

^{68}Ga -DOTATATE PET/CT in Gastroenteropancreatic Neuroendocrine Tumors (NETs):

What the abdominal radiologist needs to know.

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Learning Objectives

- To review:
 - Physiologic distribution of ^{68}Ga -DOTATATE
 - Potential pitfalls of ^{68}Ga -DOTATATE PET.
 - ^{68}Ga -DOTATATE PET in gastroenteropancreatic(GEP) NETs
 - Pathologic uptake scoring system for ^{68}Ga -DOTATATE
 - Comparison to conventional imaging
 - Impact of ^{68}Ga -DOTATATE PET to patient management

Introduction

- NETs: heterogeneous group of tumors ranging from indolent (low grade) to less common aggressive (high grade) tumors [1].

Differentiation	Grade	Criteria
Well Differentiated	Low (Typical)	<2 mitoses/10HPF & Ki67 index < 2%
Moderately Differentiated	Intermediate (Atypical)	2-20 mitoses/10HPF or Ki67 index = 3-20%
Poorly Differentiated	High	>20 mitoses/10HPF or Ki67 index > 20%

- Somatostatin receptors (SSTR) expressed on cell surface of neuroendocrine cells regulate neurotransmission, hormone secretion and cell proliferation.

Introduction

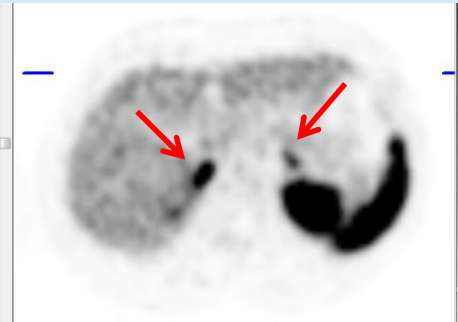
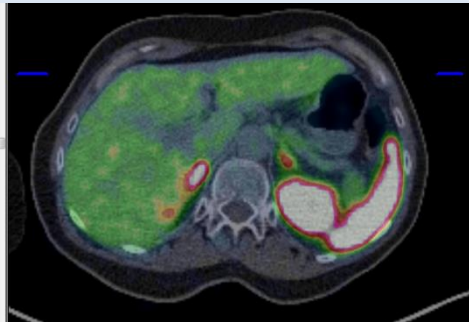
- Octreotide is a somatostatin analog.
- SSTR imaging using octreotide has been used to stage & restage patients with NETs for several decades [2].
- Recently, somatostatin analogs labeled with positron emitters have been introduced into the clinical use for the imaging of NETs. [3]
- ^{68}Ga -DOTATATE (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) is one of the most commonly available tracers.

Introduction

- Expression of SSTRs is used for imaging and therapy; theranostics.
- High-level expression of SSTR is exploited to deliver targeted radiotherapy to tumor sites (peptide receptor radionuclide therapy = PRRT) [4].
- NETs:
 - Challenging to diagnose and treat.
 - Symptoms can be vague, consisting of diarrhea, abdominal cramps, shortness of breath, blood pressure changes, headaches and rashes.
 - Tumors may not be detected by routine imaging.
 - As a result, a diagnosis is often made when the disease is at an advanced stage.

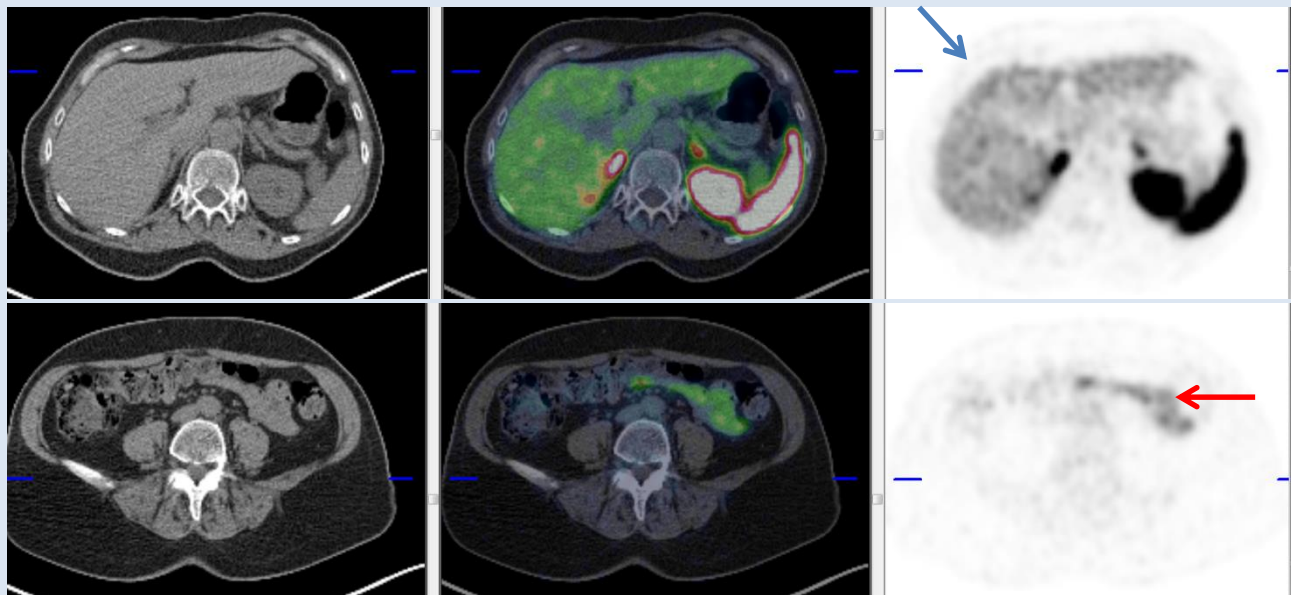
^{68}Ga -DOTATATE PET: Physiological distribution

- Most intense physiologic uptake: Spleen, kidneys pituitary (blue arrows on right MIP image), and adrenal glands (red arrows bottom axial image).



^{68}Ga -DOTATATE PET: Physiological distribution

- Moderate radiotracer uptake in liver (blue arrow), salivary glands and thyroid. Variable uptake in bowel (red arrow).
- This biodistribution reflects both specific receptor binding (eg, spleen, salivary glands) and nonspecific tissue handling of the peptide (eg, liver, kidneys) [5].

