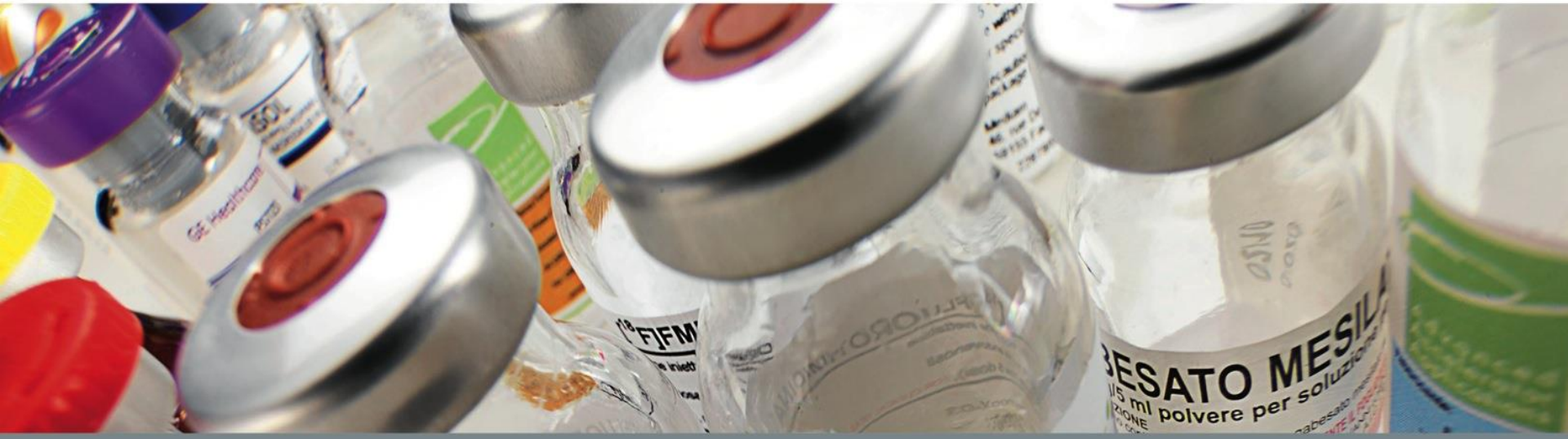
Advanced Accelerator Applications

NETSPOT™ (gallium Ga 68 dotatate) **Reader Training**



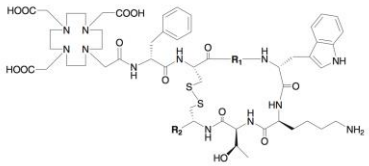
Robert R. Flavell, MD, PhD

Training Background

- Neuroendocrine tumors (NETs) are a relatively uncommon tumor with increasing incidence (50 per million) and prevalence (350 per million)[1]
- Traditional methods for imaging neuroendocrine tumors include CT, MR, and ^{111}In-pentetreotide
- Somatostatin receptor targeting (SST) PET with gallium Ga 68 dotatate is a newly-approved method for molecular imaging of neuroendocrine tumors

[1] Deppen et al. *J. Nucl Med* 2016

Training Outline



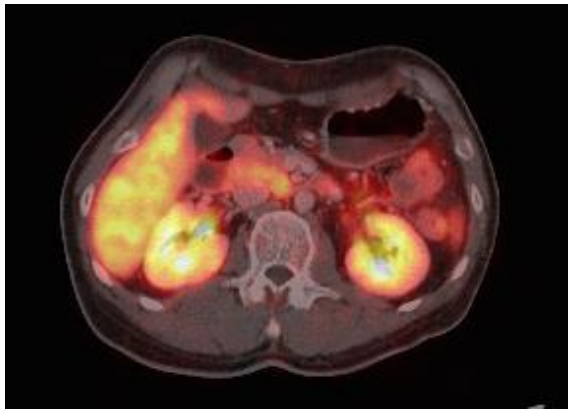
Compound	R_1	R_2
DOTA-OC	Phe	Thr(ol)
DOTA-TOC	Tyr	Thr(ol)
DOTA-TATE	Tyr	Thr
DOTA-NOC	Nal-1	Thr(ol)
DOTA-NOC-ATE	Nal-1	Thr
DOTA-BOC	BzThi	Thr(ol)
DOTA-BOC-ATE	BzThi	Thr

Review mechanism of action

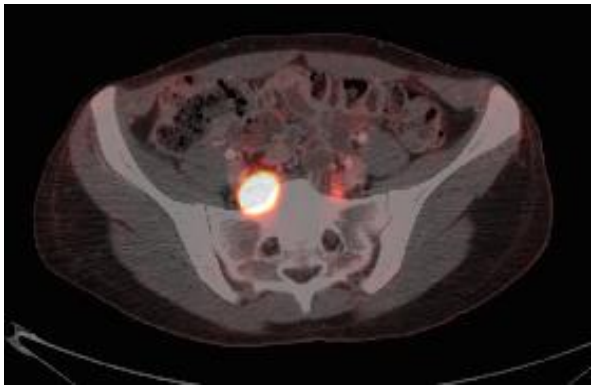
Review indications and scan technique

Discuss normal biodistribution

A practical approach to reading



Review false positives



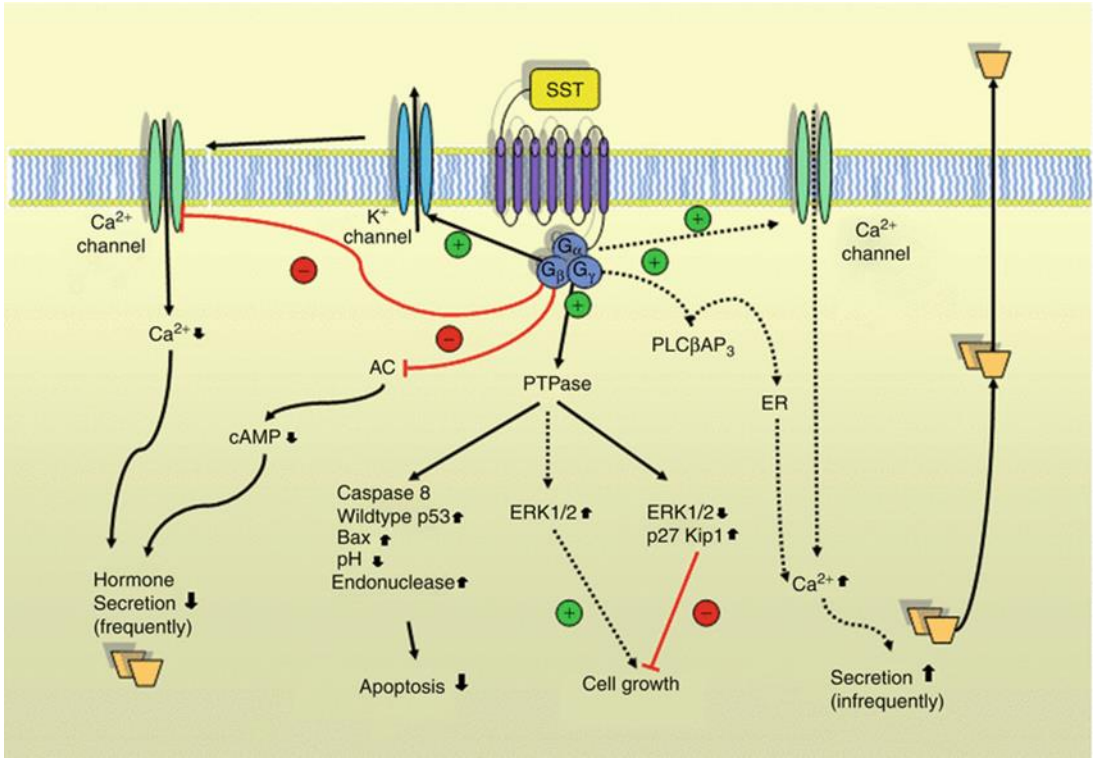
And false negatives

Learning objectives

By the end of this presentation, the reader will be able to:

1) Describe the mechanism of action of gallium Ga 68 dotatate
2) Identify the normal biodistribution in these scans
3) Understand common pitfalls in scan interpretation
4) Discuss how gallium Ga 68 dotatate imaging can change patient management
5) Interpret gallium Ga 68 dotatate PET/CT scans

Somatostatin Receptors



Somatostatin receptors:
- Are cell surface receptors
- Belong to the G-protein coupled receptors superfamily
- Are overexpressed in NETs

Indications for NETSPOT™ imaging

NETSPOT™

after radiolabeling with Ga 68, is a radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients [1]

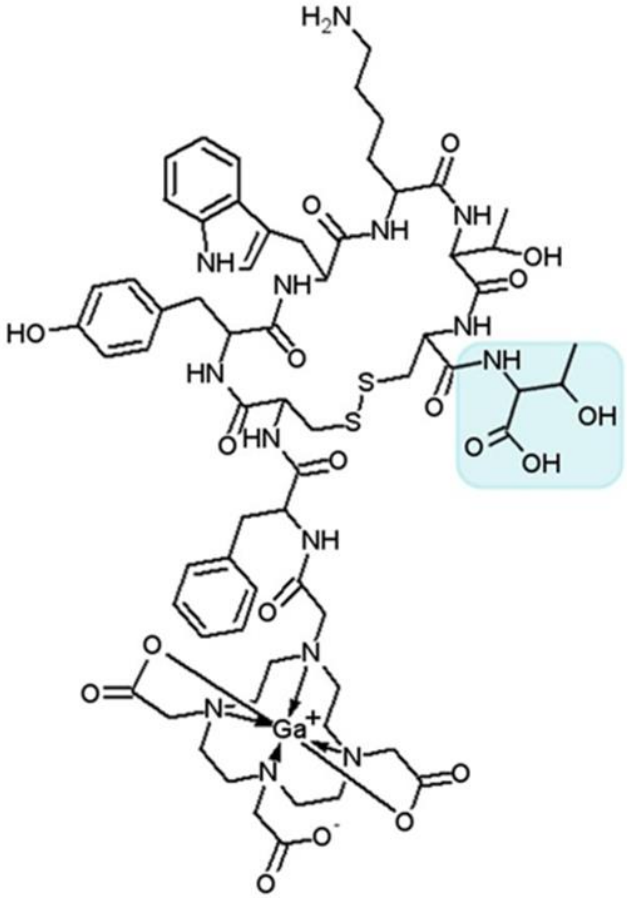
- Initial staging for patients with neuroendocrine tumors
- Restaging, detecting recurrence, and monitoring of response to therapy in patients with NETs
- Detection of unknown primary neuroendocrine tumor in patients with known metastatic NETs
- NOT APPROPRIATE: Detection of neuroendocrine tumor in patients with symptoms and/or biochemical evidence of NETs, but with no known disease

[1] **NET**SPOT ™ Prescribing Information 2016

Somatostatin Imaging

- SST receptors are overexposed in neuroendocrine tumors (NETs), but most commonly in gastro entero pancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors
- SST receptors can be imaged using labeled somatostatin analogs
- Other tumors that over express somatostatin receptors include pituitary adenoma, meningioma, paraganglioma, small cell lung cancer, carcinoid and medullary thyroid cancer

gallium Ga 68 dotatate



^{68}Ga-DOTATATE

^{68}Ga-labeled 4,7,10-tricarboxymethyl-1,4,7,10-tetraaza-cyclododecan-1-yl-acetyl-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH

Biodistribution and Dosimetry [1]

- Gallium Ga 68 dotatate distributes to all sstr2-expressing organs such as pituitary, thyroid, spleen, adrenals, kidney, pancreas, prostate, liver, and salivary glands. There is no uptake in the cerebral cortex or in the heart, and usually thymus and lung uptakes are low
- 12% of the injected dose is excreted in urine in the first four hours post-injection
- Highest absorbed dose is to adrenals, spleen, kidneys, and bladder wall
- Estimated Radiation Effective Dose (per MBq of injected activity) after a Ga 68 dotatate Dose is 0.021 mCv/MBq. From the administration of 150 MBq (4.05 mCi) to an adult weighing 75 kg, is about 3.15 mSv

[1] **NET**SPOT ™ Prescribing Information 2016

Biodistribution and Dosimetry

Estimated radiation dose (mSv/MBq)			
Target organ	Average	SD	% COV
Adrenals	1.46E+02	5.18E+04	3.55E+00
Brain	9.86E+03	5.46E+04	5.54E+00
Breasts	9.96E+03	4.26E+04	4.28E+00
Gallbladder wall	1.49E+02	6.77E+04	4.54E+00
Lower large intestine wall	1.29E+02	8.43E+04	6.52E+00
Small intestine	1.38E+02	2.60E+03	1.88E+01
Stomach wall	1.38E+02	6.47E+04	4.68E+00
Upper large intestine wall	1.29E+02	4.23E+04	3.29E+00
Heart wall	1.23E+02	3.93E+04	3.21E+00
Kidneys	9.21E+02	2.84E+02	3.08E+01
Liver	4.50E+02	1.52E+02	3.38E+01
Lungs	1.15E+02	3.52E+04	3.06E+00
Muscle	1.13E+02	4.47E+04	3.96E+00
Ovaries	1.31E+02	8.32E+04	6.35E+00
Pancreas	1.67E+02	1.37E+03	8.20E+00
Pituitary gland	4.16E+02	3.20E+02	7.70E+01
Hematopoietic cells	9.61E+03	3.47E+04	3.61E+00
Bone-forming cells	1.55E+02	7.39E+04	4.76E+00
Salivary glands	1.17E+02	7.82E+03	6.68E+01
Skin	9.66E+03	4.24E+04	4.39E+00
Spleen	2.82E+01	1.21E+01	4.28E+01
Testes	1.12E+02	6.78E+04	6.06E+00
Thymus	1.09E+02	4.93E+04	4.51E+00
Thyroid	1.87E+02	1.05E+02	5.65E+01
Urinary bladder wall	1.25E+01	6.18E+02	4.96E+01
Uterus(estimated)*	1.47E+02	1.56E+03	1.06E+01
Total body	1.34E+02	2.83E+04	2.11E+00
Effective Dose	2.57E+02	2.85E+03	1.11E+01

Critical Organs:

- Spleen
- Uroepithelium of the bladder
- Kidneys
- Liver

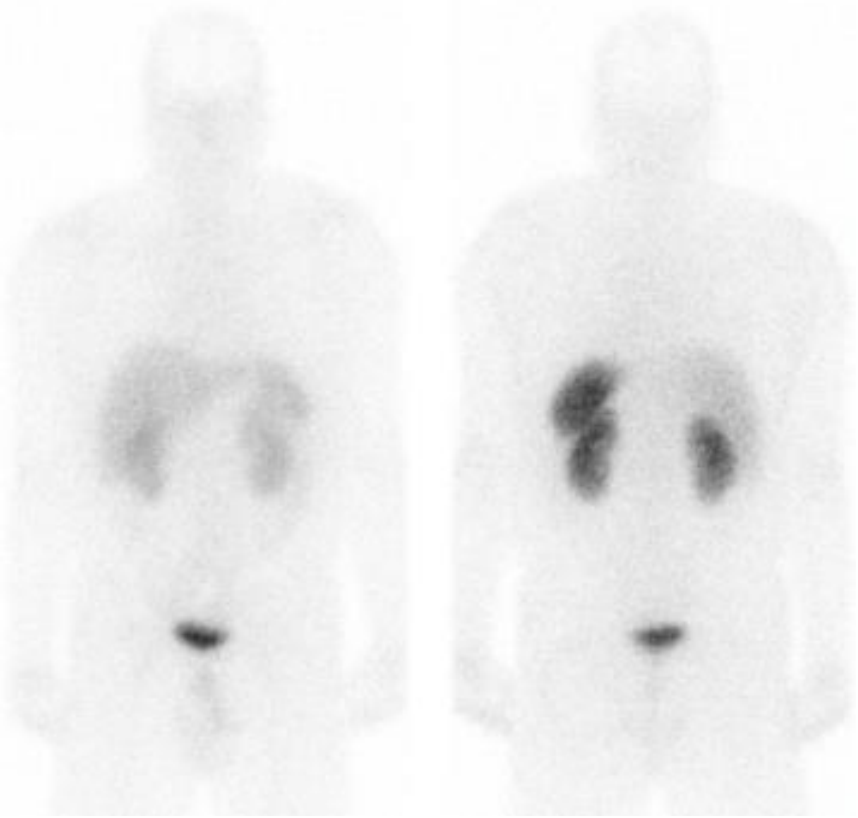
*COV: coefficient of variation

**Uterus dosimetry is estimated since all subjects were male.

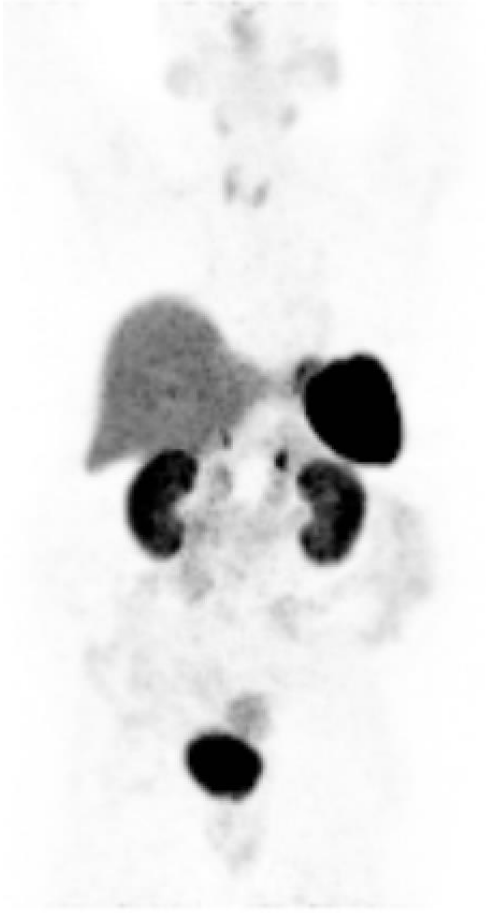
Walker, et al. *J Nucl Med 2013*

Normal Biodistribution

^{111}In- pentetreotide

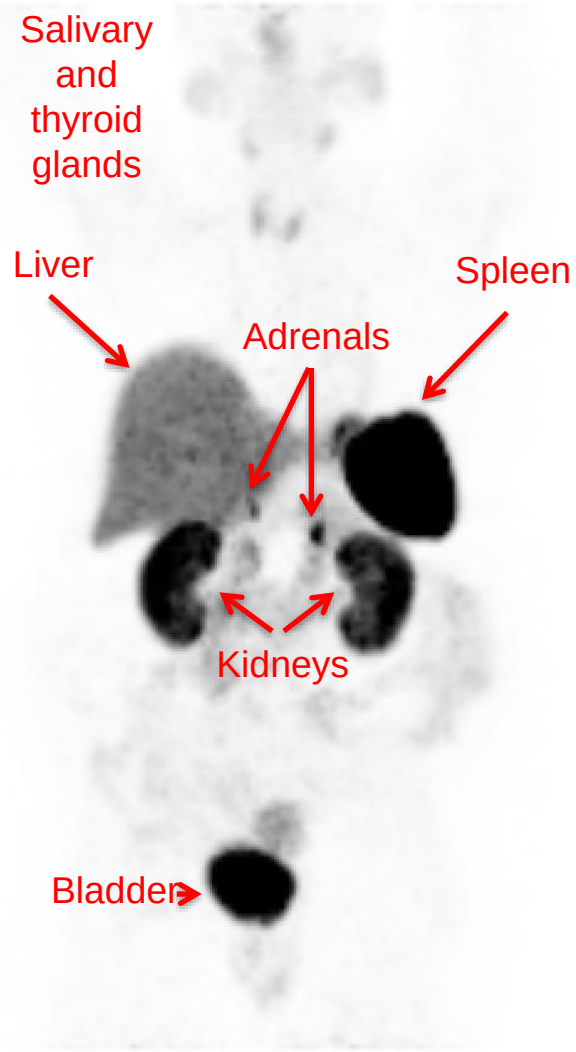


^{68}Ga-dotatate

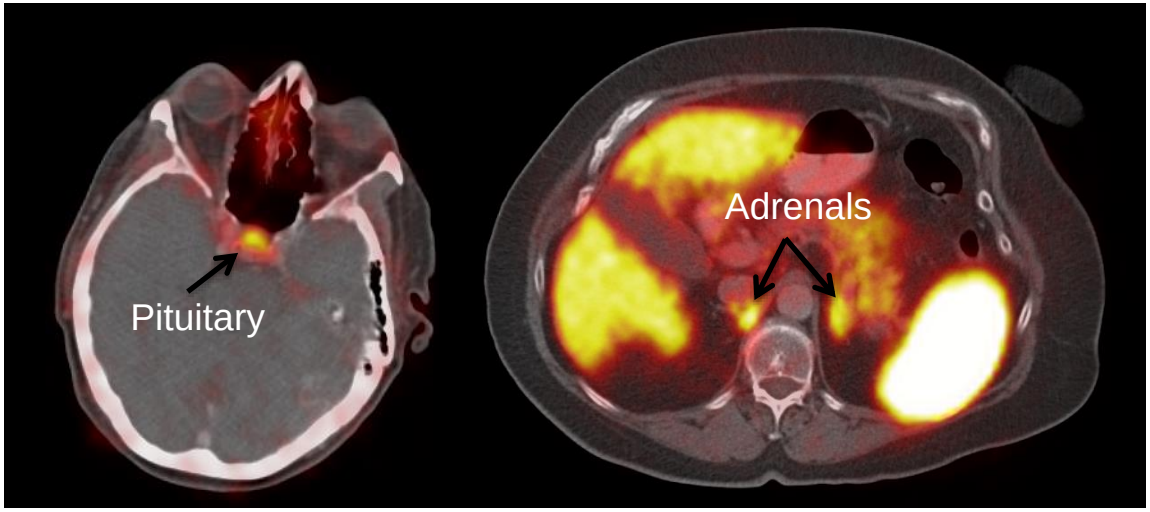


^{111}In-pentetreotide is the traditional approach for staging neuroendocrine tumors Normal ^{111}In-pentetreotide (anterior and posterior planar images, left) and gallium Ga 68 dotatate scans (right) have similar biodistribution.

Normal Biodistribution



^{68}Ga-dotatate MIP



- There are differences between gallium Ga 68 dotatate and ^{111}In-pentetreotide imaging
- gallium Ga 68 dotatate uptake is commonly seen in the pituitary gland (above, left), and in the adrenal glands (above, right)
- These areas of normal uptake should not be confused with pathology

Acquisition Technique

Parameter	Setting
Scanner	Consult PET or PET/CT scanner vendor for appropriate acquisition time and post-processing.
Patient Preparation	• Instruct patients to drink sufficient amount of water to ensure hydration prior to administration of Gallium Ga 68 dotatate. Drink and void frequently during the first hours following administration to reduce radiation exposure. Ideally withdraw long-acting somatostatin analogs prior to imaging (image immediately prior to next long-acting dose) • For midgut tumors: 2 hours prior to scan NPO except clear liquids
Acquisition Mode	3D (if available)
CT	• High-quality CT, 3mm slice thickness maximum • Optional oral and IV contrast, if indicated
Administered Dose	In adults and pediatrics recommended amount of activity to be administered for PET imaging is 2 MBq/kg of body weight (0.054mCi/kg) up to 200 MBq (5.4 mCi)
Scan Range	For Gallium Ga 68 dotatate PET imaging, acquisition must include a whole body acquisition from skull to mid-thigh
Image Acquisition	Images can be acquired 40 to 90 minutes after intravenous administration of Gallium Ga 68 dotatate. Adapt image acquisition delay and duration according to the equipment used and the patient characteristics in order to obtain the best image quality
Scan range/direction	Skull to mid-thigh, with arms above the head
Minutes per bed position	in order to obtain the best image quality for most current scanners, 4 to 5 minutes per bed position is recommended.

Advantages of NETSPOT™

	OctreoScan®	NETSPOT™
Diagnostic accuracy	Good	Superior for detection of small lesions (particularly lung and bone)
Patient convenience	Two-day protocol (4 and 24 hour images)	One day, 2-hour protocol
Radiation dose	Higher (12 mSv)	Lower (4.3 mSv)
Availability	Readily available	Now commercially available through Advanced Accelerator Applications

Buchmann et al., *Eur. J. Nucl. Med. Mol. Imag.*, 2007
Hofman et al. *J. Med. Imag. Rad. Oncol*. 2012
Mojtahedi et al. *Am. J. Nucl. Med. Mol. Imag.* 2014
Menda et al. *Pancreas* 2014
Balon et al. *J. Nucl. Med. Tech.* 2011

Change in management with NETSPOT™ PET/CT

- A recent study surveying referring clinicians found that 60% of all patients referred for dotatate PET/CT underwent a change in management as the result of the scan [1]
- gallium Ga 68 dotatate imaging resulted in a major change in treatment modality in 19/78 (24%) of patients. Of the 19, 8 patients had surgery cancelled or had a radical change in type of surgery. [2]

[1] Hermann et al. *J. Nucl. Med.* 2015
[2] Deppen et al. *J. Nucl. Med.* 2016

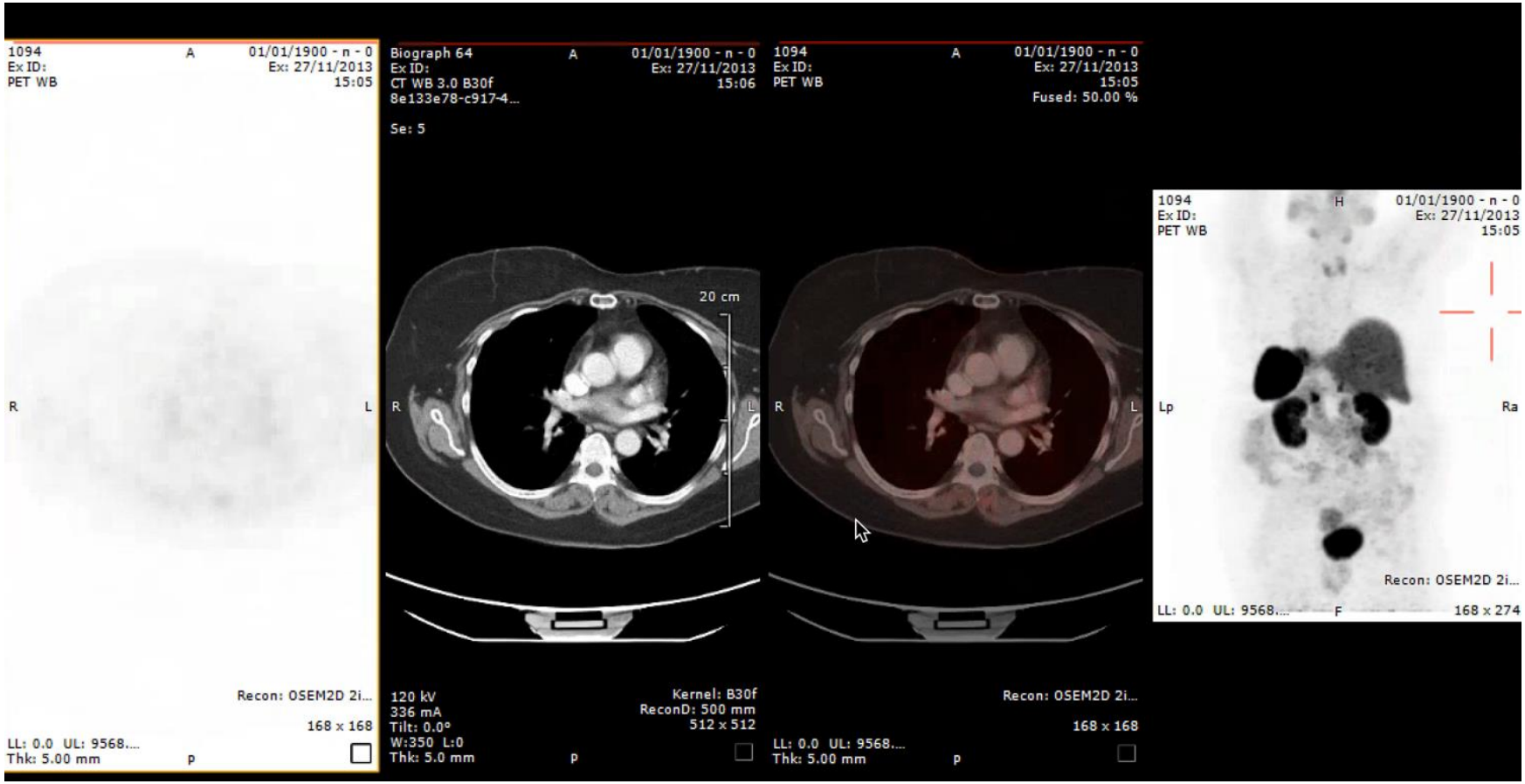
Accuracy

Several studies have demonstrated superior sensitivity of [^{68}Ga] dotatate when compared against CT/MRI, [^{111}In]pentetreotide, or [^{123}I]MIBG

Study	Sensitivity	Specificity
Haug et al. 2014	90%	82%
Hofman et al. 2012	88%	80%
Srirajaskanthan et al. 2010	87%	100%
Win et al. 2007	100%	100%
Schmid et al. 2013	100%	100%

