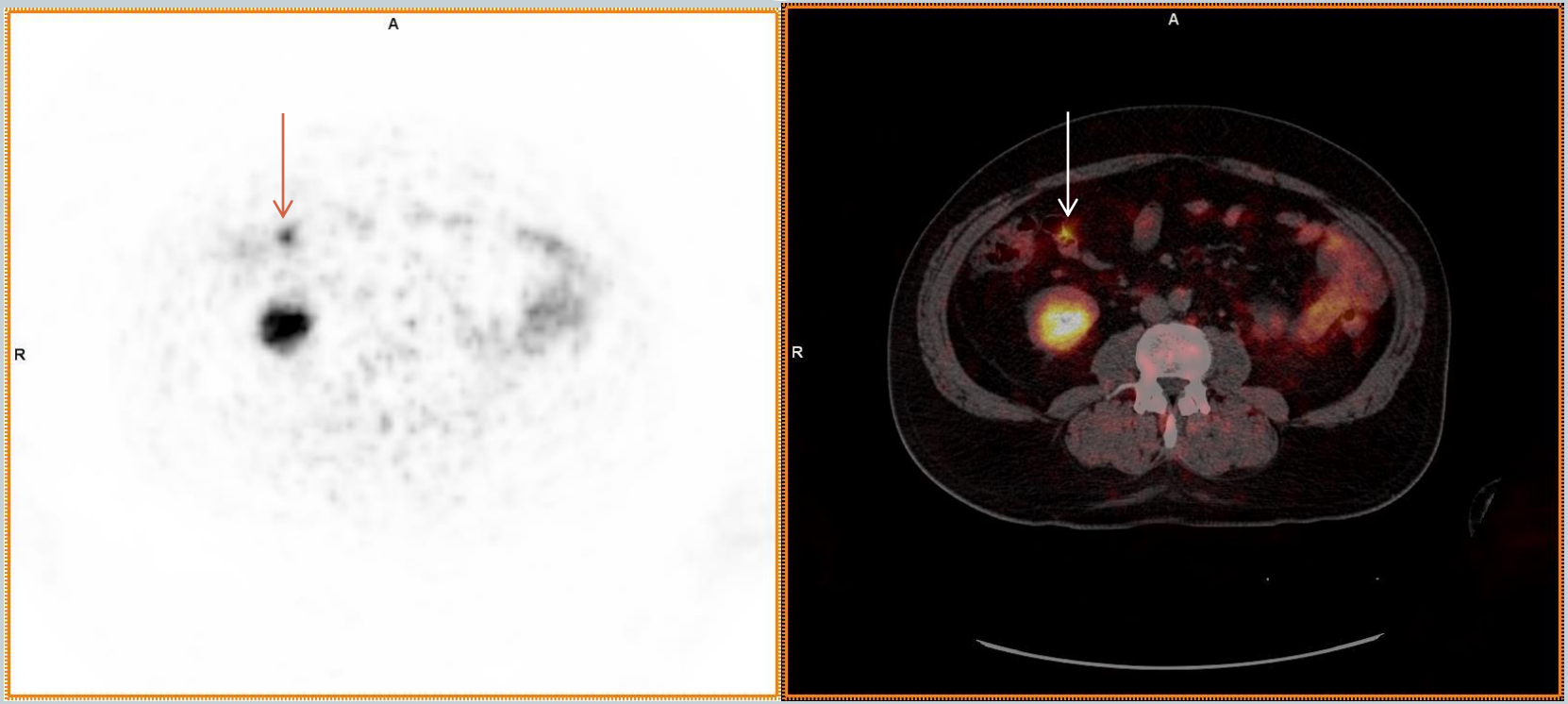
Axial PET and fused PET-CT Ga-68 DOTATATE