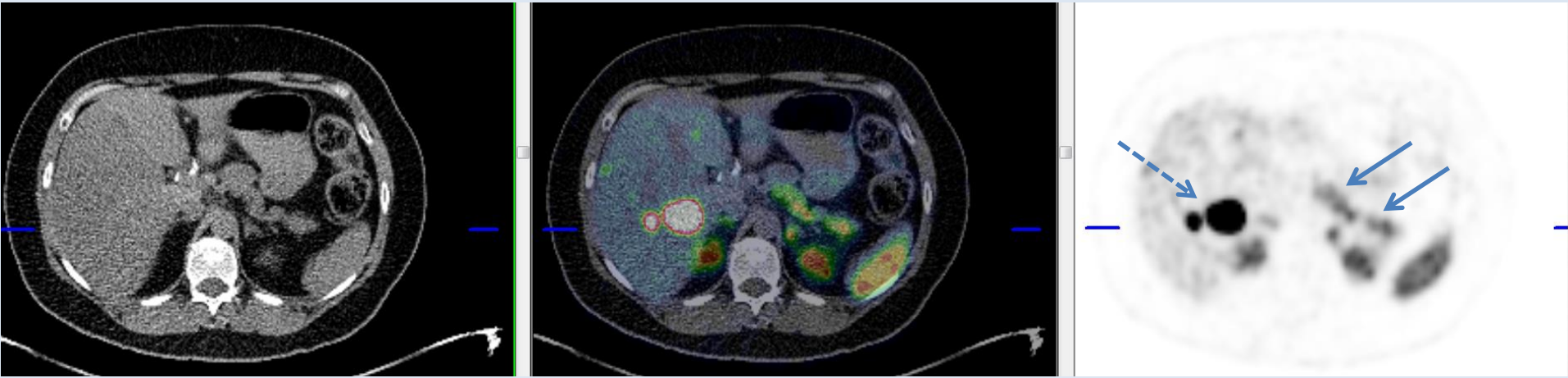


Potential pitfalls

- *Exaggerated physiological uptake in pancreas*: most common in uncinate process of pancreas.
- Reported in ~ one-third of patients.
- Uptake may be intense
- Thought to represent exaggerated physiological uptake due to prominent/hypertrophied islet cell clusters [5].

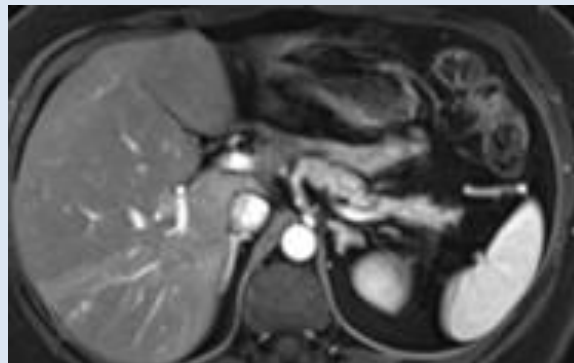
Potential Pitfalls:

Exaggerated physiological ^{68}Ga -DOTATATE Uptake in Pancreas- Case 1



Post Whipple's procedure for well-differentiated pancreatic NET; 0/14 nodes involved; Ki 67, 3%.

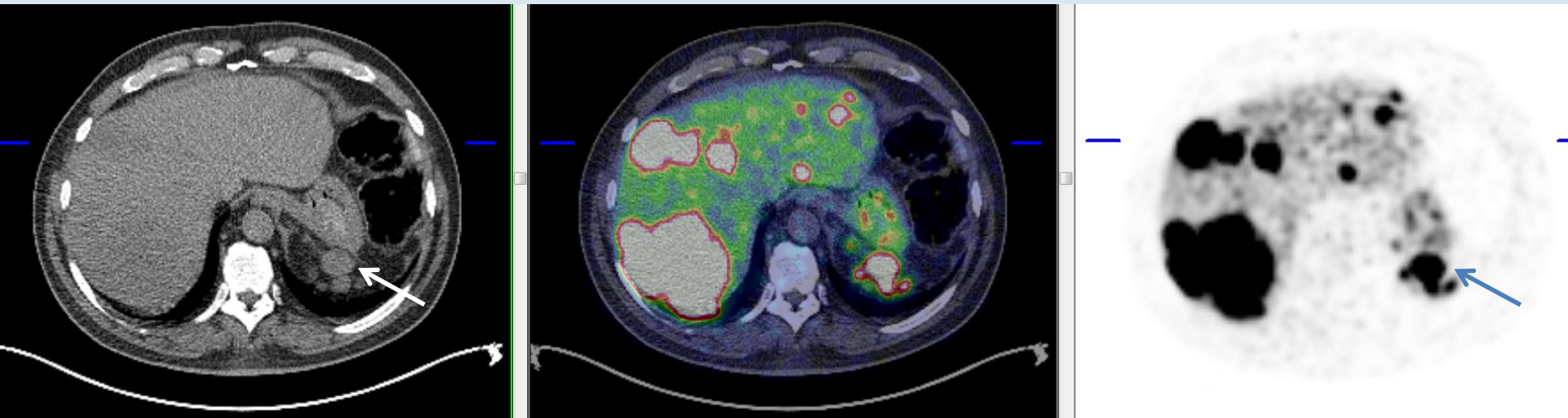
^{68}Ga -DOTATATE PET/CT: liver metastases (dotted arrows) & moderately intense diffuse radiotracer uptake in remaining pancreas (arrows). Normal pancreas on concurrent MR (contrast-enhanced T1 VIBE, below); also stable 1 year later (not shown).



Potential Pitfalls:

Splenosis – Case 2

- Splenectomy is often performed as part of en-bloc resection of pancreatic tail tumors.
- **Splenosis** post splenectomy and splenules are common and may be mistaken for peritoneal deposits on CT and 68Ga-DOTATATE PET due to the intense physiological radiotracer activity in splenic tissue.
- Intrapancreatic splenule may pose a diagnostic dilemma. Denatured red blood cell scan can help confirm the diagnosis and exclude tumor.