Advanced Accelerator Applications

Sample normal case



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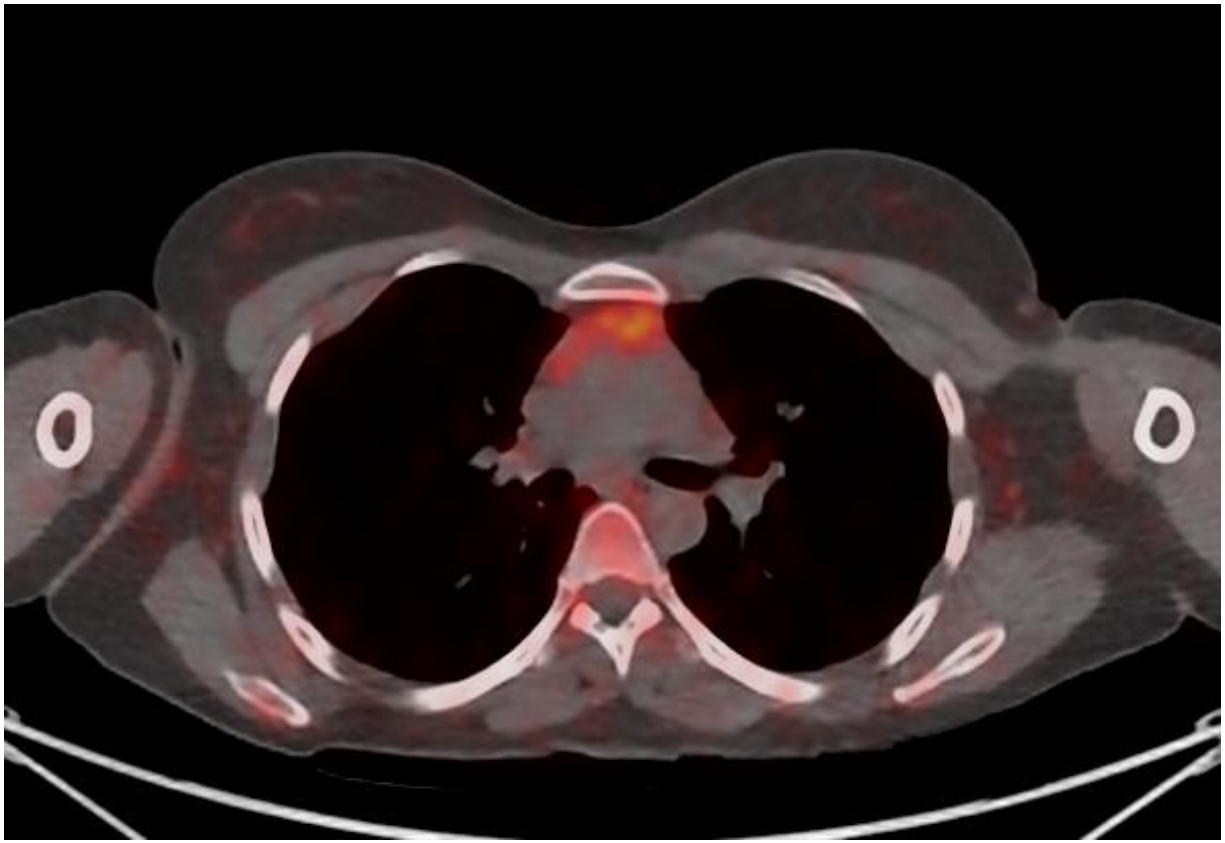
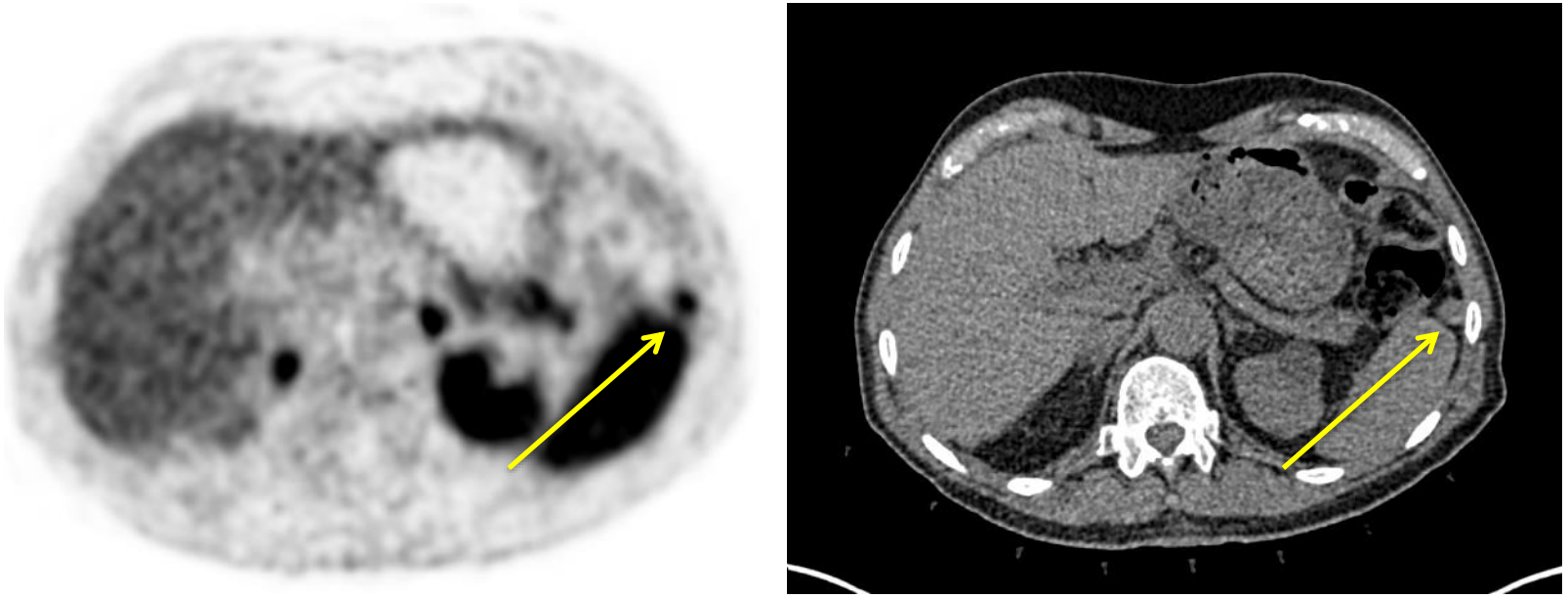
Normal variant: thymus uptake



- Uptake may be due to expression of SST receptors on thymic lymphoid tissues [1]

[1] Ferone et al. *Ann. Med.* 1999

Normal variant: splenule



- Splenules demonstrate intense uptake of gallium Ga 68 dotatate
- Most common in perisplenic location, should be stable compared to prior imaging and have attenuation characteristics identical to spleen
- If diagnostically challenging due to lack of prior imaging and unusual location, ^{99m}Tc-sulfur colloid or heat damaged red blood scan could be used for confirmation

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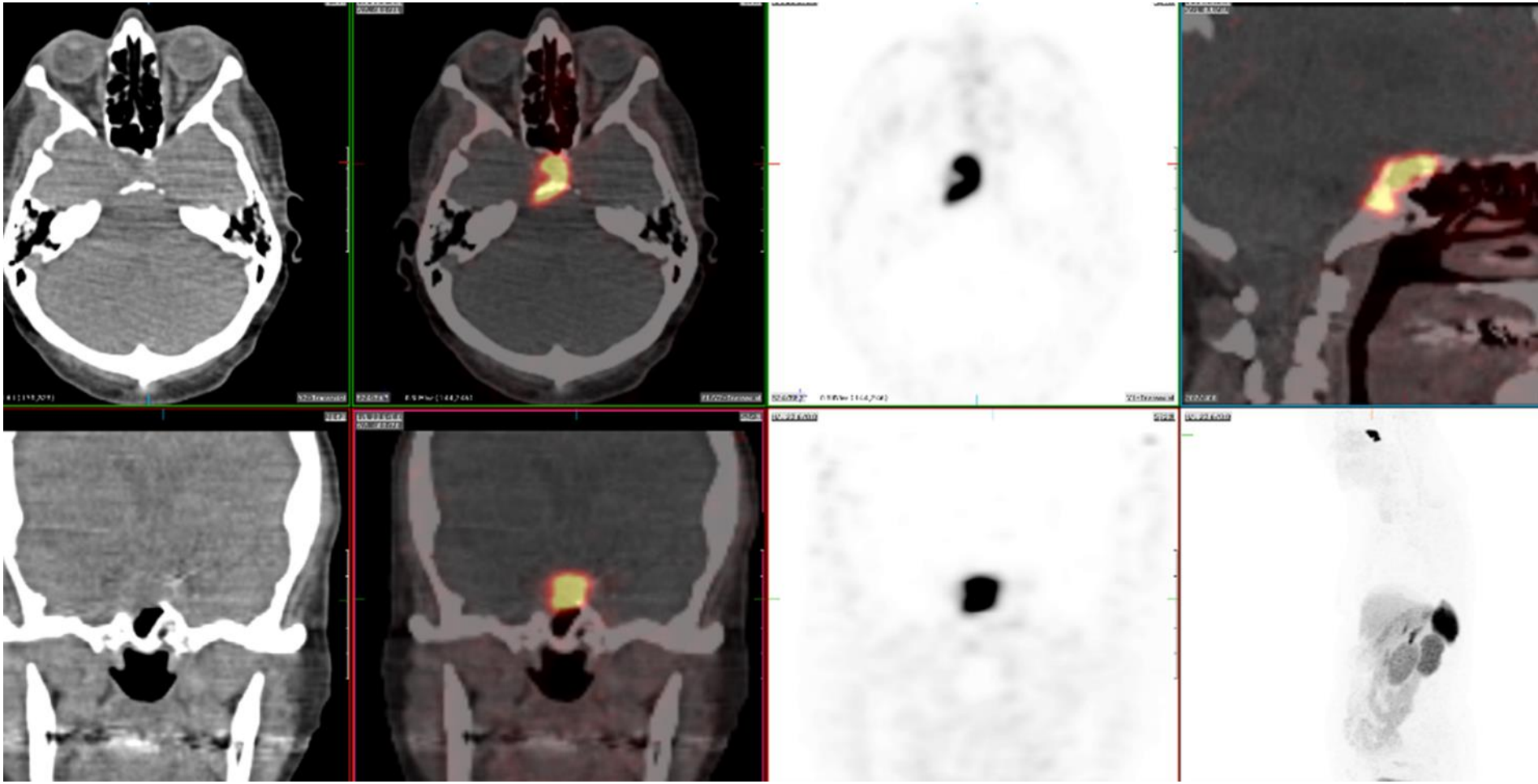
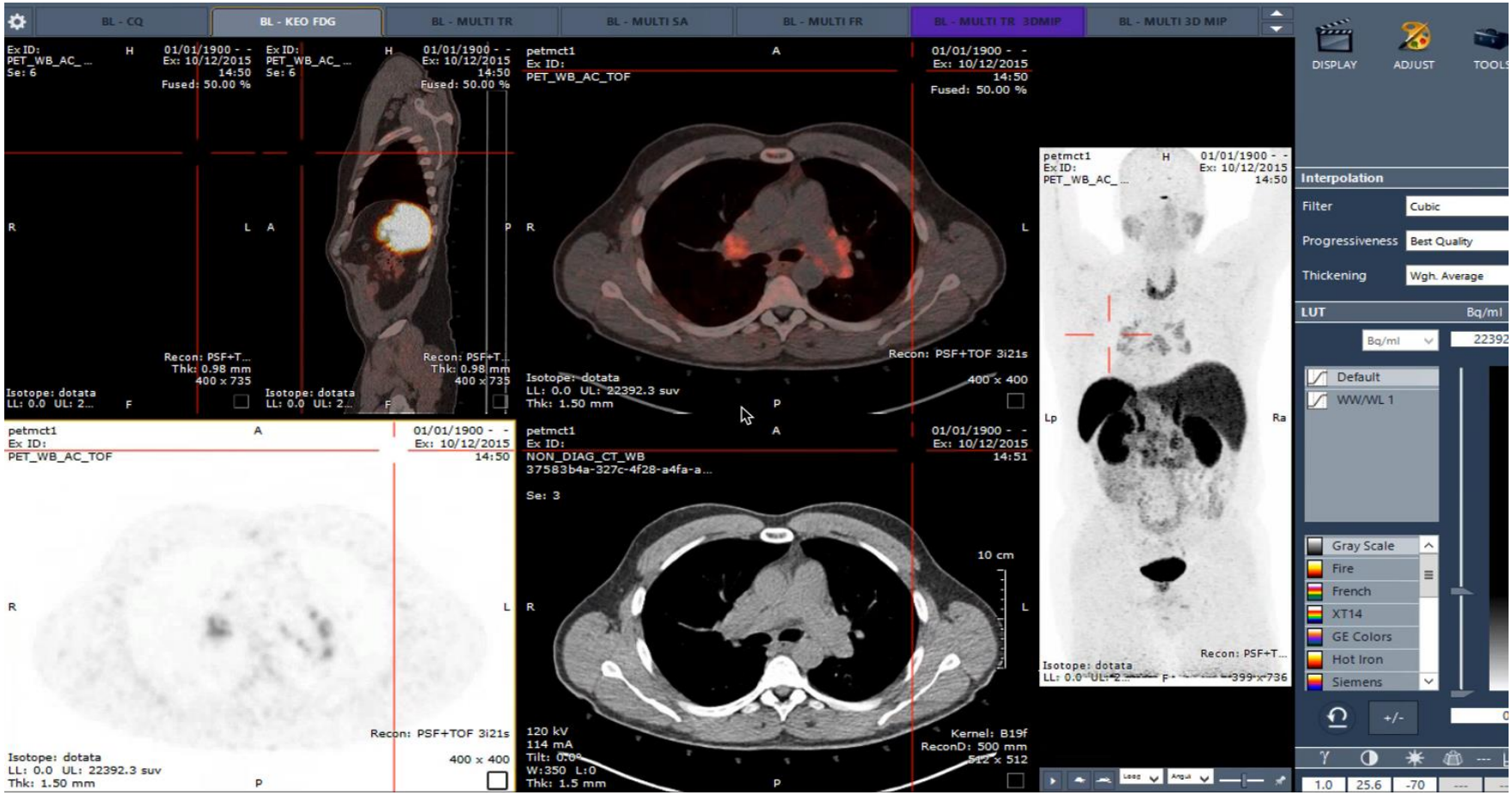
Other neoplasm with increased uptake: pituitary macroadenoma