Neuroendocrine tumors: The DOTAs



Axial PET and fused PET-CT in patient with metastatic NET of unknown origin

Neuroendocrine tumors: The DOTAs



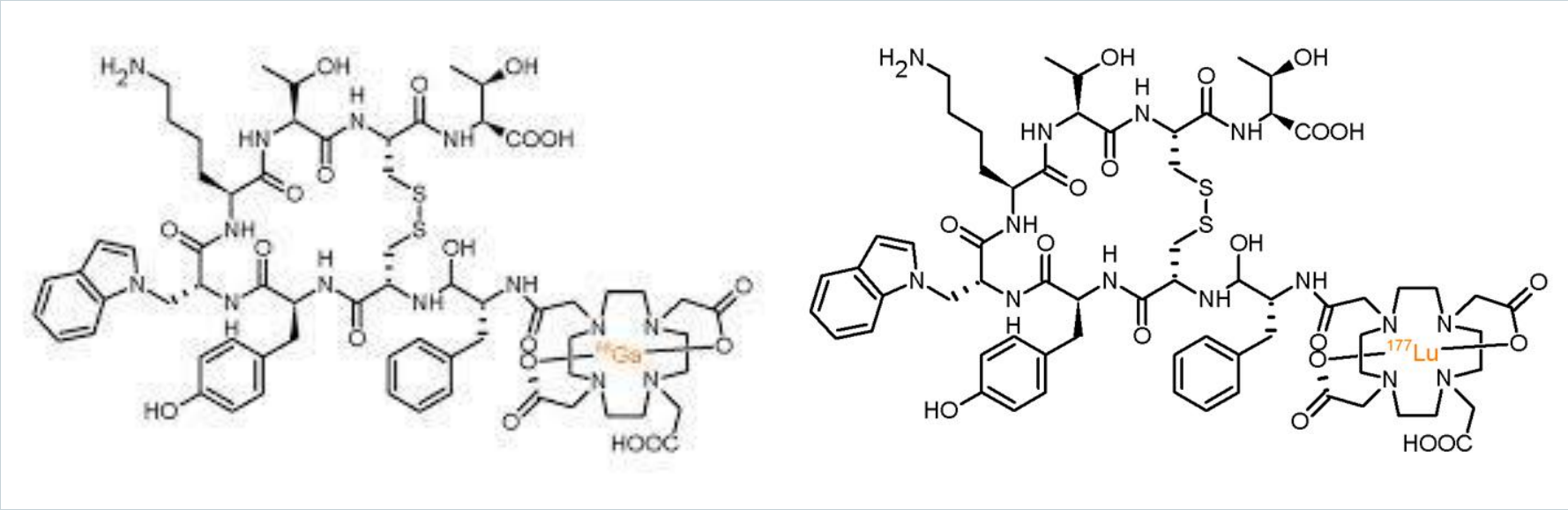
Axial PET and fused images in same patient shows uptake in terminal ileum. Primary lesion confirmed at surgery.

Neuroendocrine tumors: Theranostics

- Theranostics is the evolving discipline in molecular imaging where the agent used to a 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



Neuroendocrine tumors: Theranostics

- 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

Neuroendocrine tumors: Theranostics

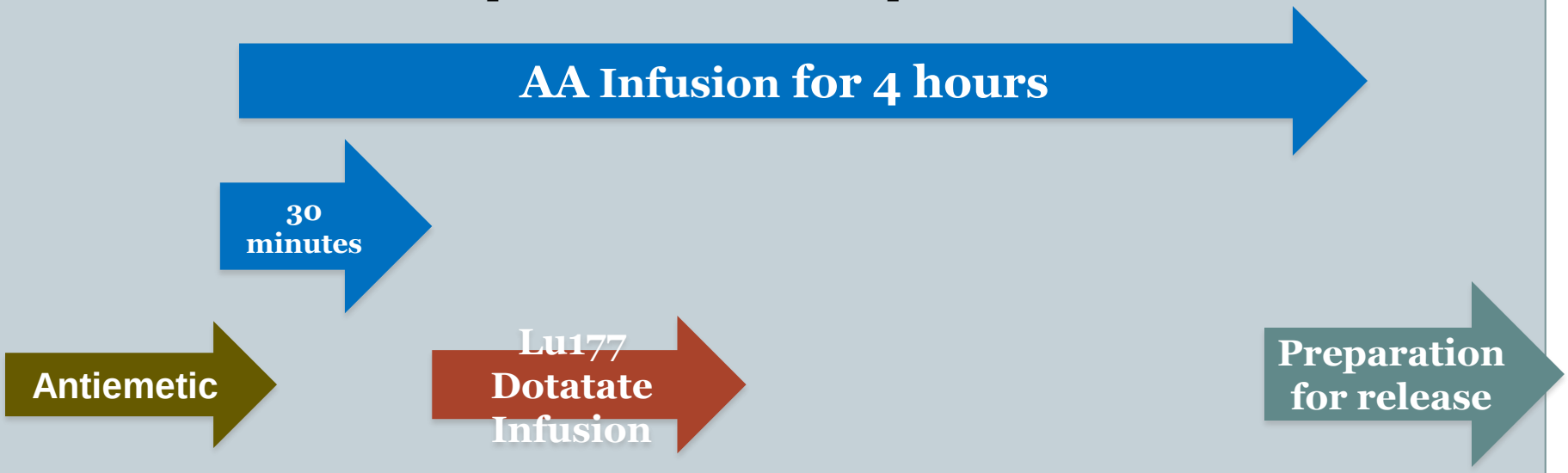
- Lu-177 DOTA currently not FDA approved but available through an expanded access protocol through clinicaltrials.gov
- Initial indication was for midgut neuroendocrine tumors but has recently expanded to include all neuroendocrine tumors
- Inclusion criteria include pts with metastatic, locally advanced 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)