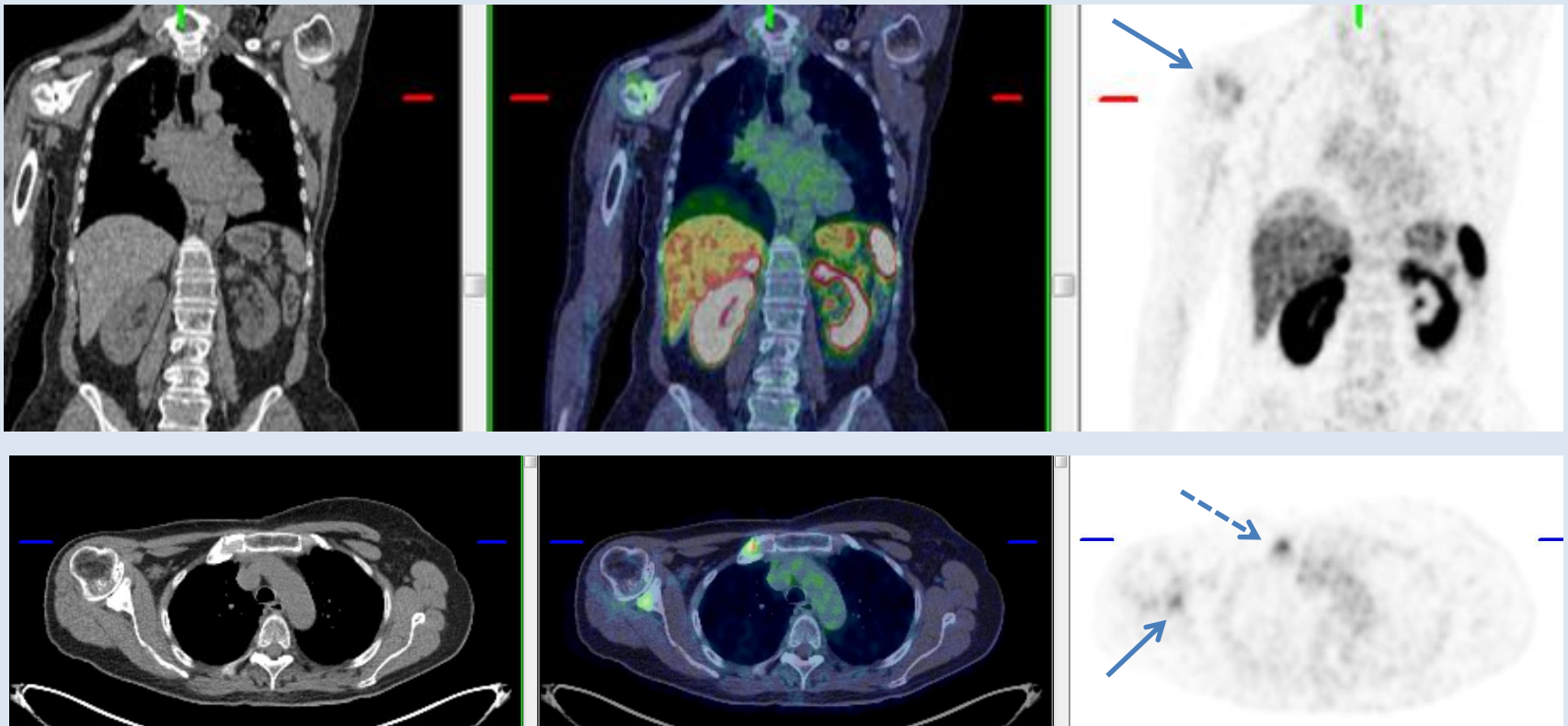


Metastatic pancreatic tail NET post distal pancreatectomy and splenectomy. Intense radiotracer uptake is seen in splenosis (arrow).

Potential Pitfalls:

Osteoblastic activity – Case 3

- Osteoblasts express somatostatin receptors (SSTR-2; therefore, any process with increased osteoblastic activity may demonstrate increased ^{68}Ga -DOTATATE uptake [6].
- Low level tracer uptake in benign bone tumors: e.g hemangioma/ fibrous dysplasia.

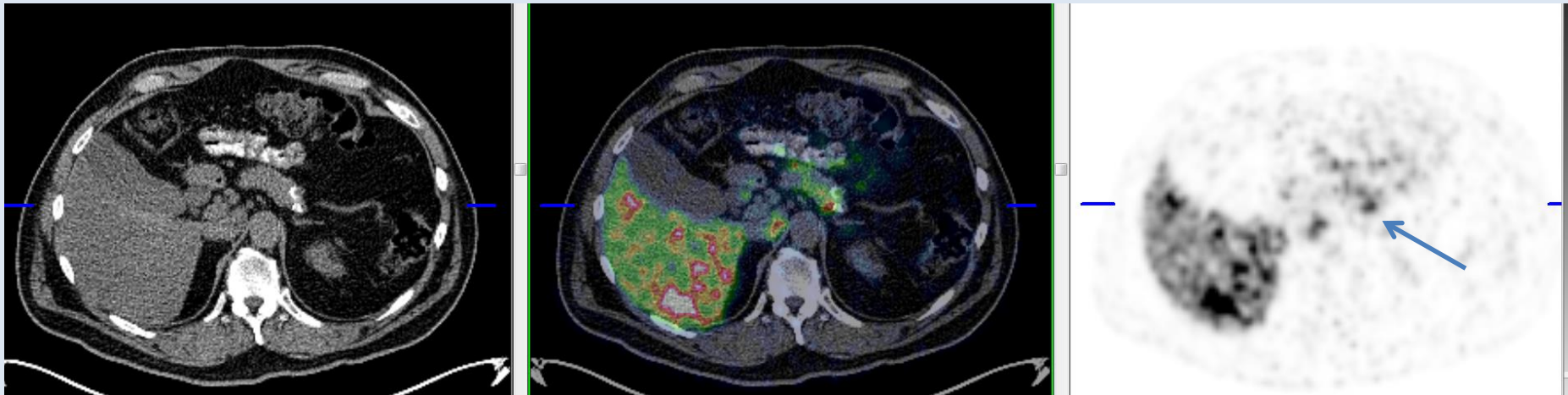


Right shoulder osteoarthritis (arrow on upper coronal and bottom axial image; Degenerative costochondral changes (dotted arrow lower image) show moderate tracer uptake

Potential Pitfalls:

Inflammation – Case 4

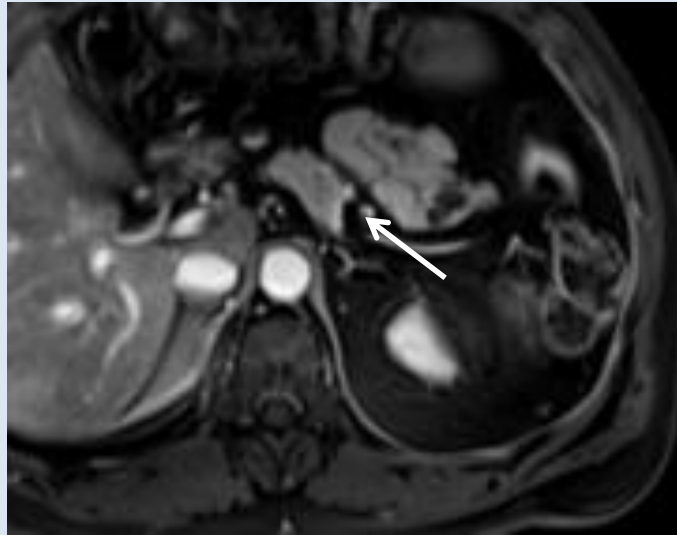
- Inflammatory cells, such as macrophages, exhibit type 2 somatostatin receptors.
- This may be utilized for imaging inflammation in atherosclerotic plaques [7], but needs to be recognized to avoid diagnostic pitfalls.



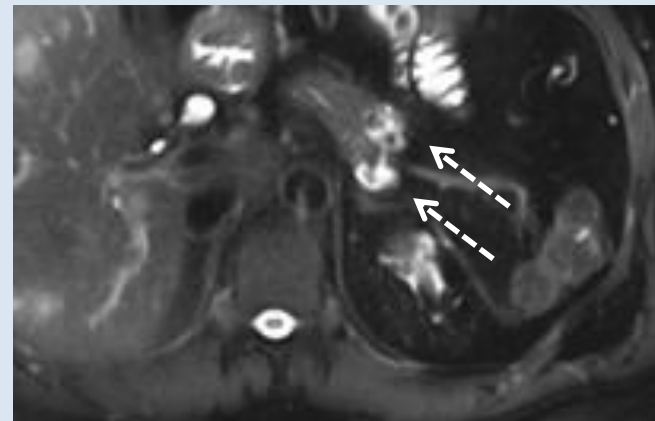
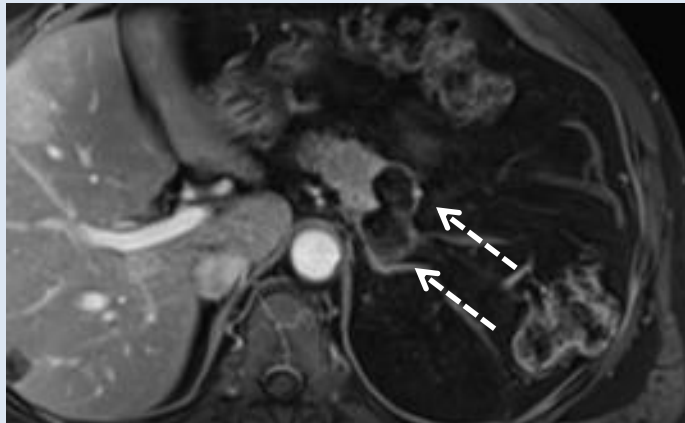
Post distal pancreatectomy for NET:

Moderate focal radiotracer uptake along resection margin of pancreas (arrow).