One case (134), 3 normal variants



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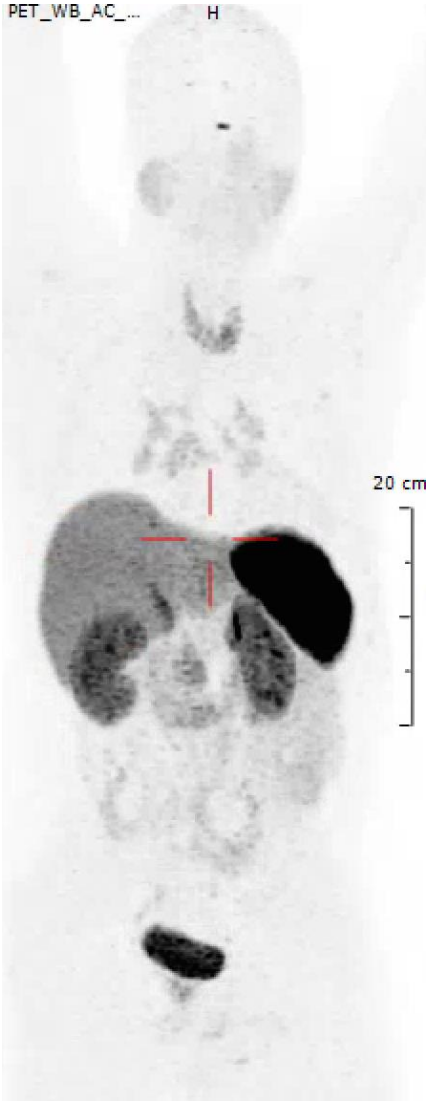
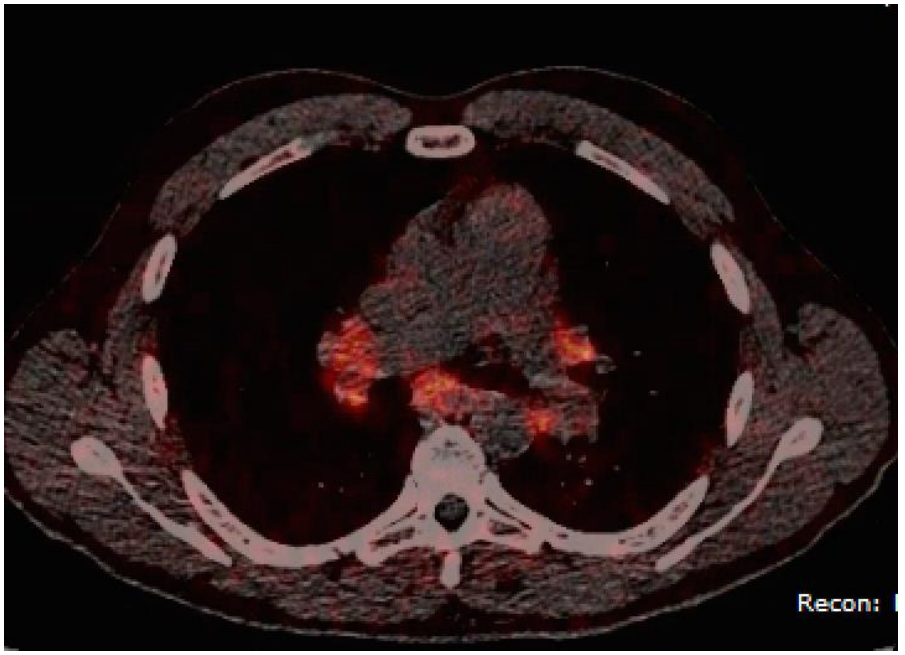
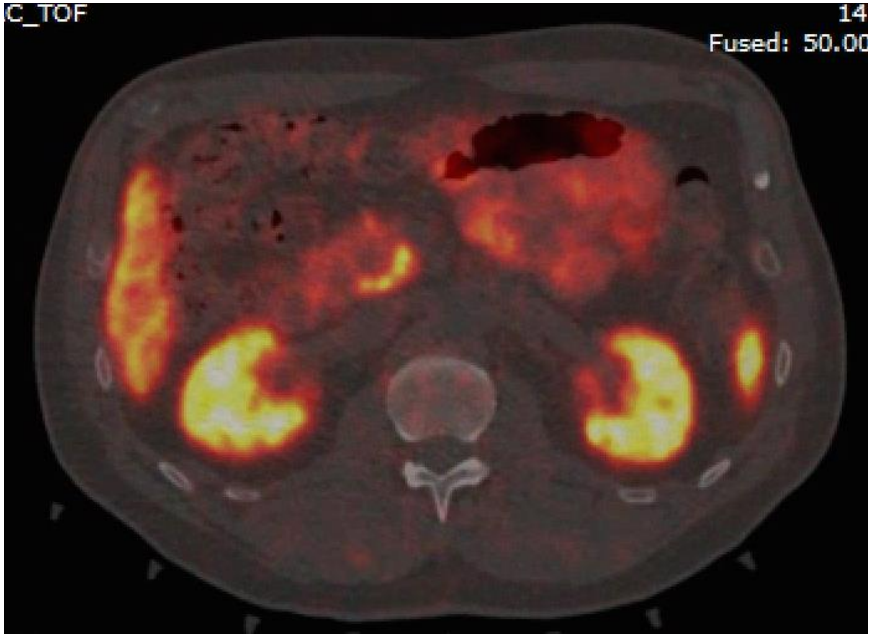
False positive: inflammation (case 134)

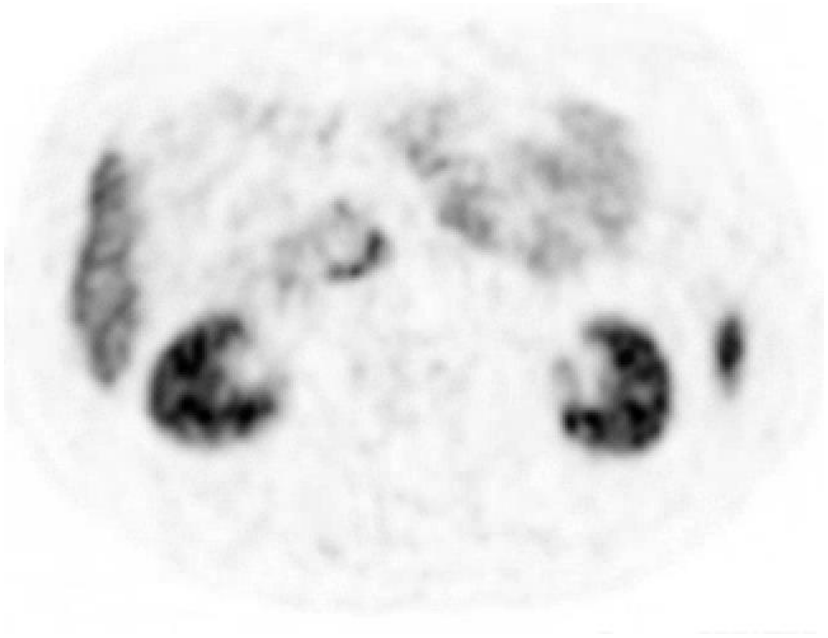




- 49 year old man with known history of sarcoidosis
- Symmetric hilar and mediastinal lymphadenopathy with low level radiotracer uptake, secondary to inflammation
- Enlarged thyroid with increased radiotracer uptake representing Hashimoto's thyroiditis

False positive: Pancreatic uncinate process uptake





- Diffuse, low level uptake in the pancreatic uncinate process
- Should be no correlate on CT imaging

False positive: Pancreatic uncinate process uptake

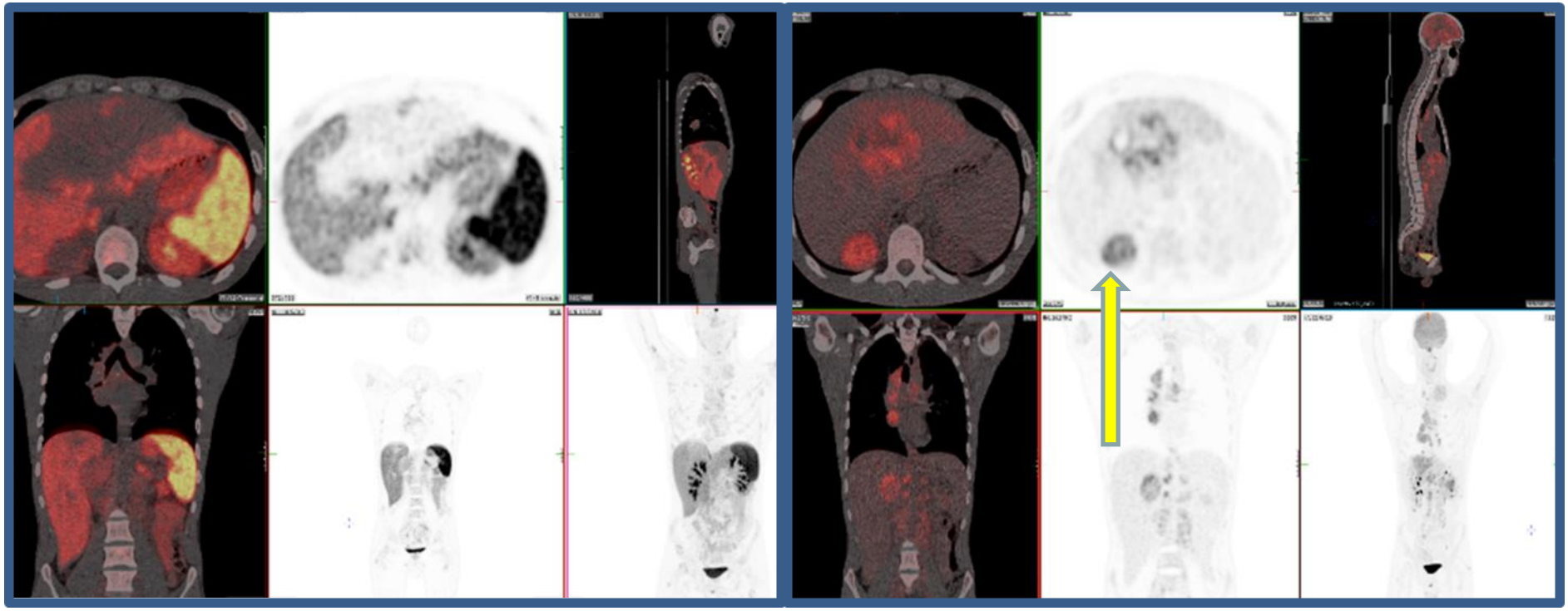
- Pancreatic uncinate process activity is a common physiologic variant which may cause confusion since the pancreas is a common location for primary neuroendocrine tumors
- One study found that 47% of patients undergoing ^{68}Ga-SST PET/CT had focal uncinate uptake, of which the vast majority were benign [1]
- If the uptake is low level (SUV max 1.5 or less), it is very likely physiologic
- This finding is thought to represent focal regions of pancreatic polypeptide-containing cells expressing somatostatin receptors [2]

[1] Al-Ibraheem et al. *Eur. J. Nucl. Med. Mol. Imag.* 2011
[2] Jacobsson et al. *Clin. Nucl. Med.* 2012

False Negative: Poorly Differentiated NET

Gallium Ga 68 dotatate PET/CT

^{18}FDG PET/CT

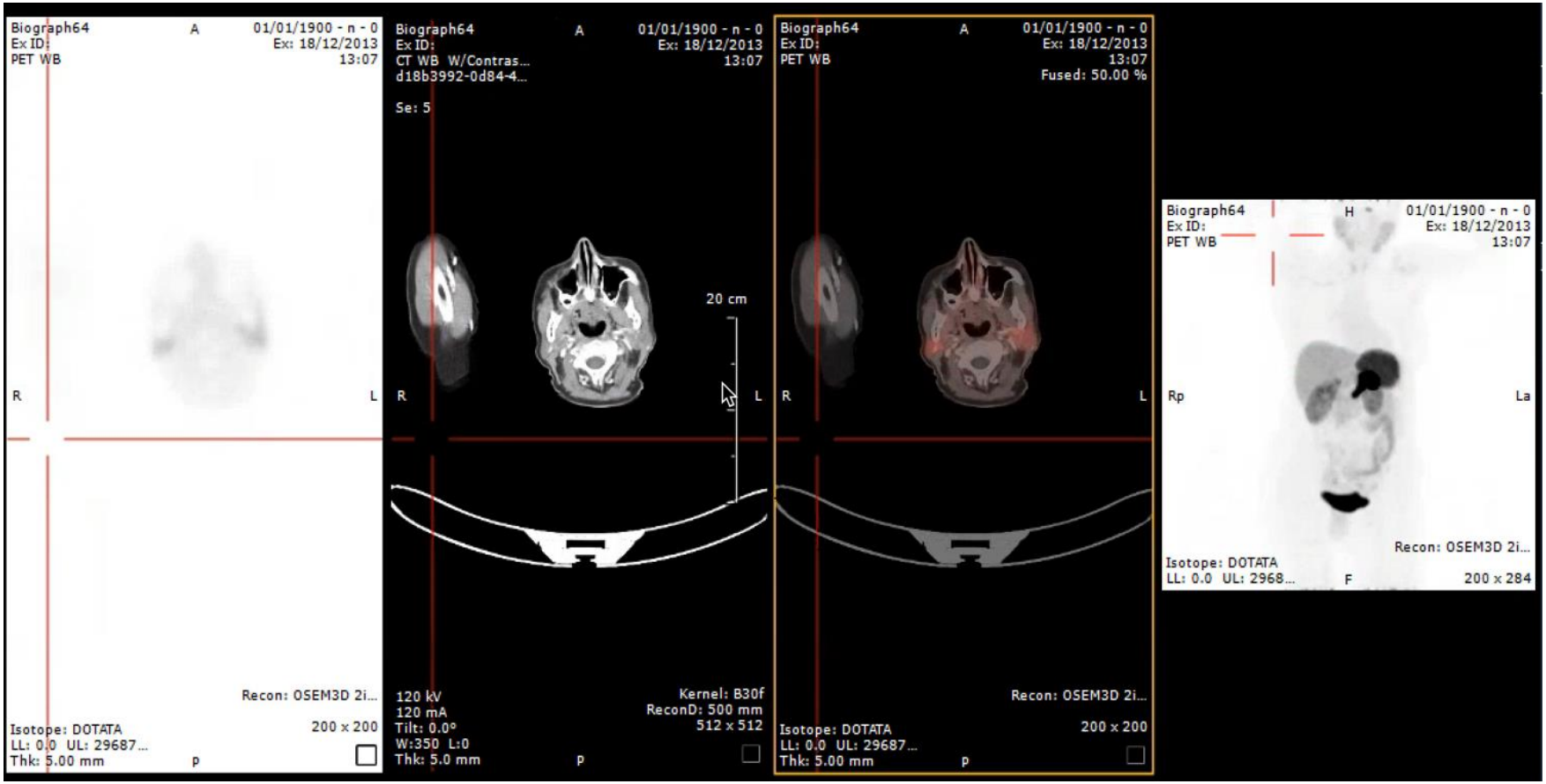


- Poorly differentiated NETs do not express somatostatin receptors -> no gallium Ga 68 dotatate uptake
- These tumors typically demonstrate relatively intense ^{18}F-FDG uptake

Elements of a good report

- Describe location of primary tumors as well as any metastases
- Compare against prior exams, including more remote priors as many NET are slow growing
- Describe postoperative changes, complications
- Describe any masses without radiotracer uptake, which may represent second malignancy or a poorly differentiated NET

Reader training: (case 101)



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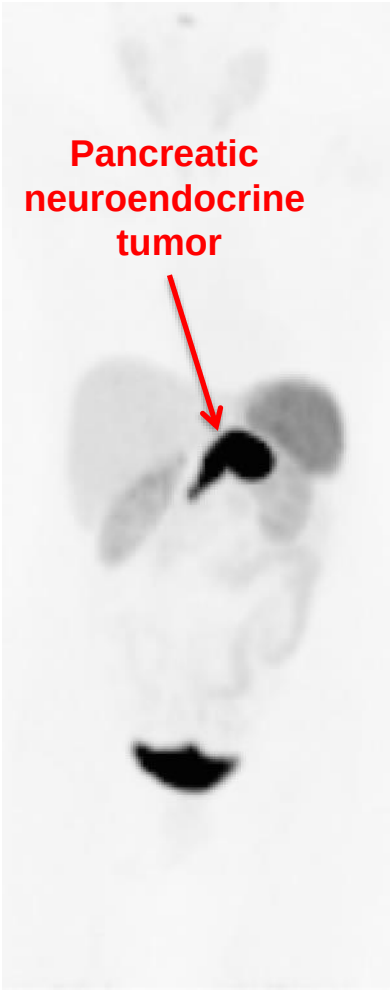
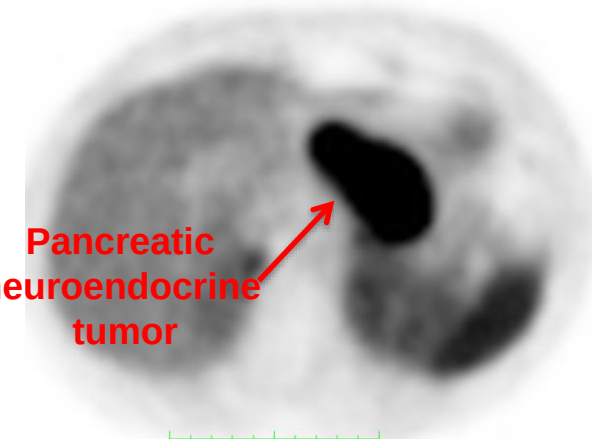
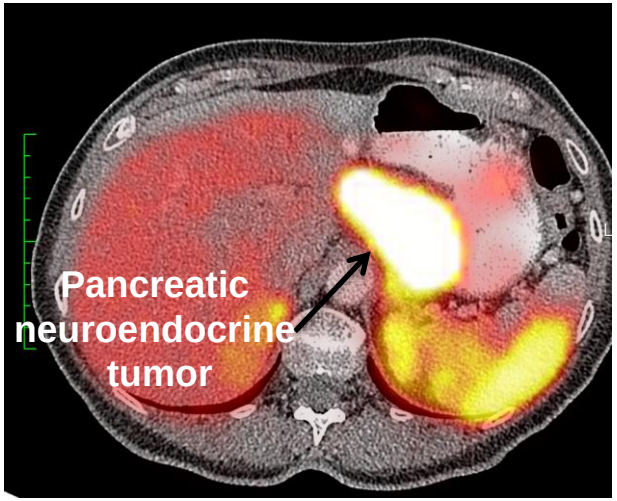
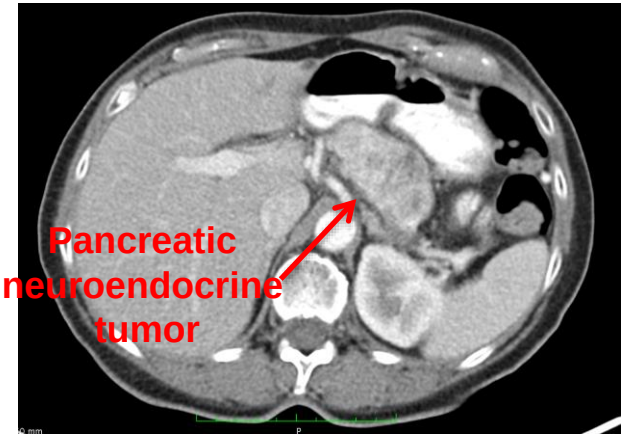
Key findings: Case 101