Neuroendocrine tumors: Theranostics

- 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

Neuroendocrine tumors: Theranostics

Proposed administration procedure



Premedication: May include odansetron, dexamethasone, famotidine for nausea and gastric protection

Neuroendocrine tumors: Theranostics

- Our premedication regiment is:
  - Fosaprepitant 150mg IV over 30 minutes
  - Kytril 1mg IV push 30 minutes before Lutathera
- Breakthrough anti-emetics are:
  - Odansetron 8mg po q8 prn(1^{st})
  - Compazine 10mg po q6 prn(2^{nd})
  - Ativan 1mg IV q4 prn(3^{rd})
  - Zyprexa 5mg x 1(4^{th})*

* Caution advised due to possible sedation

Neuroendocrine tumors: Theranostics

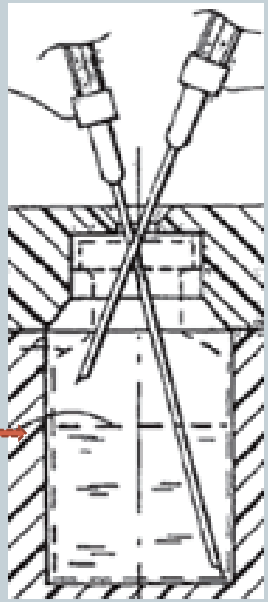
- In the exapanded access program, doses are made in Italy and sent to the US for distribution to the facility
- The day of treatment, one or two IVs may be placed for infusion of the Lutathera and the amino acids
- The Lutathera is delivered in a protected vial
- To deliver therapy, a short needle is 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