Concurrent post contrast T1 axial MR image (bottom left): shows linear enhancement along resection margin in keeping with postoperative change (arrow).



MR (contrast-enhanced T1 VIBE (bottom middle) and Axial T2 (bottom right) performed ***one year earlier***, show postoperative collections along resection margin (dotted arrows).



^{68}Ga -DOTATATE PET in management of patients with GEP NETs: Initial diagnosis

- ^{68}Ga -DOTATATE PET should be considered as first-line diagnostic imaging in patients with clinical & biochemical suspicion of GEP NETs when conventional workup is negative or equivocal.
- A meta-analysis comprising 567 NET patients has shown a pooled patient-level sensitivity and specificity of 93% and 91%, respectively [8].
- In patient with NET metastases with an unknown primary, identification of the primary site is of prime importance to patient management, prognosis, treatment outcome, and survival.
- ^{68}Ga -DOTA peptide PET may detect a primary tumor in approximately 60% of patients with unknown primary, often midgut tumors [9].

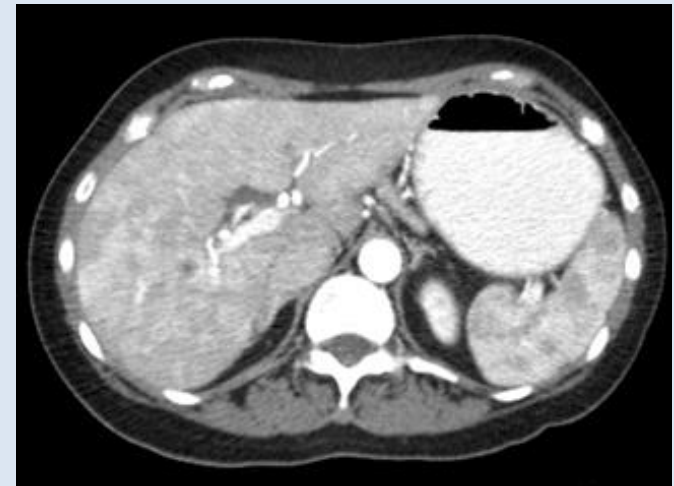
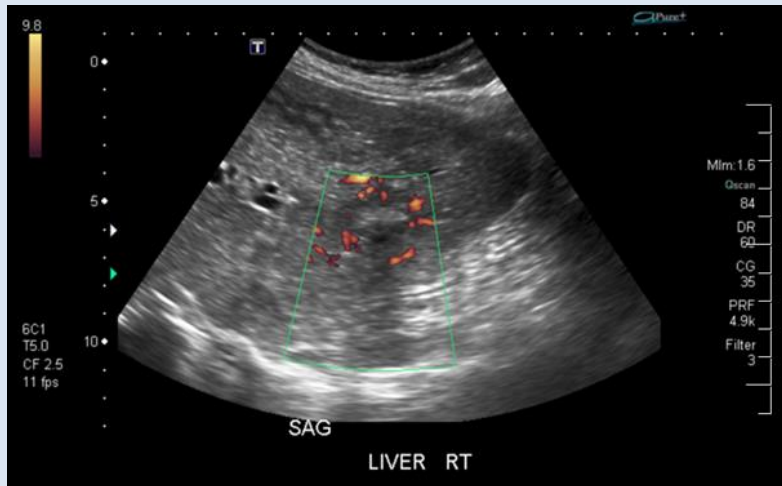
Initial diagnosis - Case 5:

52 year-old. History of nasopharyngeal carcinoma. Now: melena. Workup included:

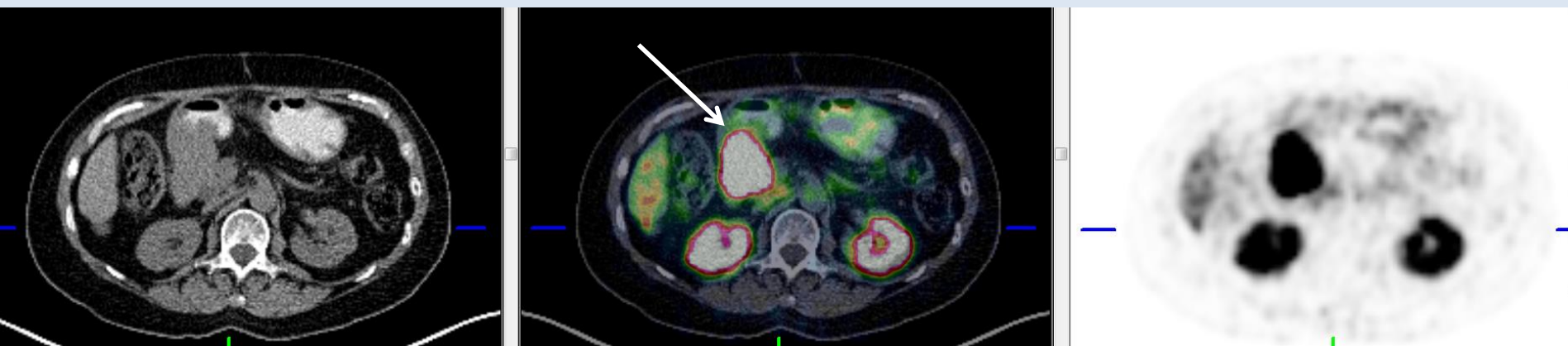
Gastroscopy: nonspecific duodenal ulcer; biopsies negative for malignancy.



US abdomen and multiphasic CT: Multiple hypervascular liver deposits.



Liver biopsy: Well-differentiated NET, WHO grade 2.



^{68}Ga -DOTATATE PET/CT shows abnormal radiotracer uptake in duodenal mass (SUVmax, 38.7; arrow).