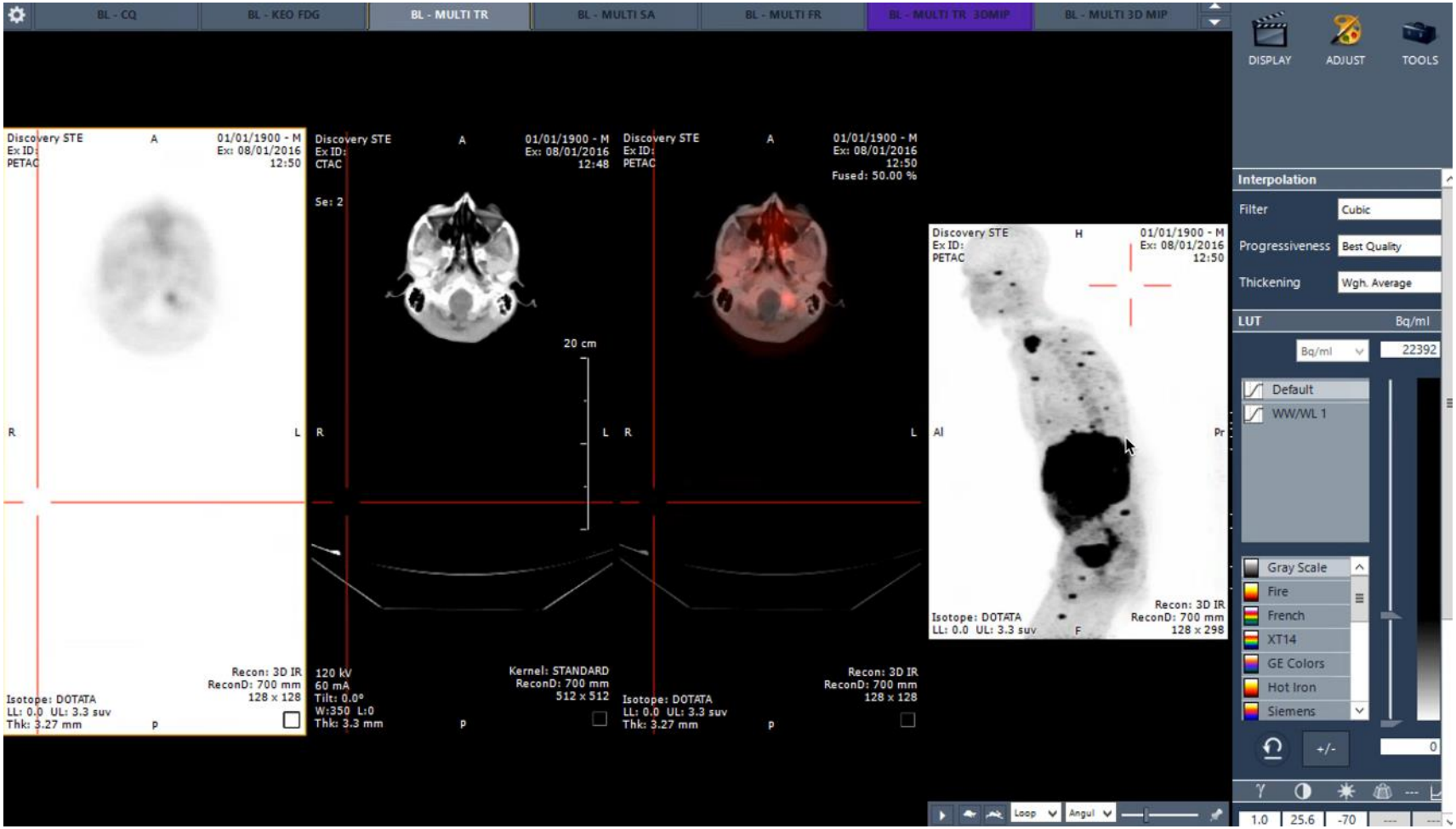






- 70 year old woman with known primary pancreatic NET
- Primary pancreatic body and tail tumor
- No metastases
- Potentially surgically resectable

Reader training: (case 102)



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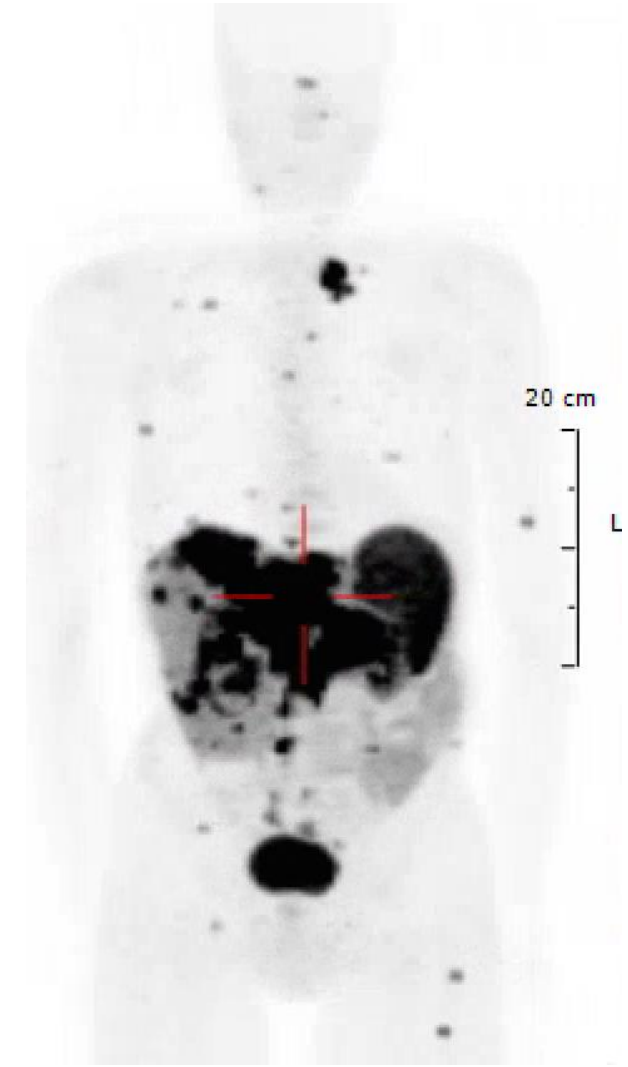
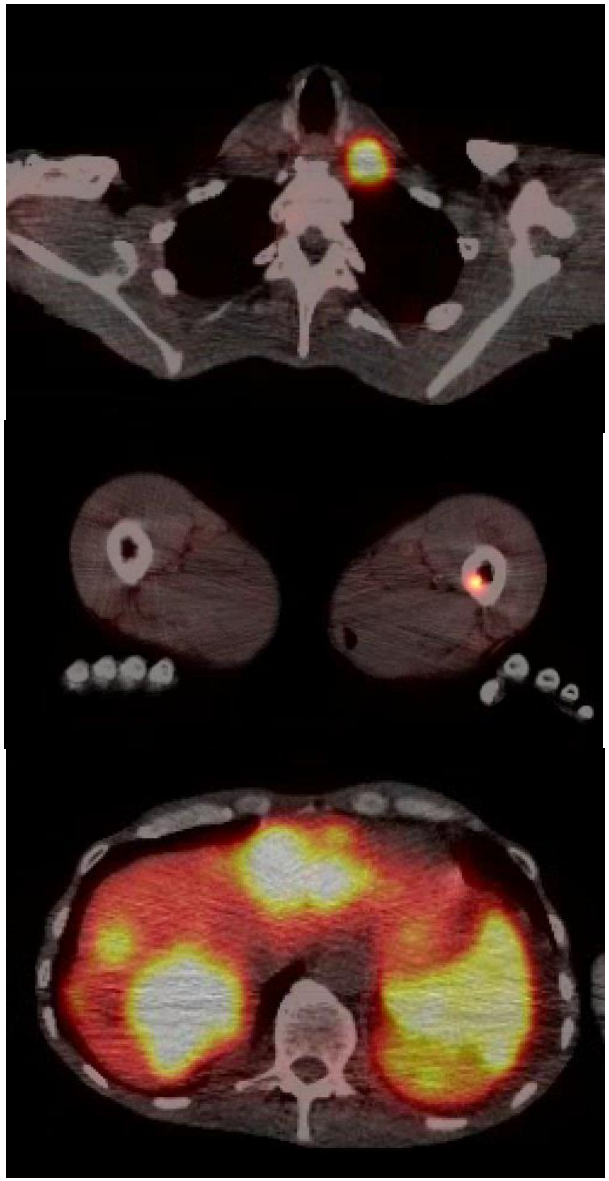
Key findings: Case 102





- 60 year old woman with history of cecal primary NET
- Widespread somatostatin receptor expressing metastasis involving lymph nodes, liver, and bones

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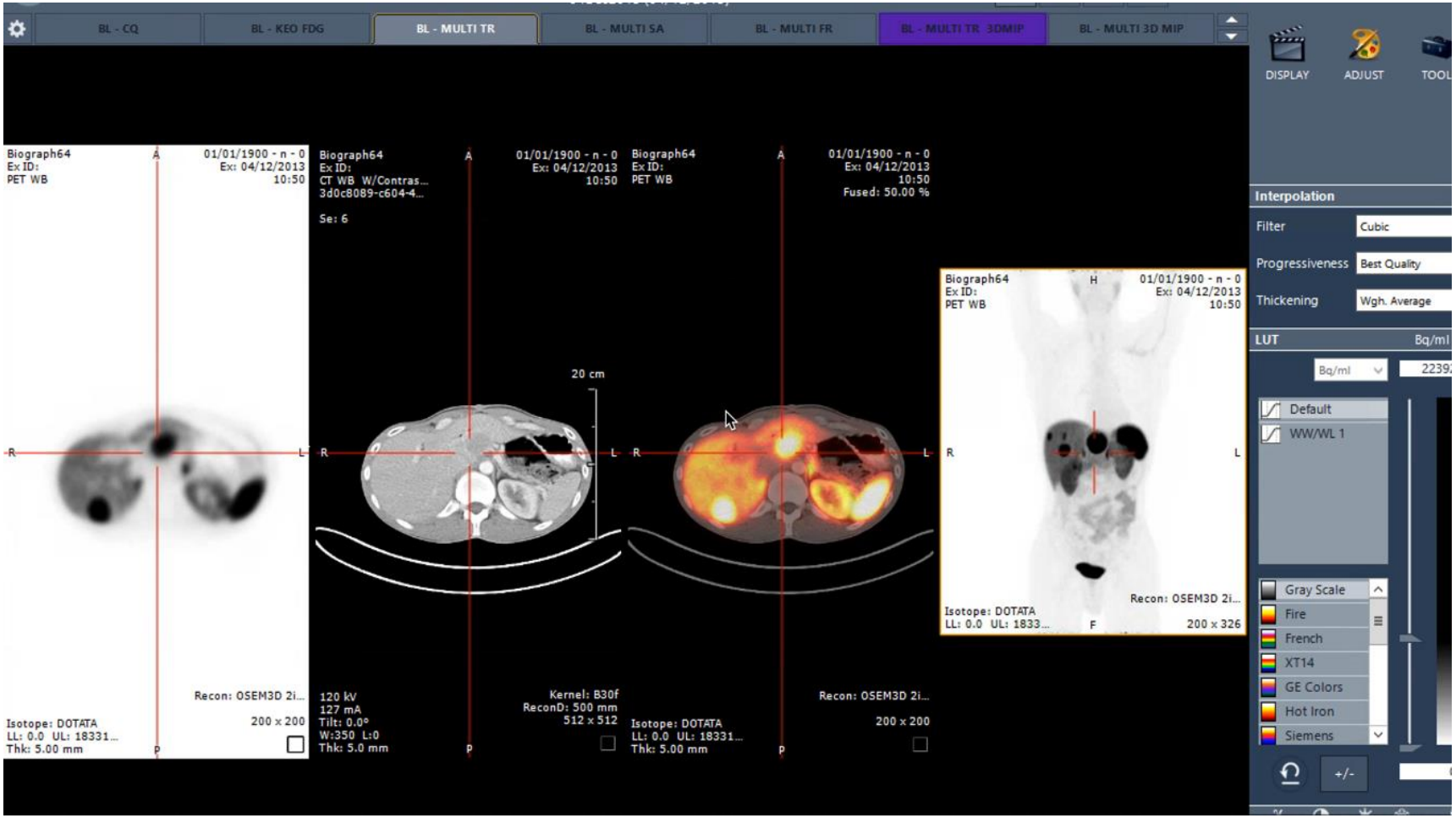
Reader training: (case 105)