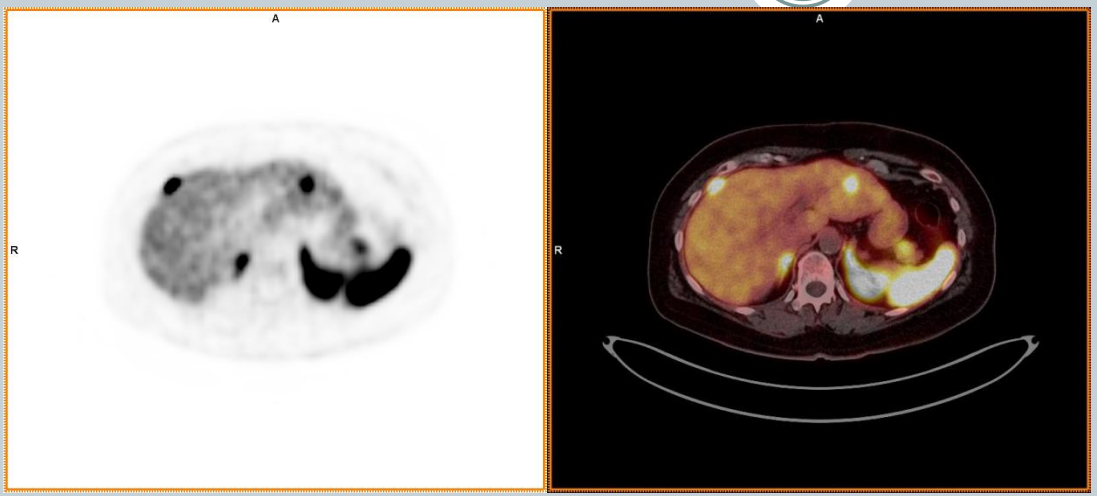


Fluid interface

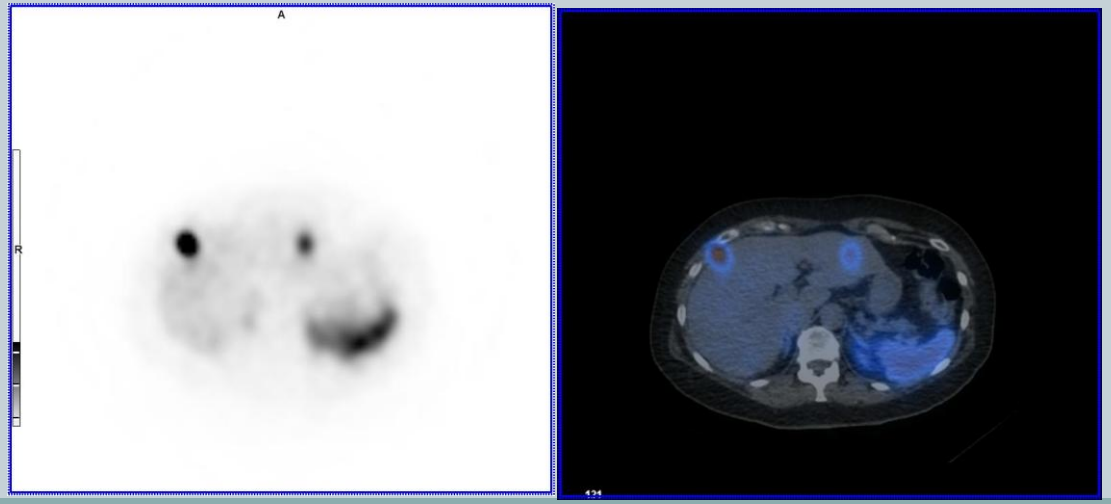
Neuroendocrine tumors: Theranostics

- 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

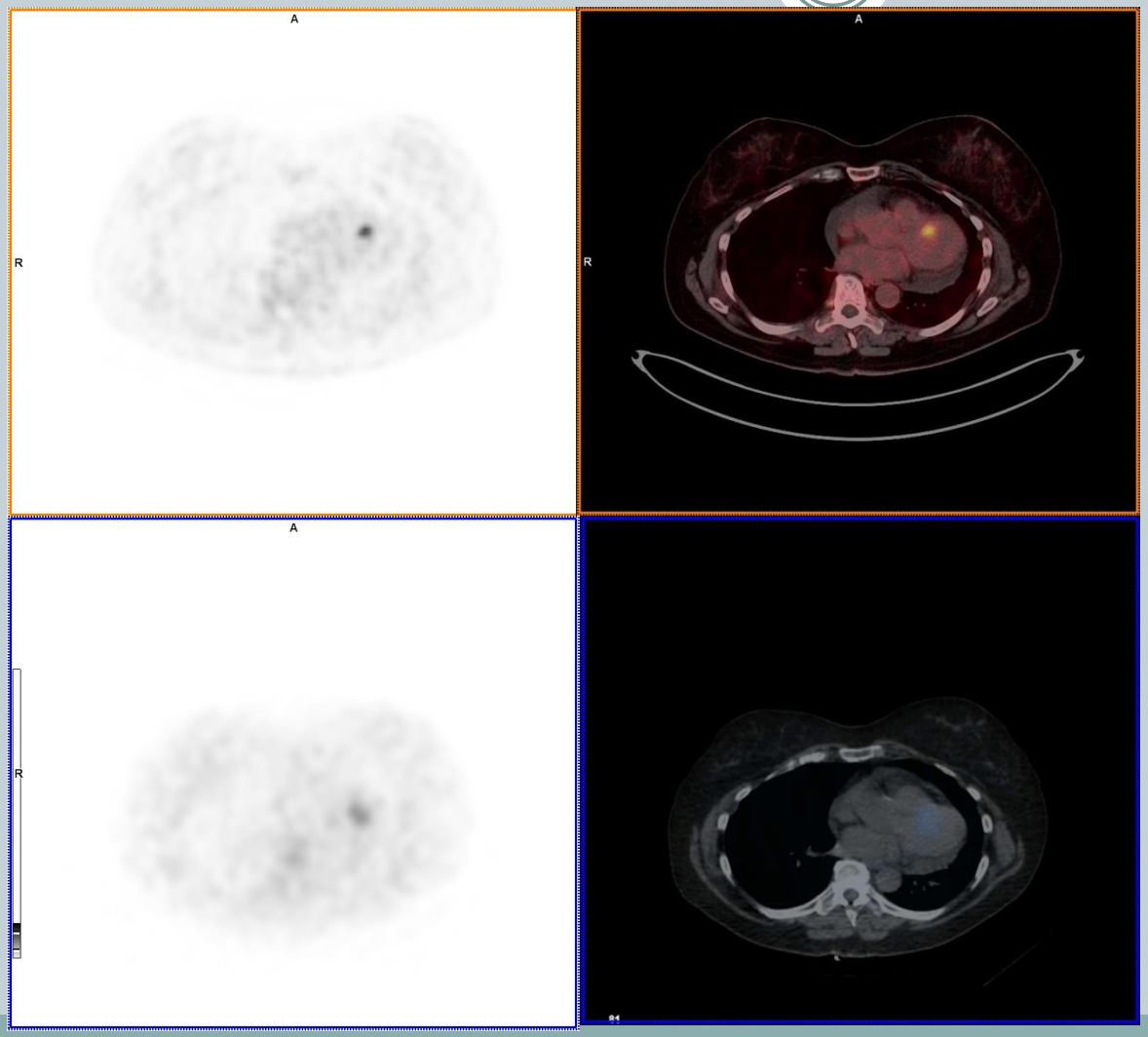


Ga-68 DOTATATE PET-CT



Lu-177 DOTATATE SPECT-CT