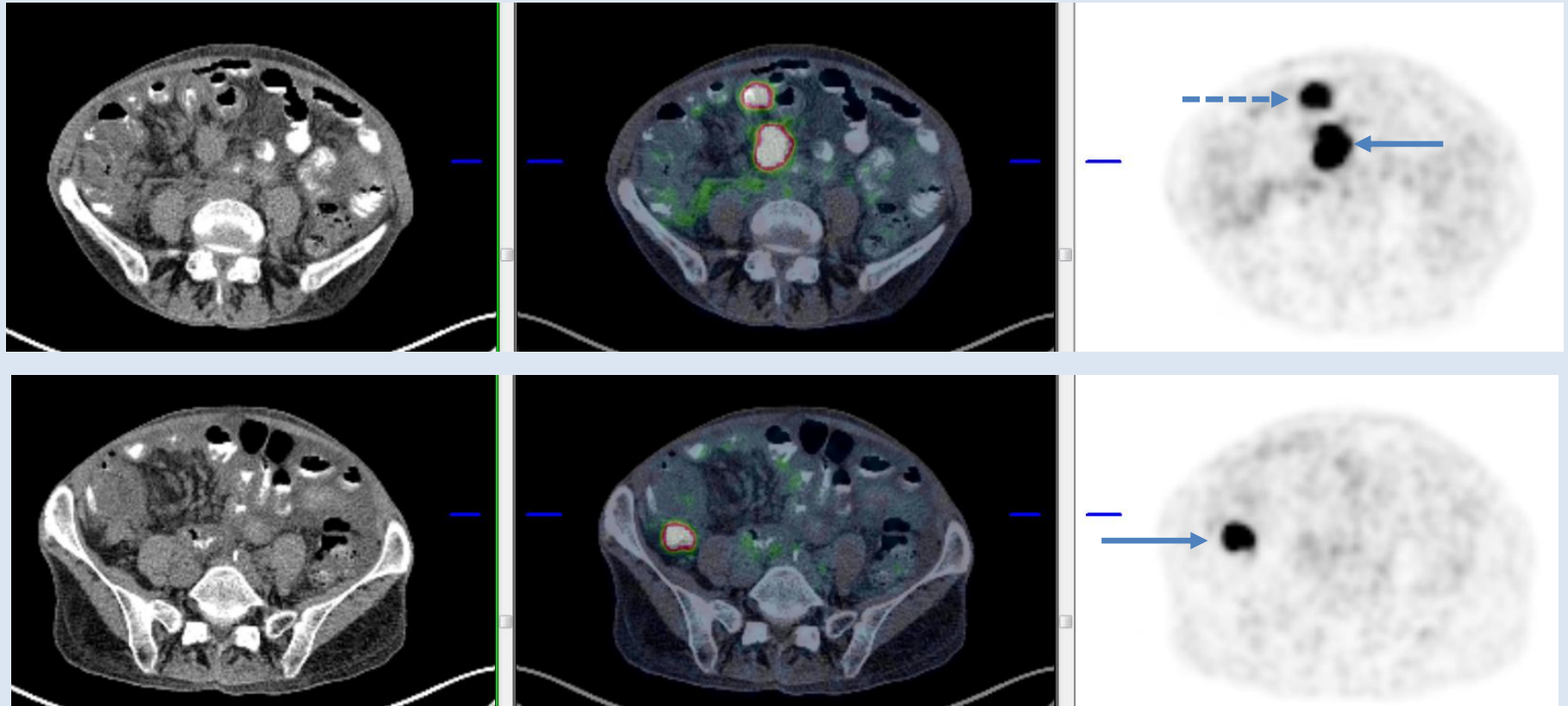
Findings confirmed at laparotomy.

^{68}Ga -DOTATATE PET in management of patients with GEP NETs:

Preoperative staging for patients with localized primary and/or limited metastases

- ^{68}Ga - PET has higher sensitivity than conventional imaging (CT, MRI, US) in detecting primary tumor (78.3% vs 63.8%, $p < 0.001$) & metastases (97.4% vs 81.8%, $p < 0.001$) [10].
- Improved detection of lymph node metastases (sensitivity: 92% vs 64%, $p = 0.0156$); bone metastases (sensitivity, 100% vs 47%, $p = 0.0039$) with higher specificity for both [11, 12].
- More specific than CECT for the detection of pulmonary metastases (95% vs 82%, $p = 0.0313$), with equal sensitivity [13].
- Overall, change in management may occur in over 1/3 of patients, with the majority of the changes involving surgical planning & patient selection for PRRT.

60 year old female with mesenteric mass shown to represent well-differentiated NET; primary unknown – Case 6



^{68}Ga -DOTATATE PET/CT shows metastatic mesenteric nodal mass (solid arrow, top image), primary small bowel tumor (dotted arrow, top image) and peritoneal deposit in right paracolic gutter (dotted arrow, bottom image).

^{68}Ga -DOTATATE PET in management of patients with GEP NETs:

To determine somatostatin receptor status and suitability for peptide receptor radionuclide therapy.

- PRRT: an important component of the treatment paradigm for NET patients.
- Localized radiation delivered by radionuclides -eg lutetium-177 (^{177}Lu) or yttrium-90 (^{90}Y), to NET cells by internalization after binding to somatostatin receptors.
- A prospective randomized phase 3 trial showed prolonged progression-free survival in patients with midgut NETs after treatment with ^{177}Lu -DOTATATE compared with high-dose octreotide [14].
- ^{68}Ga -DOTA peptide PET can be used in place of In-111 pentetreotide scintigraphy for patient selection.
- Tracer uptake is predictive of therapeutic response to PRRT [15], although criteria for patient selection with PET are still evolving.

Krenning score system

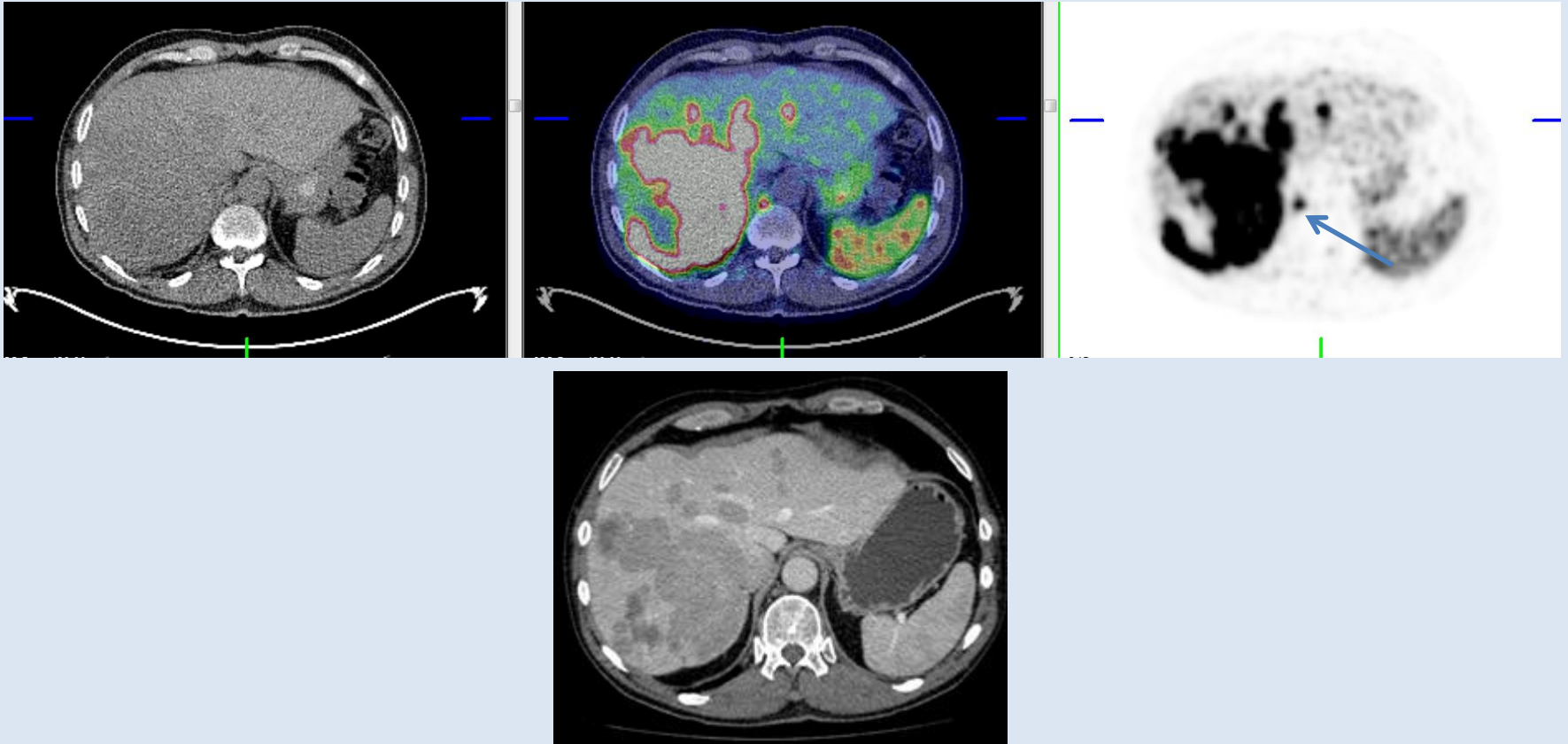
- **Krenning score** was proposed as a scale to describe degree of tracer uptake in octreotide scintigraphy [8].
- It has been recently adopted in the reporting of ^{68}Ga -DOTA peptide PET [9].
- Most common application is to assess candidacy for peptide receptor radionuclide therapy (PRRT), such as ^{177}Lu -DOTATATE (usually with a Krenning score > 2).