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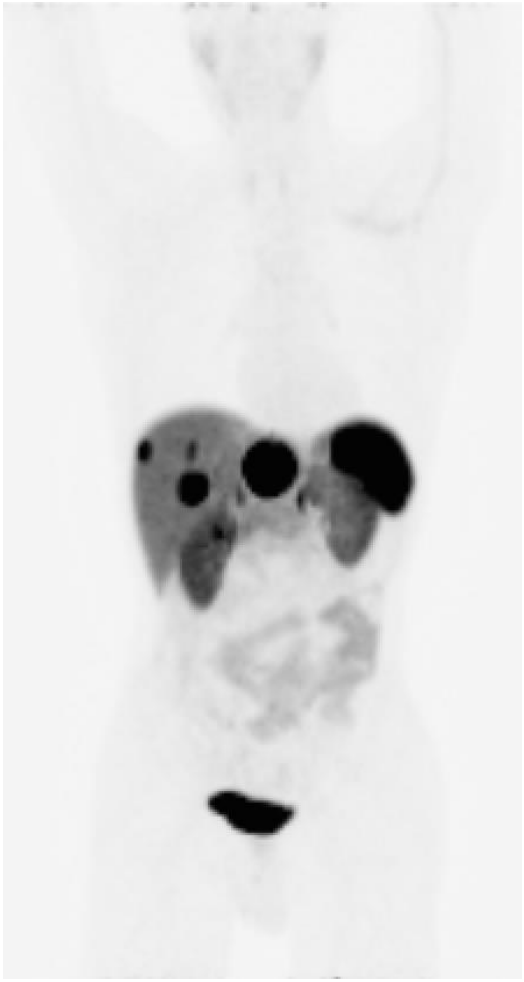
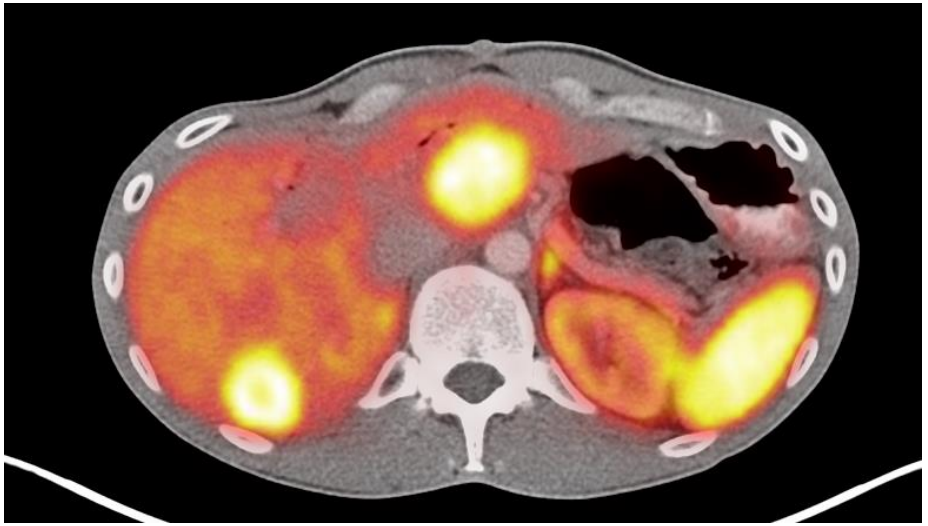
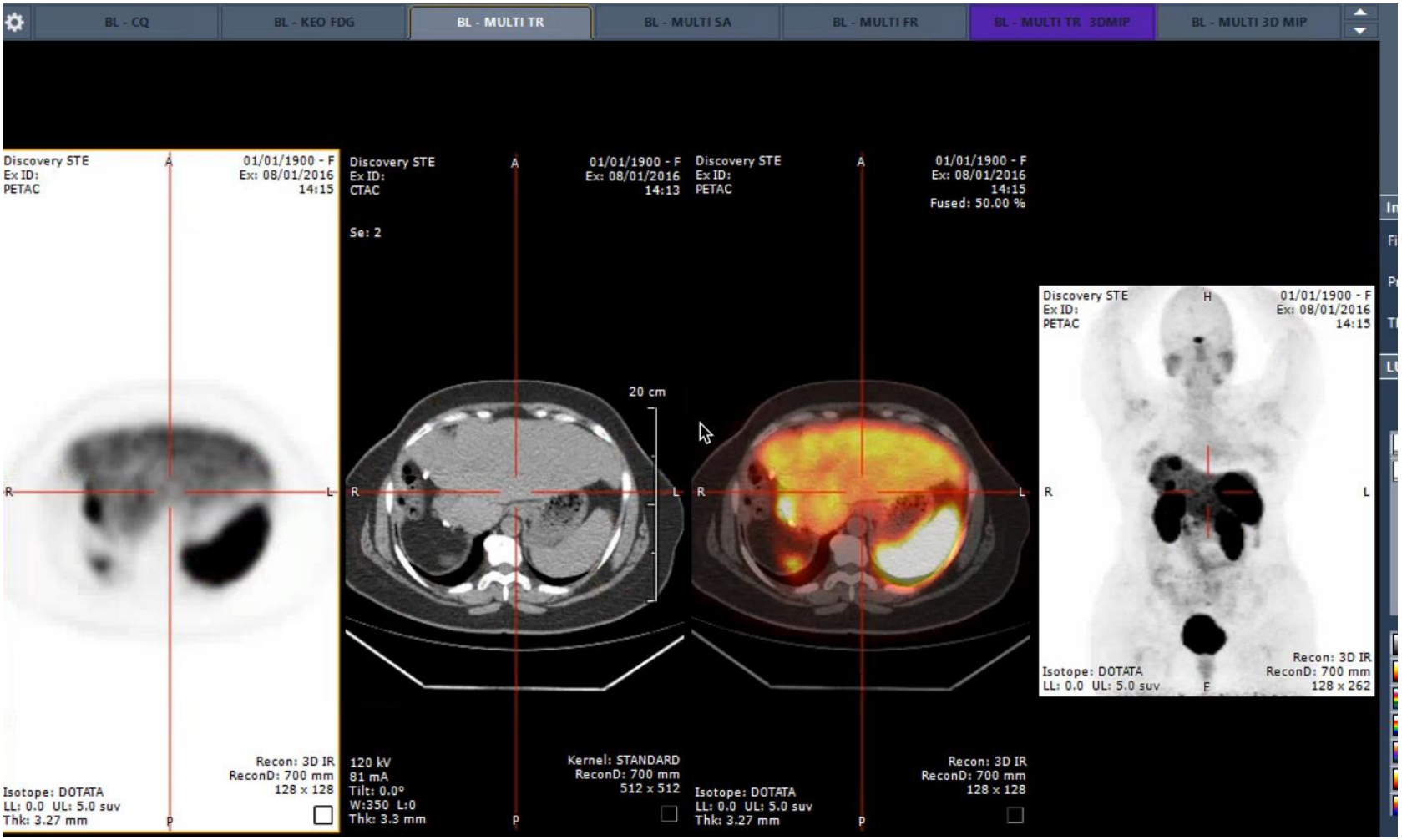
Key findings: Case 105





- 36 year old man with history of pancreatic neuroendocrine tumor post Whipple procedure
- Multiple somatostatin receptor expressing liver metastases
- Status post Whipple procedure

Reader training: (case 112)



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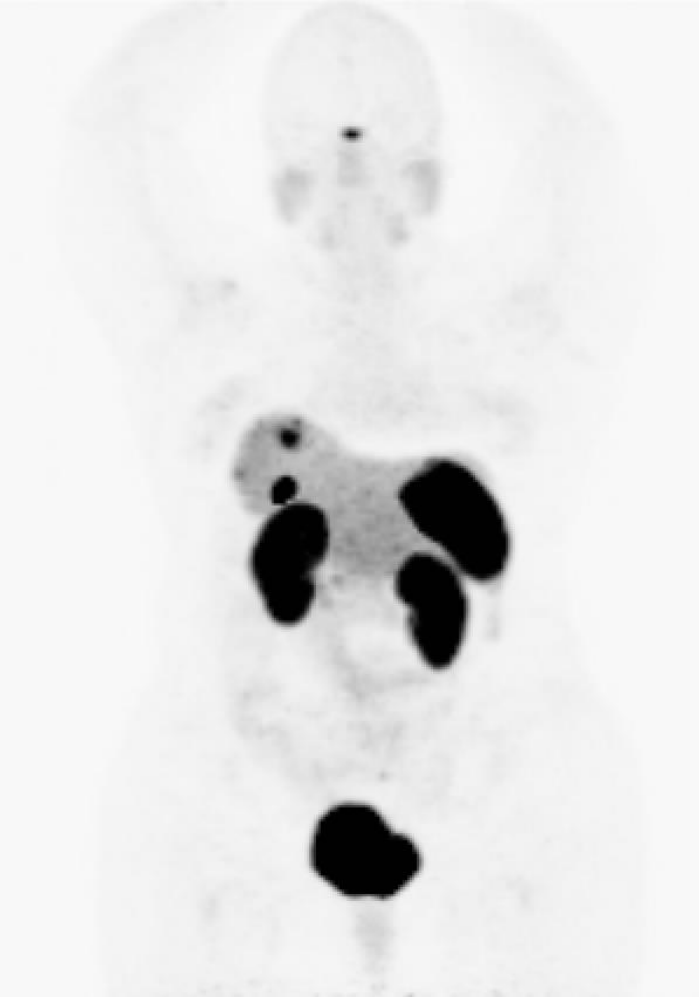
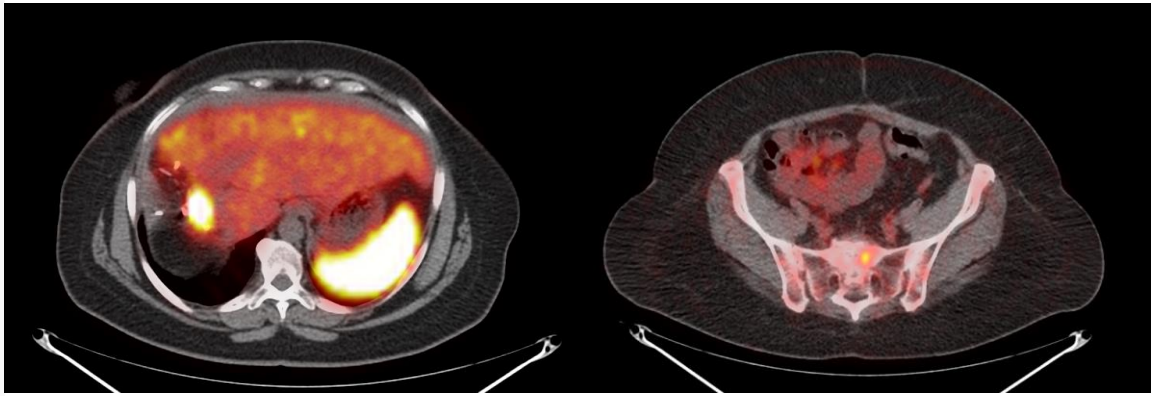
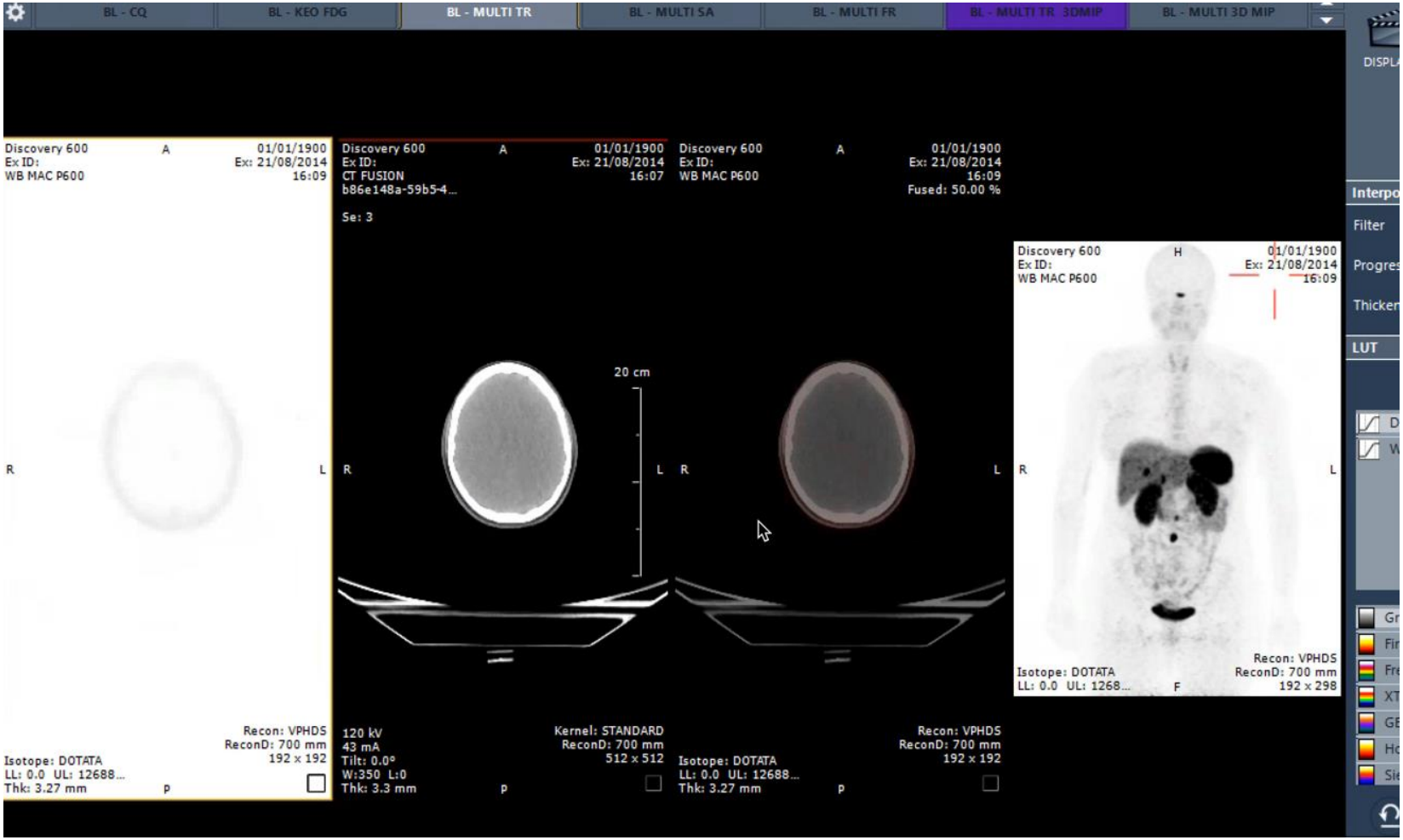
Key findings: Case 112





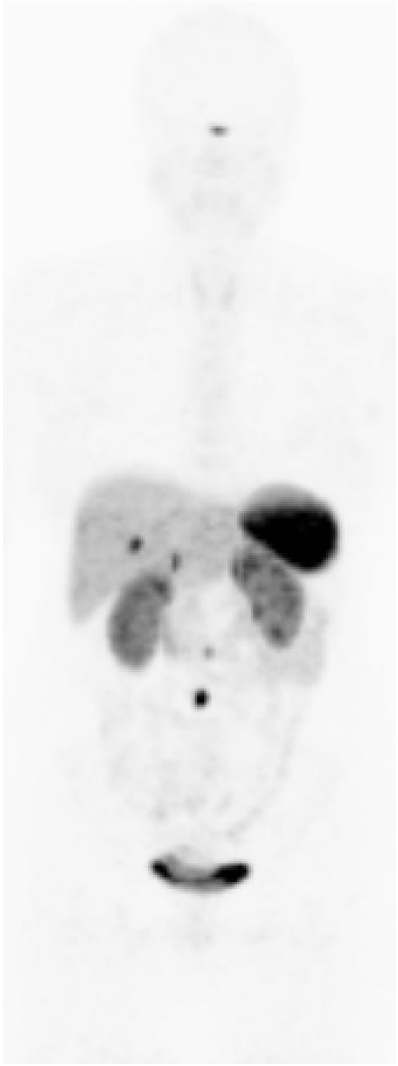
- 60 year old woman with history of duodenal primary neuroendocrine tumor post resection
- Status post right hepatectomy with two liver metastases
- Sacral metastasis