Neuroendocrine tumors: Theranostics



Ga-68 DOTATATE PET-CT

Lu-177 DOTATATE SPECT-CT

Carilion Infusion Device and Method

- 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

Carilion Infusion Device and Method

Our Solution

Carilion Infusion Device and Method

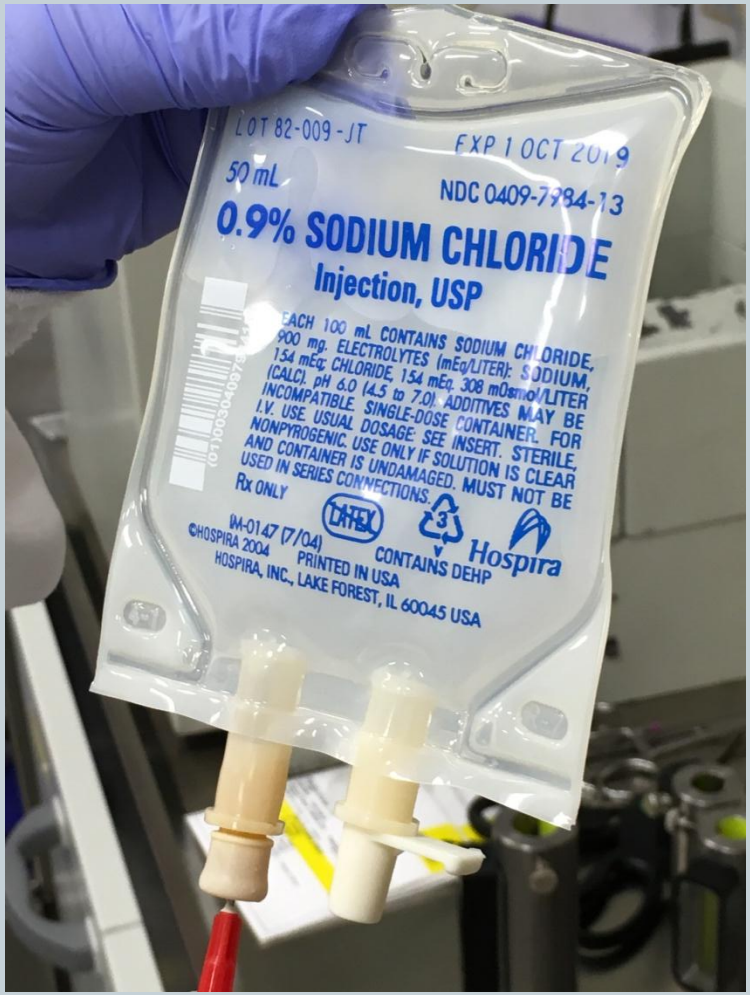