Krenning Scoring System	
Score	Intensity of Uptake
0	None
1	Very low
2	\leq Liver
3	$>$ Liver
4	$>$ Spleen

Uptake is assessed visually according to the relevant reference tissue.

Krenning score system:

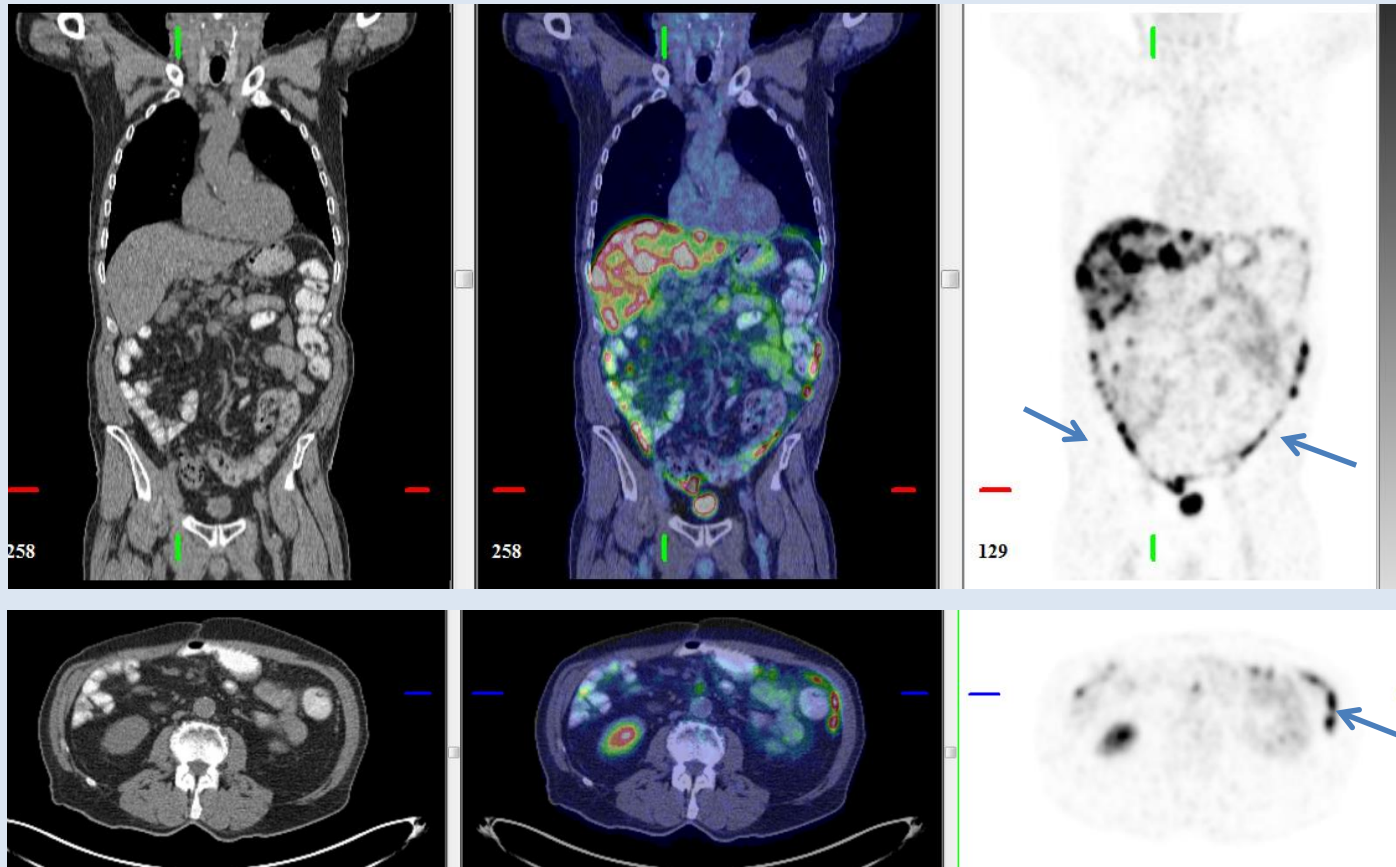
Example - Case 7



- A. Top row: 68Ga-DOTATATE PET/CT - Extensive liver metastases as well as retrocrural lymph node (arrow) showing intense radiotracer uptake, higher than background spleen (Krenning score, 4).
- B. Bottom row: Corresponding contrast-enhanced CT image (portal venous phase).

Krenning score system & Response to PRRT

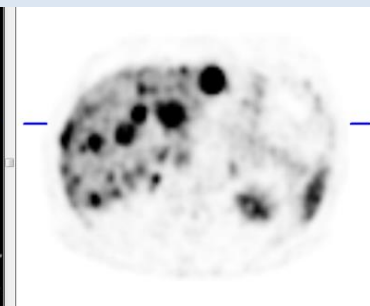
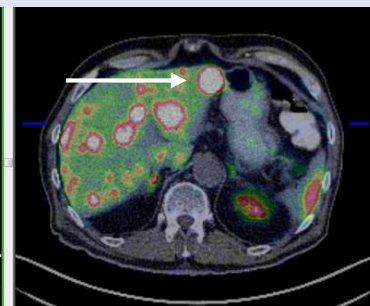
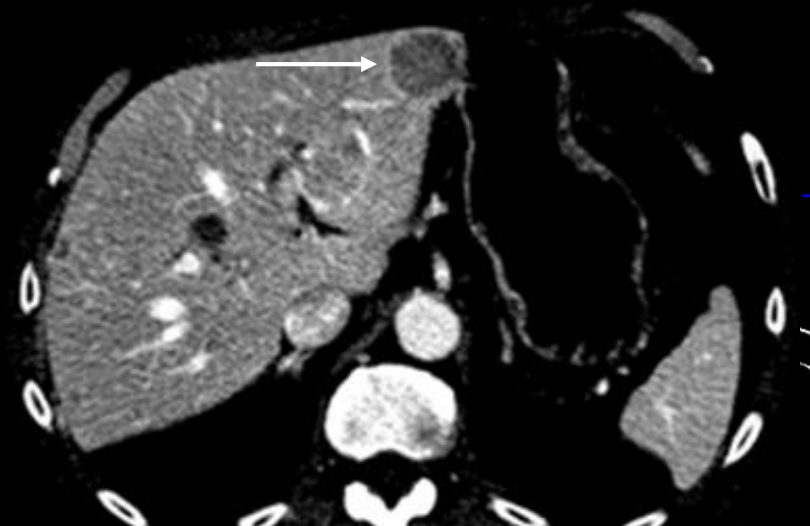
Example - Case 8



76 year old male with metastatic small bowel NET, Ki 67 = 3%; being considered for PRRT.