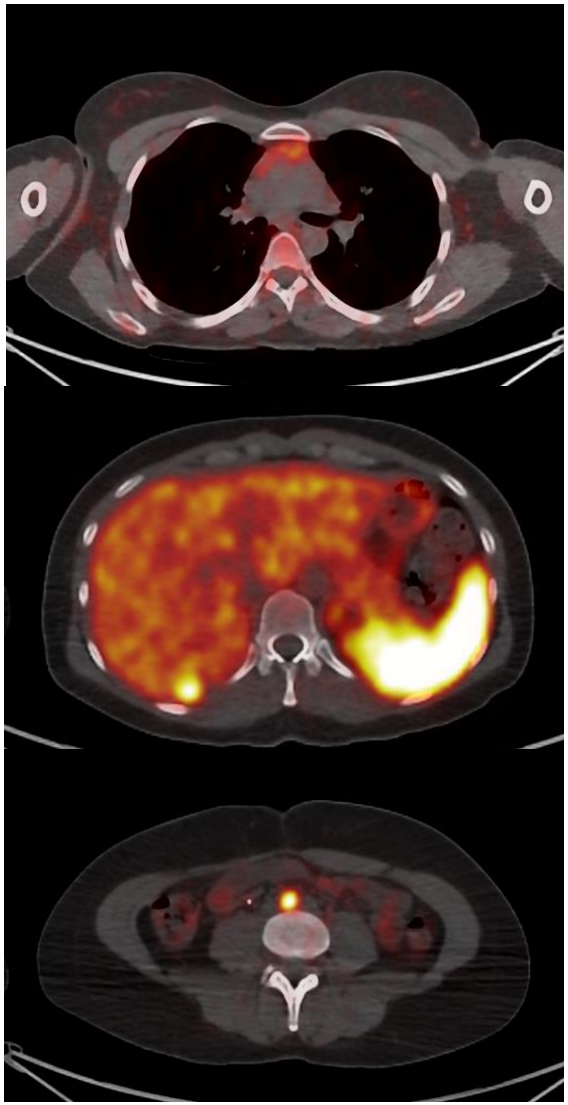
Reader training: (case 114)

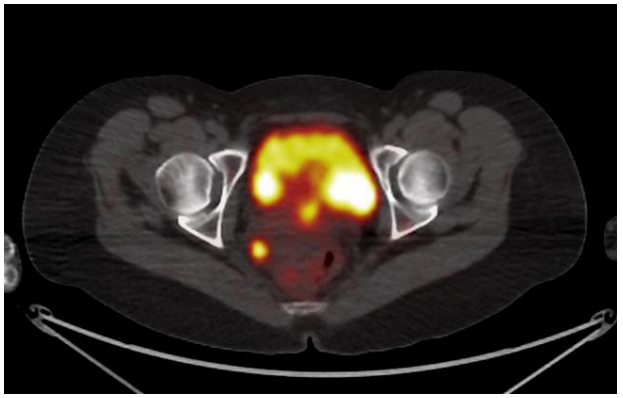


[Click Here to Play]

Key Findings: Case 114

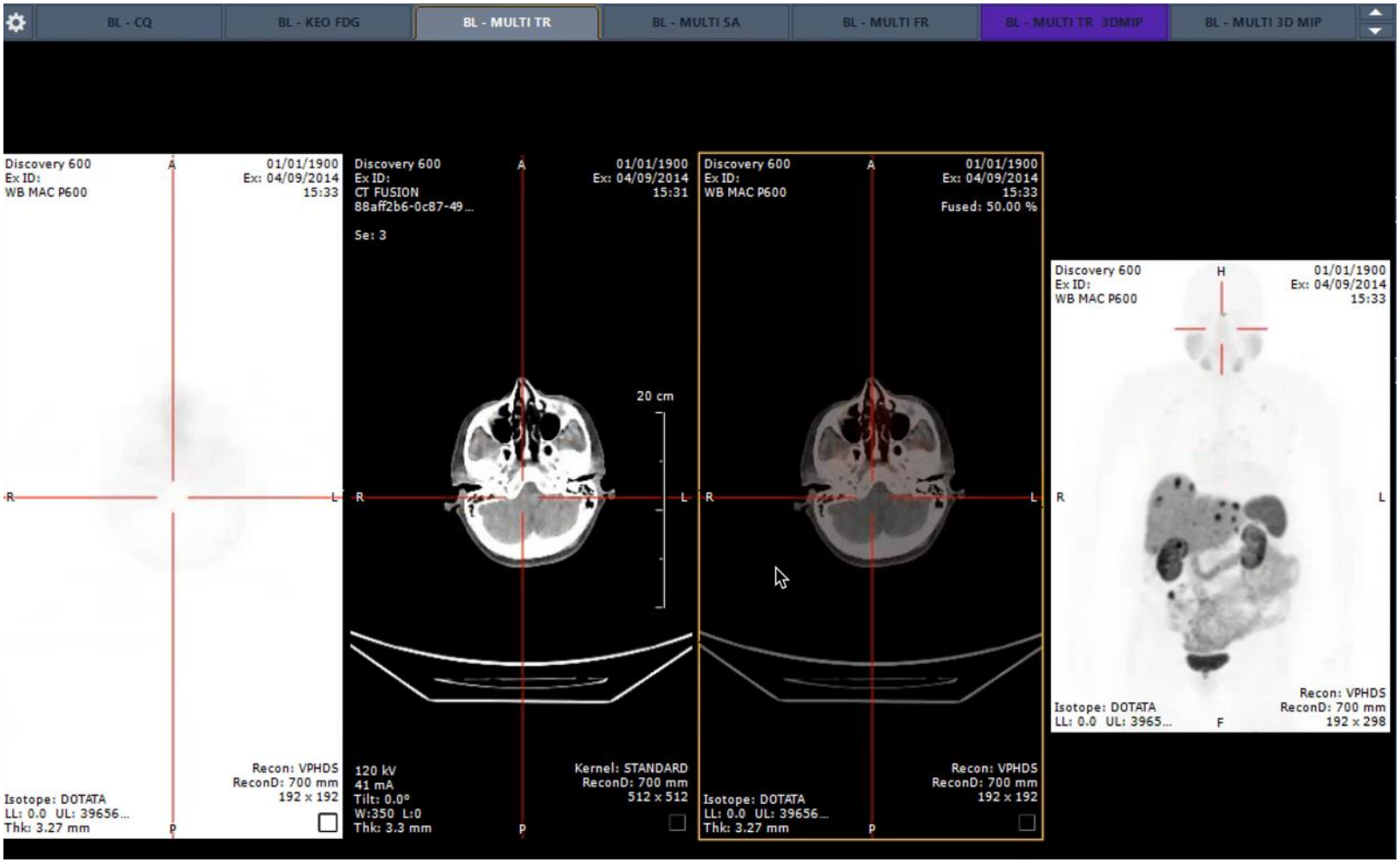






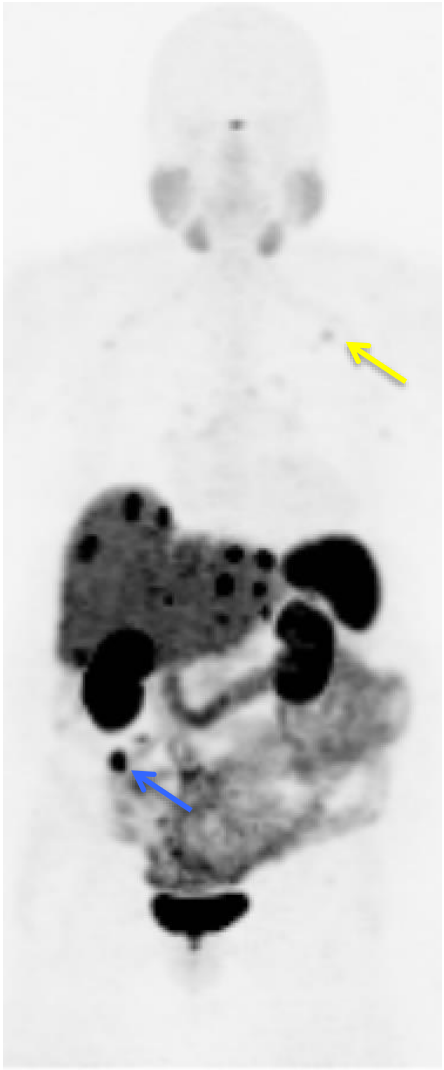
- 31 year old woman with history of small bowel NET
- Liver metastases, retroperitoneal and pelvic lymph node metastases
- Low level, physiologic thymus uptake
- Evidence of prior small bowel resection and lymph node dissection

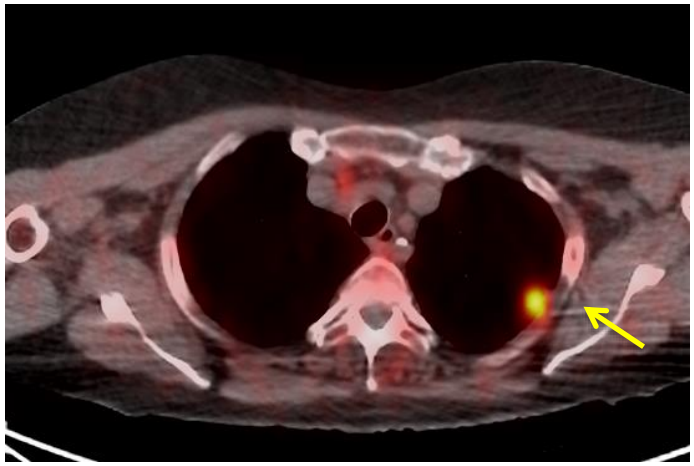
Reader training: (case 116)

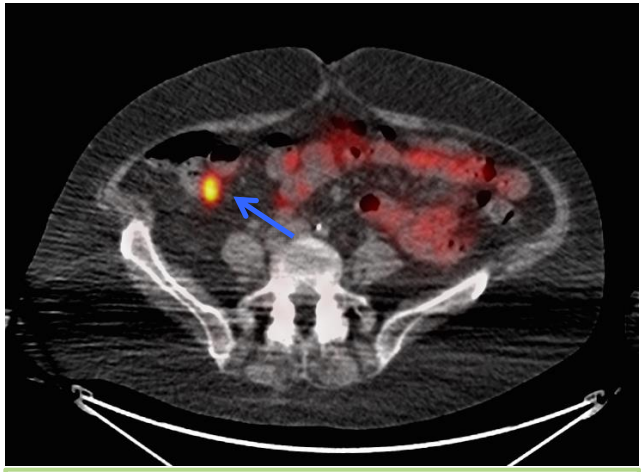


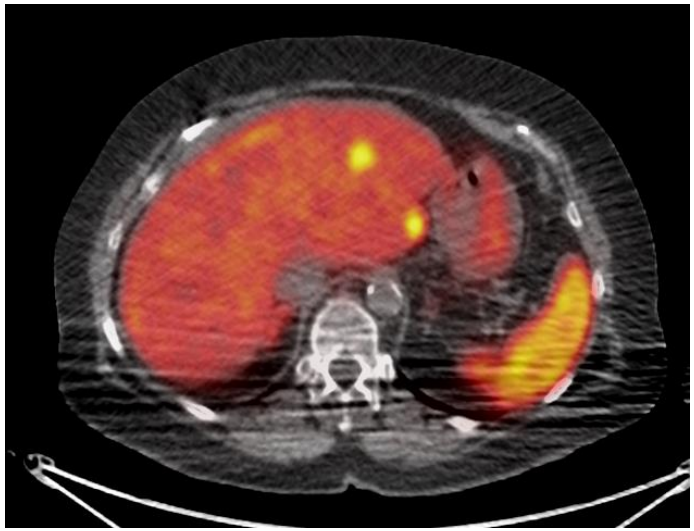
[Click Here to Play]

Key findings: Case 116



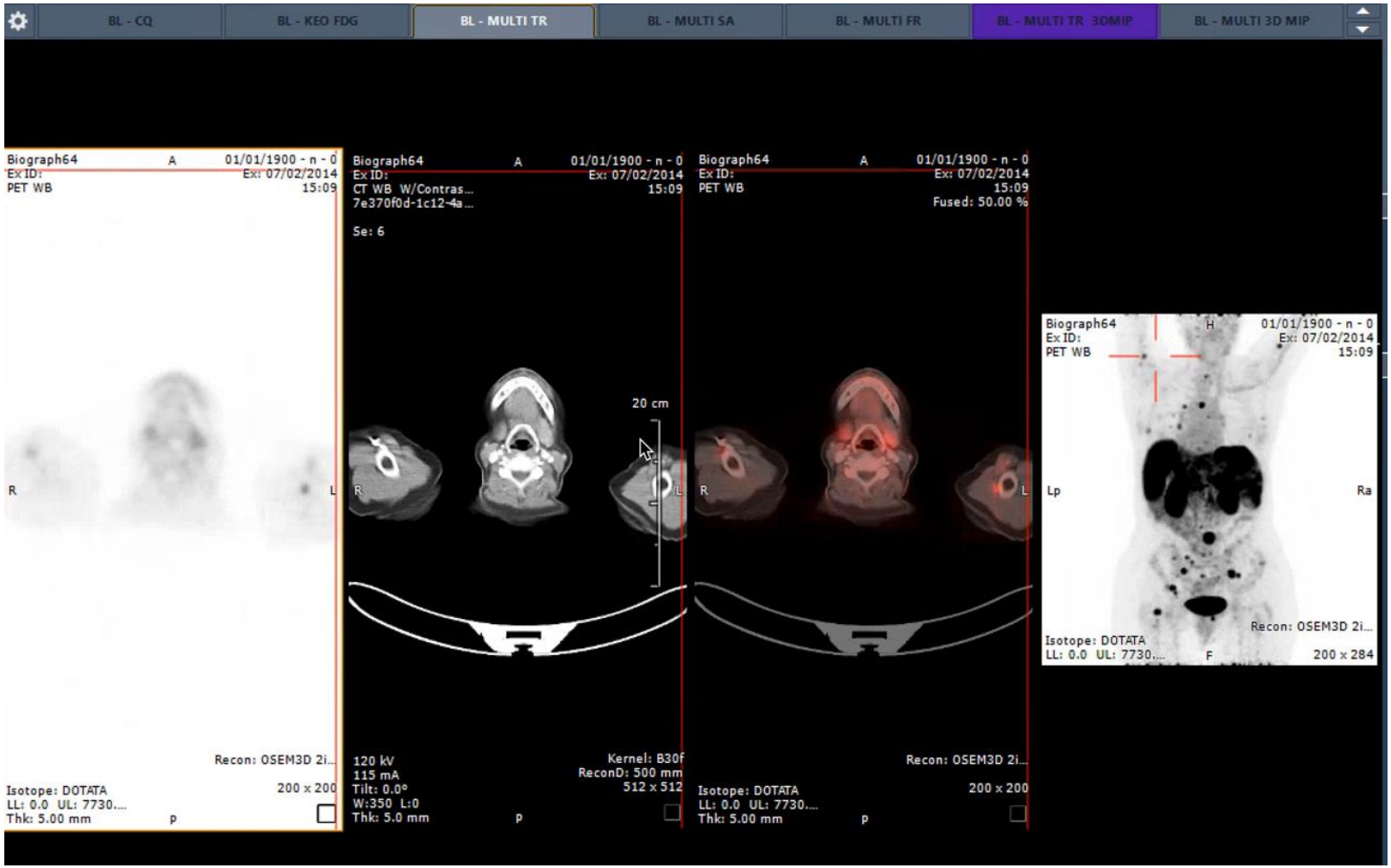






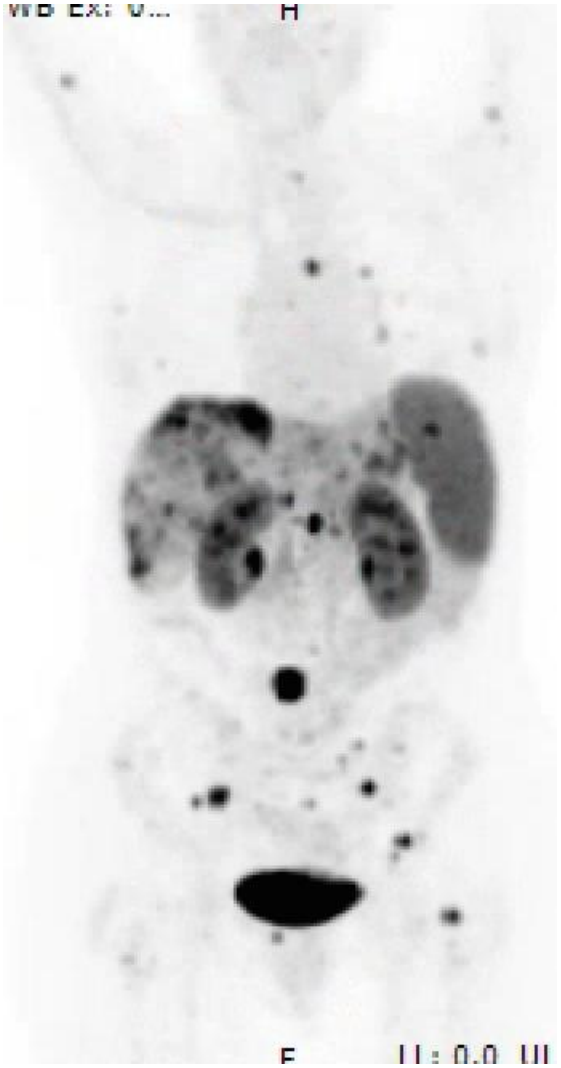
- 73 year old woman with history of metastatic NET
- Lung and lymph node metastases (yellow arrow)
- Liver metastases
- Terminal ileum primary tumor (blue arrow)