Carilion Infusion Device and Method

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

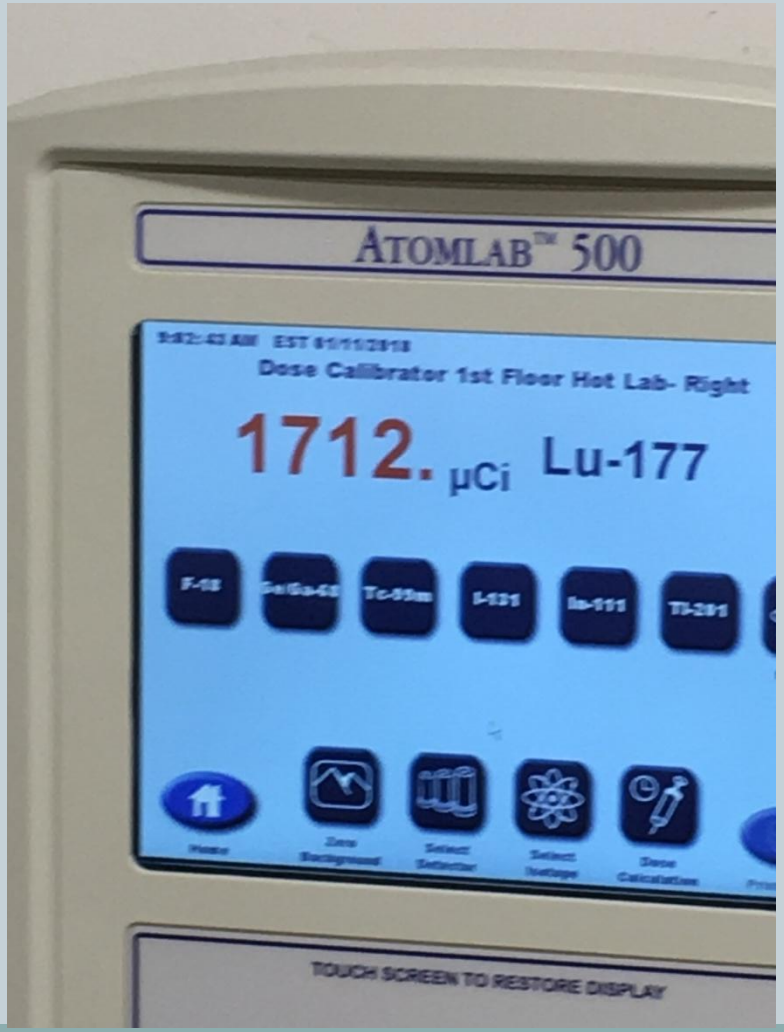
Carilion Infusion Device and Method

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

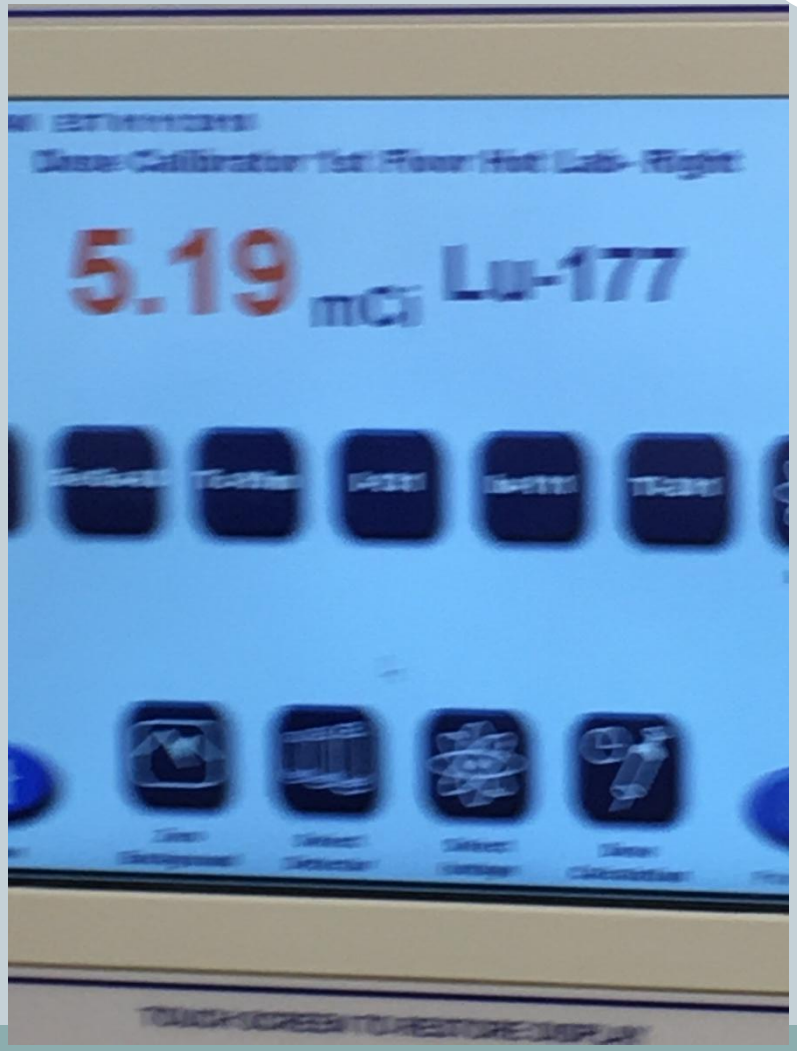


Residual in vial after withdrawal of dose