Coronal PET/CT image (top) shows intense ^{68}Ga -DOTATATE uptake in extensive liver metastases as well as peritoneal metastases along the pericolic gutters also seen on axial image (bottom); Krenning score, 4; arrows.

Patient was found suitable for PRRT.



Baseline imaging: contrast-enhanced CT shows deposit in segment 2 of the liver (arrow, upper left image); ^{68}Ga -DOTATATE PET/CT shows multiple liver metastases including in segment 2 (arrow, above)

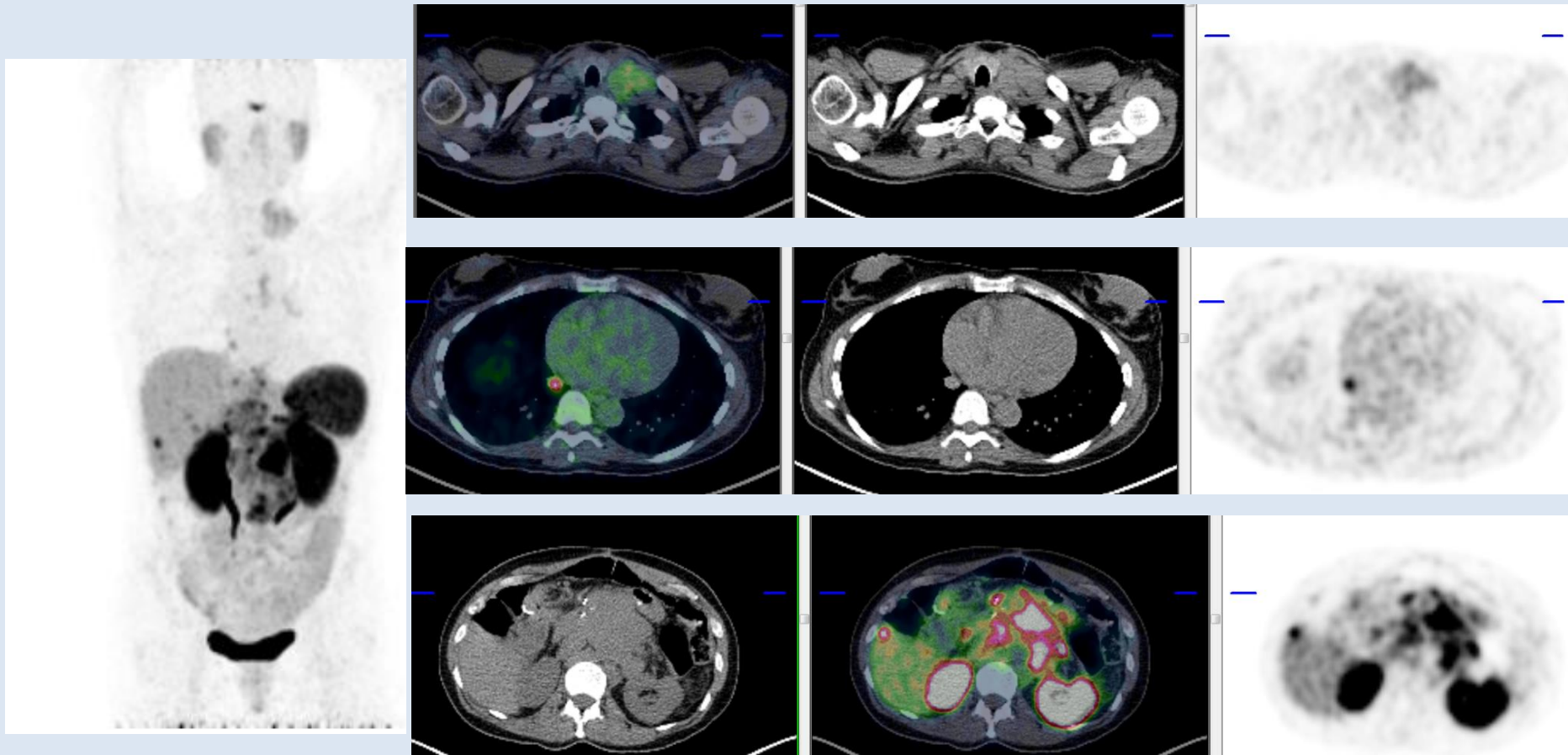


Follow-up contrast enhanced CT 14 months later (6 months after completion of PRRT) shows decrease in size of the target liver deposit, indicating response to therapy (dotted arrow, left).

Role of Dual Isotope ^{68}Ga -DOTATATE & ^{18}F -FDG PET in Patient Selection for PRRT

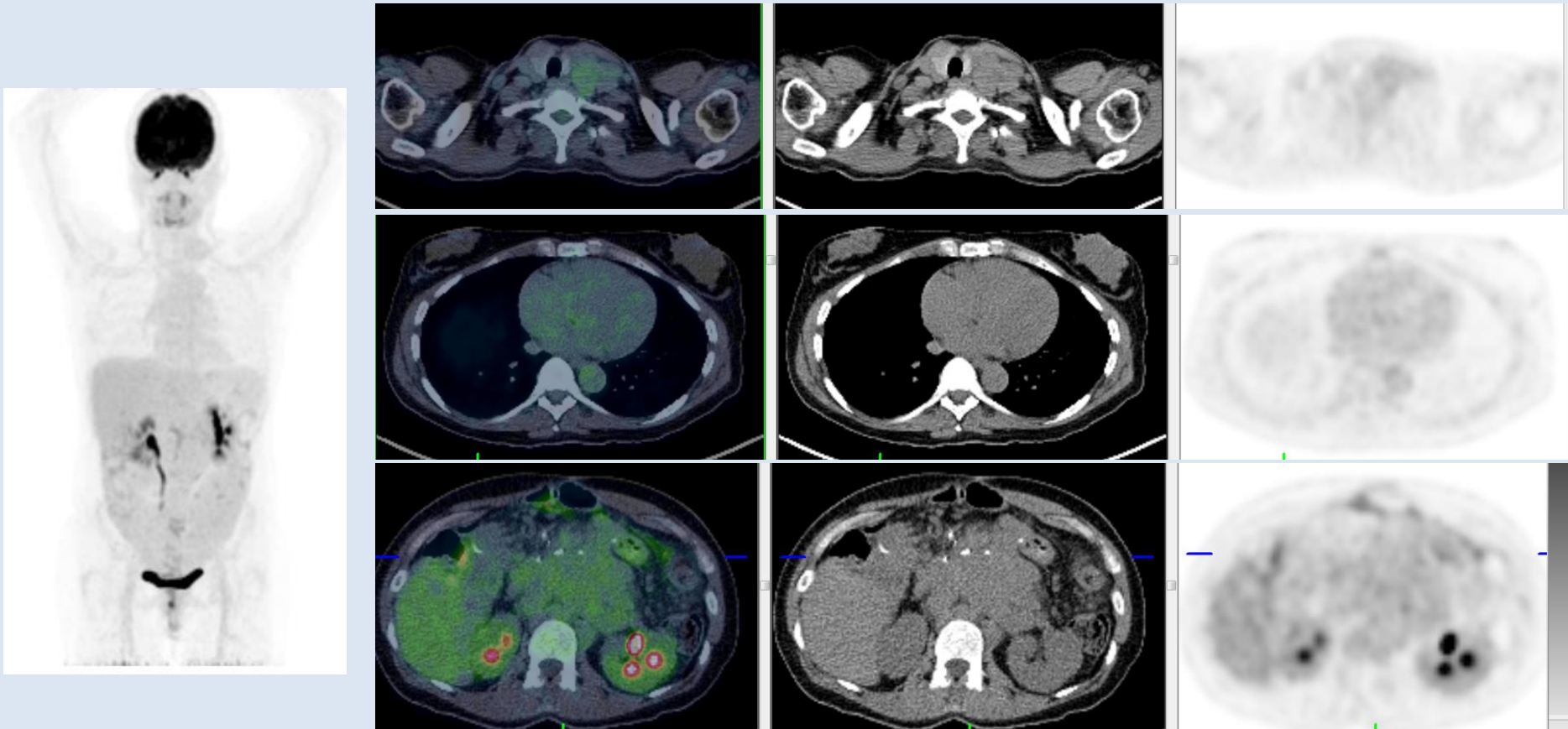
- Typically, high-grade NECs have lower SSTR expression and are better imaged with ^{18}F -FDG-PET [16].
- FDG PET can be positive in 40% of patients with grade I disease and 93% of patients with grade 3 disease [17].
- Significant tumor heterogeneity can occur in patients, with the coexistence of both well-differentiated and poorly-differentiated deposits [16-18].
- Patients with FDG avid disease have poorer overall survival [19].
- Given that SSTR-targeted PRRT delivers a therapeutic radionuclide to areas of somatostatin receptor uptake, FDG-avid lesions that have no appreciable uptake on ^{68}Ga -DOTATATE PET would not be targeted effectively by PRRT.