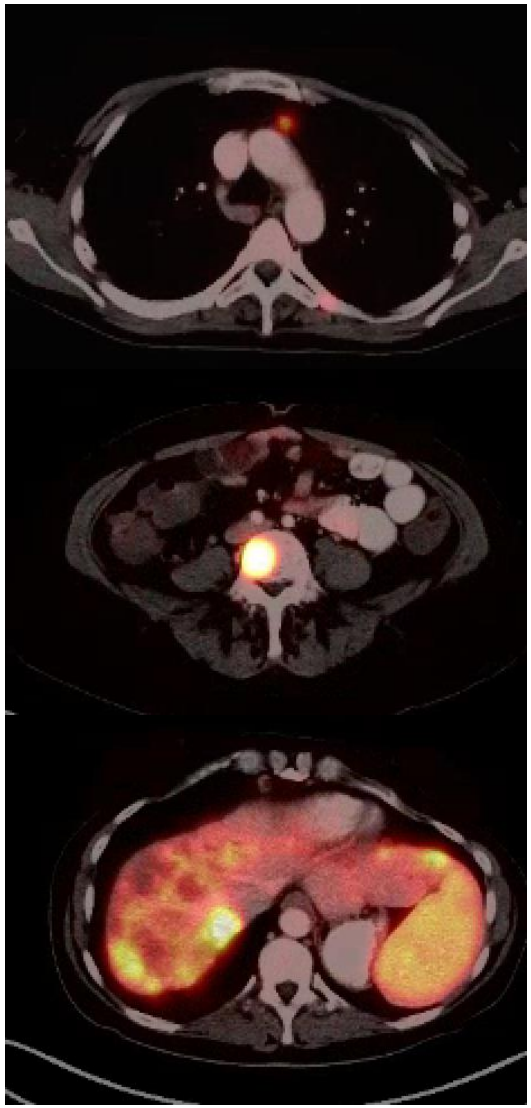
Reader training: (case 119)



[Click Here to Play]

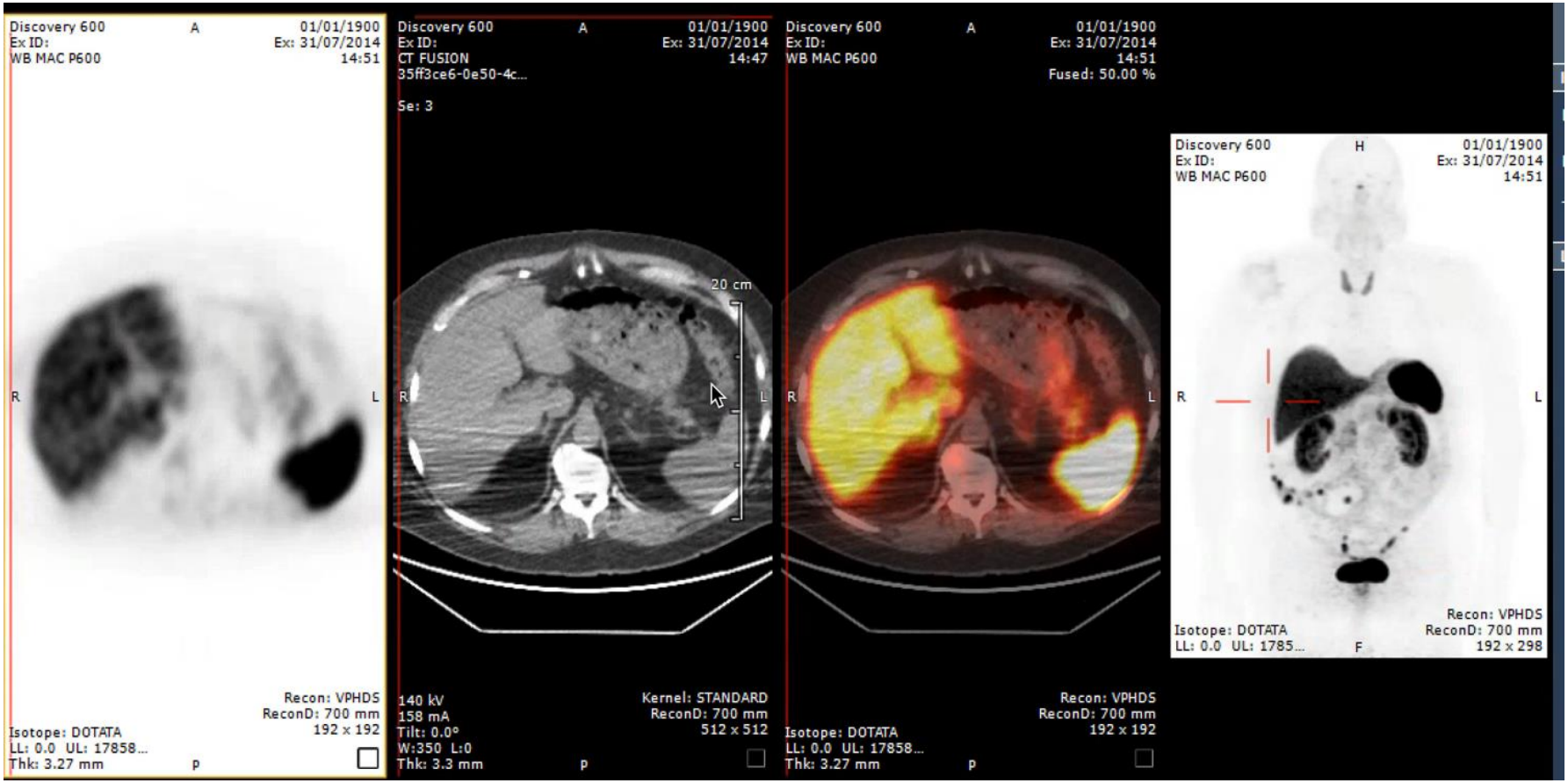
Key findings: Case 119





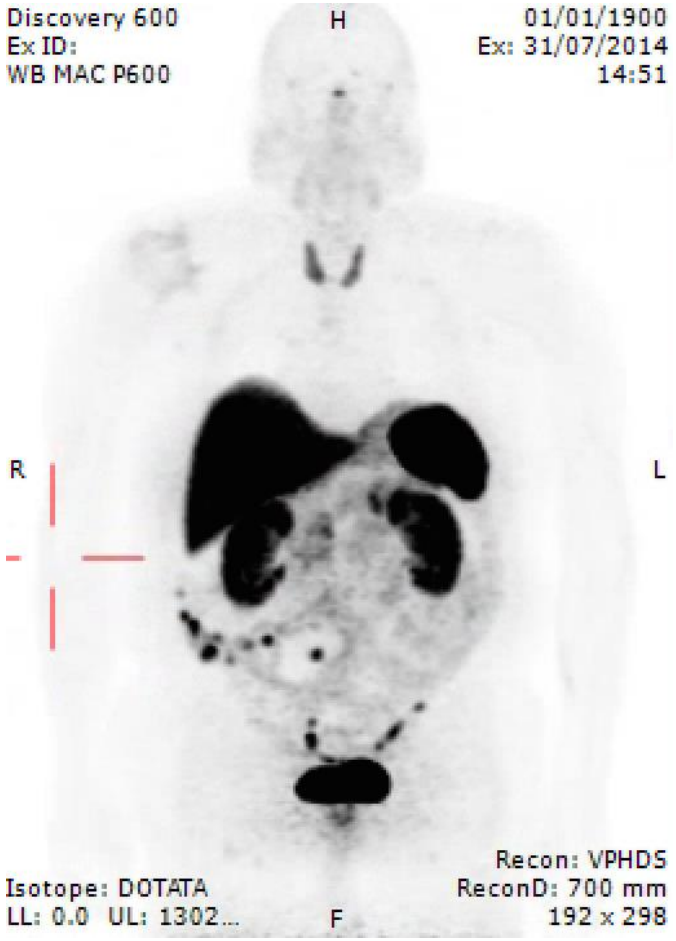
- 45 year old woman with history of pancreatic NET
- Widespread metastatic disease involving liver, lymph nodes, and bones

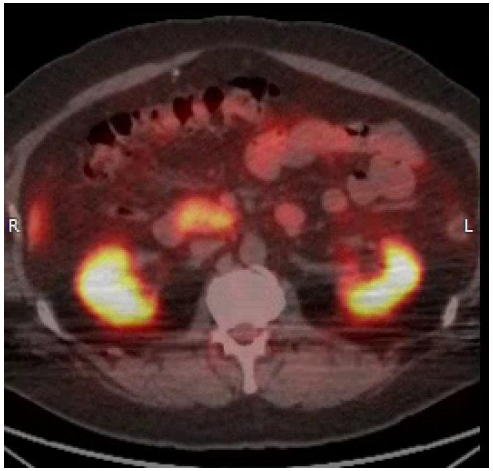
Reader training: (case 132)

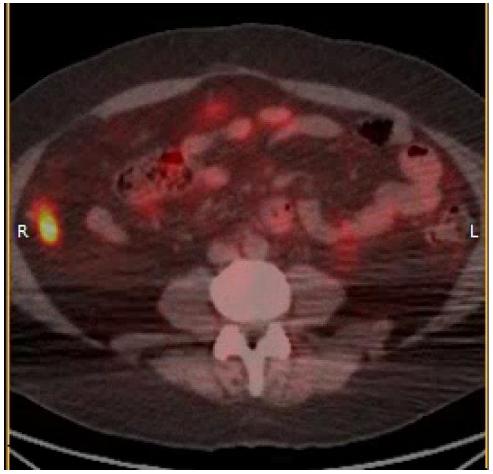


Click Here to Play

Key findings: Case 132







- 70 year old woman with history of terminal ileum NET
- Multiple mesenteric and pelvic metastases
- Physiologic pancreatic uncinate process uptake (normal variant)

Summary

- **NET**SPOT™ PET is more sensitive for the detection of NET than Octreoscan® [1]
- Normal biodistribution of **NET**SPOT™ includes pituitary, adrenal, liver, spleen, and urinary clearance [2]
- False positives include pancreatic head (uncinate process) uptake, splenules, adrenal adenomas, sarcoidosis, thymus, and pituitary adenoma
- **NET**SPOT™ PET can change management by detecting additional primary, recurrent, or metastatic tumors, or excluding them [3]

[1] Deppen et al. J. Nucl. Med. 2016
[2] **NET**SPOT ™ Prescribing Information 2016
[3] Srirajaskanthan et al . J Nucl Med. 2010

Important Safety Information

INDICATIONS AND USAGE

NETSPOT, after radiolabeling with Ga 68, is a radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

• None

WARNINGS AND PRECAUTIONS

Radiation Risk

• Ga 68 dotatate contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer

• Ensure safe handling and preparation reconstitution procedures to protect patients and health care workers from unintentional radiation exposure

Radiation Safety

Drug Handling

• Use waterproof gloves, effective radiation shielding and appropriate safety measures when preparing and handling Ga 68 dotatate injection

• Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides

Patient Preparation

• Instruct patients to drink a sufficient amount of water to ensure adequate hydration prior to administration of Ga 68 dotatate

• Patients should drink and void frequently during the first hours following administration to reduce radiation exposure

Risk for Image Misinterpretation

• The uptake of Ga 68 dotatate reflects the level of somatostatin receptor density in NETs. However, uptake can also be seen in a variety of other tumor types (e.g. those derived from neural crest tissue)

• Increased uptake might also be seen in other pathologic conditions (e.g. thyroid disease or subacute inflammation) or might occur as a normal physiologic variant (e.g. uncinate process of the pancreas)

• Uptake may need to be confirmed by histopathology or other assessments

• Tumors that do not bear somatostatin receptors will not be visualized

ADVERSE REACTIONS

• The safety of Ga 68 dotatate was evaluated in three single center studies and in a survey of the scientific literature. No serious adverse reactions were identified

DRUG INTERACTIONS

• Non-radioactive somatostatin analogs competitively bind to the same somatostatin receptors as Ga 68 dotatate. Image patients with Ga 68 dotatate PET just prior to dosing with long-acting analogs of somatostatin

• Short-acting analogs of somatostatin can be used up to 24 hours before imaging with Ga 68 dotatate

USE IN SPECIFIC POPULATIONS

Pregnancy

• There are no studies with Ga 68 dotatate in pregnant women to inform any drug-associated risks; however, all radiopharmaceuticals, including Ga 68 dotatate have the potential to cause fetal harm

• Animal reproduction studies have not been conducted with Ga 68 dotatate

• In the U.S general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively

Lactation

• There is no information on the presence of Ga 68 dotatate in human milk, the effect on the breastfed infant, or the effect on milk production

• The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Ga 68 dotatate injection and any potential adverse effects on the breastfed child from Ga 68 dotatate injection or from the underlying maternal condition

• Advise a lactating woman to interrupt breastfeeding and pump and discard breast milk for 12 hours after Ga 68 dotatate administration in order to minimize radiation exposure to a breastfed infant

Pediatric

• The efficacy of Ga 68 dotatate PET imaging in pediatric patients with neuroendocrine tumors is based on extrapolation from adult studies, from studies demonstrating the ability of Ga 68 dotatate to bind to somatostatin receptors, and from a published study of Ga 68 dotatate PET imaging in pediatric patients with somatostatin receptor positive tumors

• The safety profile of Ga 68 dotatate is similar in adult and pediatric patients with somatostatin receptor positive tumors

• The recommended Ga 68 dotatate injection dose in pediatric patients is weight based as in adults

Important Safety Information

Geriatric

• Clinical studies of Ga 68 dotatate injection did not include sufficient numbers of subjects aged 65 and over, to determine whether they respond differently from younger subjects

• Other reported clinical experience has not identified differences in responses between the elderly and younger patients

OVERDOSAGE

• In the event of a radiation overdose, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by reinforced hydration and frequent bladder voiding. A diuretic might also be considered

• If possible, an estimate of the radioactive dose given to the patient should be performed

Please see full Prescribing Information.

To report SUSPECTED ADVERSE REACTIONS, contact Advanced Accelerator Applications USA, Inc. at 1-212-235-2380 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Manufactured by:
Gipharma S.r.l.
Strada Crescentino snc-1
3040 Saluggia (Vc), Italy

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Advanced Accelerator Applications USA, Inc., NY 10118