Carilion Infusion Device and Method

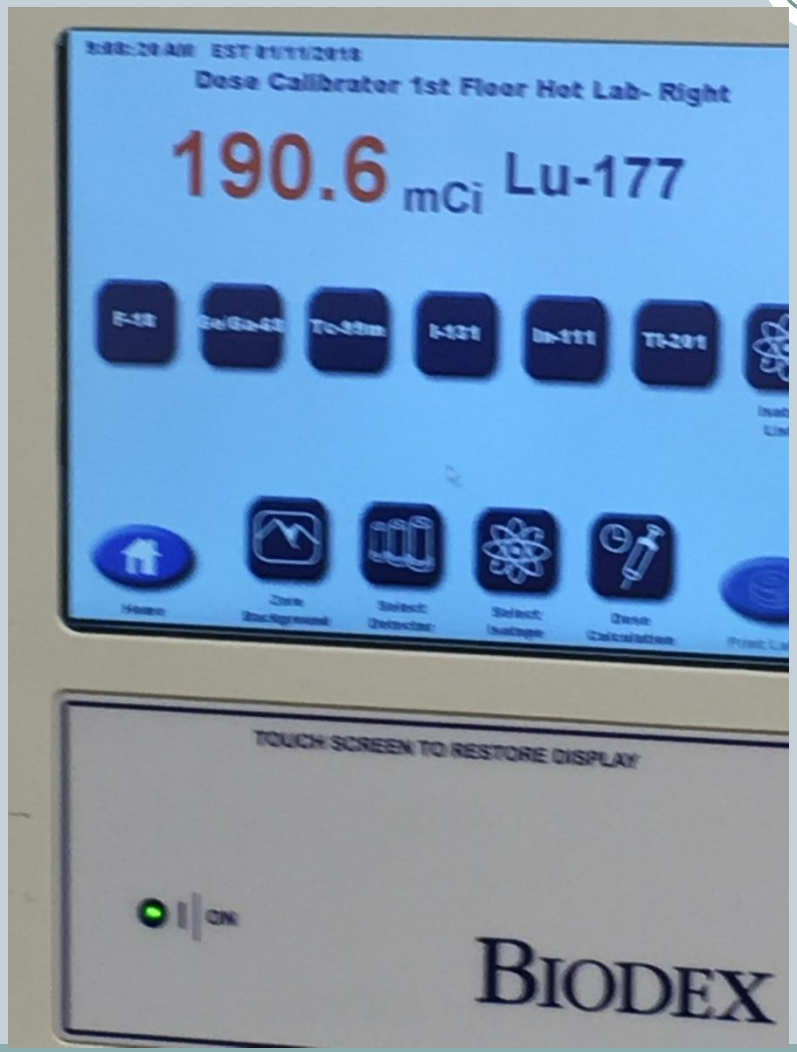
Injecting Lu-177 into 50cc saline bag

Carilion Infusion Device and Method



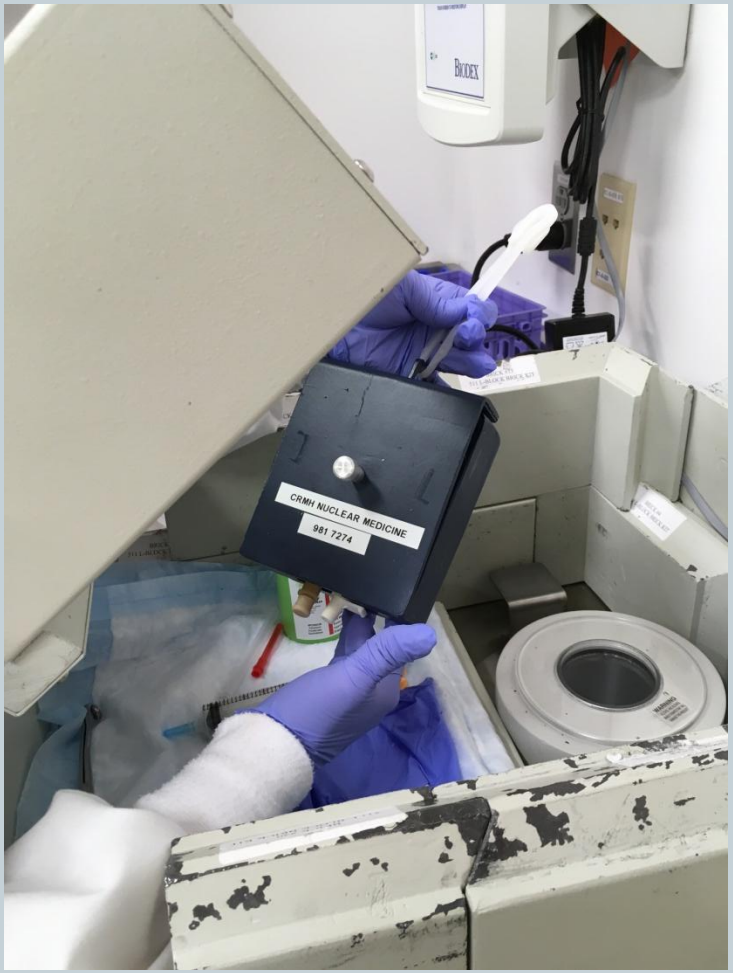
Residual in syringe after delivery into saline bag

Carilion Infusion Device and Method