52 year old woman with metastatic pancreatic NET to liver, nodes and lung – Case 9 part I



^{68}Ga -DOTATATE PET/CT: heterogeneous, moderately intense radiotracer uptake in the large confluent mesenteric & retroperitoneal lymphadenopathy, liver deposits (arrow bottom image), lung deposit (arrowhead, middle image); Krenning score 3-4. Low level uptake in metastatic left supraclavicular nodal mass (Krenning score, 2).

Patient referred to FDG PET/CT to exclude high grade disease which would not be responsive to PRRT – Case 9 part II



^{18}F - FDG PET/CT: no significant uptake at any of the disease sites to suggest high grade disease.

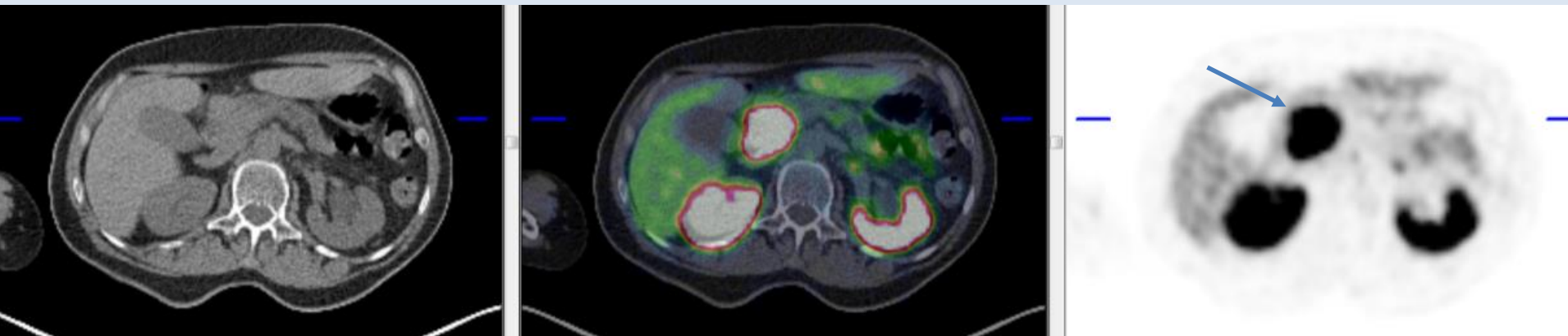
The combination of data from ^{68}Ga -DOTATATE PET and FDG PET may help in appropriate patient selection for PRRT.

^{68}Ga -DOTATATE PET in management of patients with GEP NETs:

Re/staging of patients with NETs where detection of occult disease will alter management

Case 10:

Post oophorectomy for ovarian mass, with histological diagnosis of well-differentiated neuroendocrine tumor. CT subsequently performed suggests pancreatic primary (not shown). Staging ^{68}Ga -DOTATATE PET was performed to help determine optimal patient management.

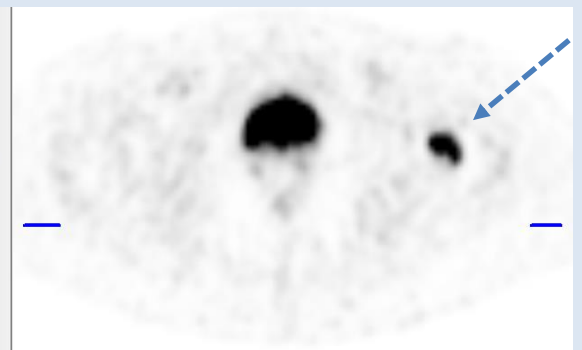
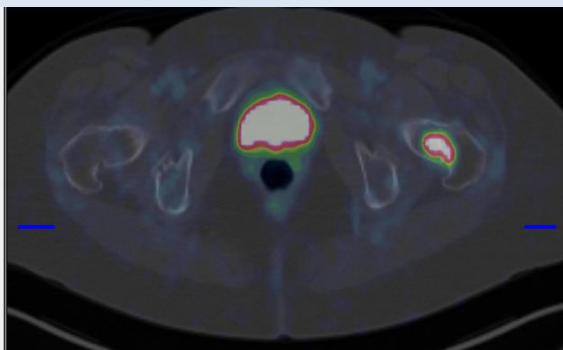
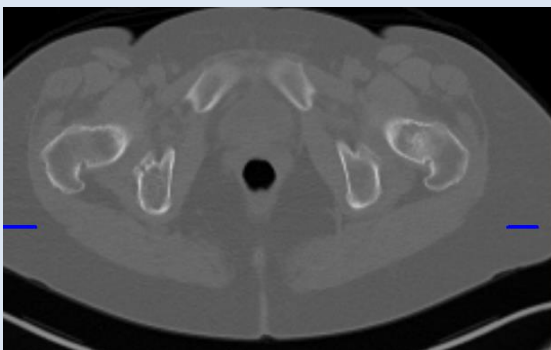


^{68}Ga -DOTATATE PET shows intense radiotracer uptake in known pancreatic head mass (arrow).



PET also shows bone metastases at C1, T7, and left proximal femur (dotted arrows left image & bottom image).

Patient was referred for PRRT.



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Thanks you!