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

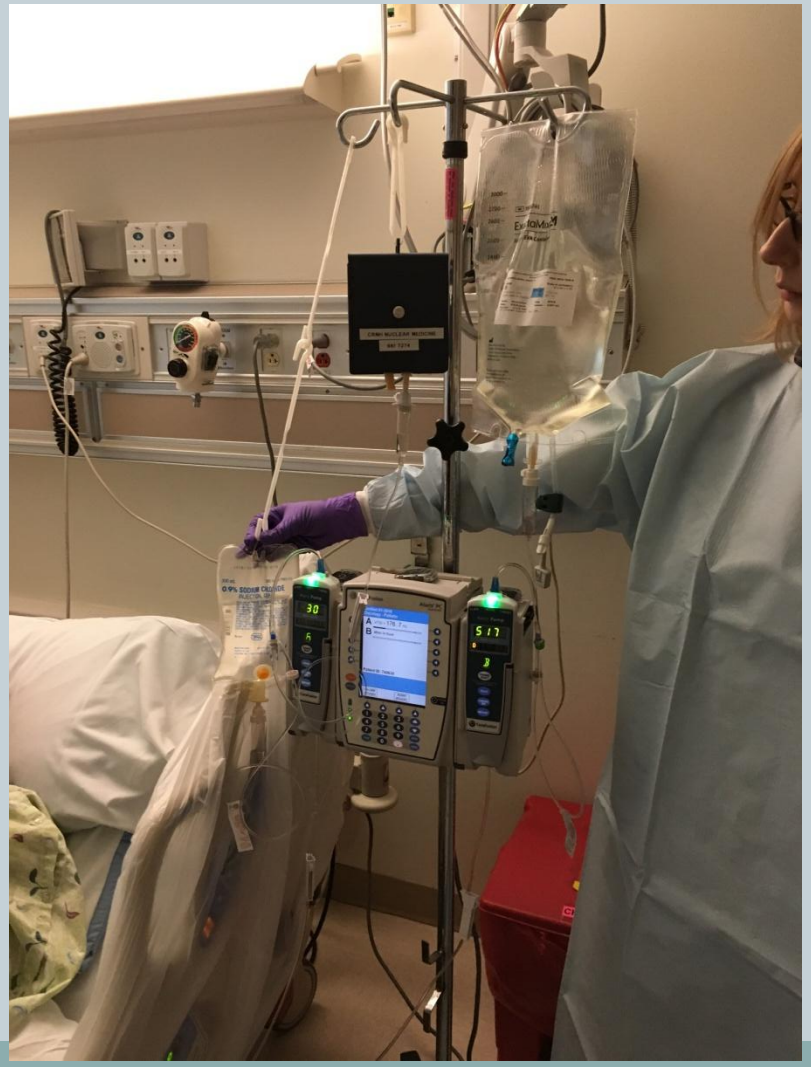
Carilion Infusion Device and Method

Adding saline to the syringe used to remove the Lu-177 from vial to capture the residual

Carilion Infusion Device and Method

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”