

Imaging in NET: Contribution of isotopic scanning



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Tandem Talk 1

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Barcelona, Spain

Sirtex - Consultant



Isotopic imaging in the era of hybrid imaging

PET/CT



SPECT/CT



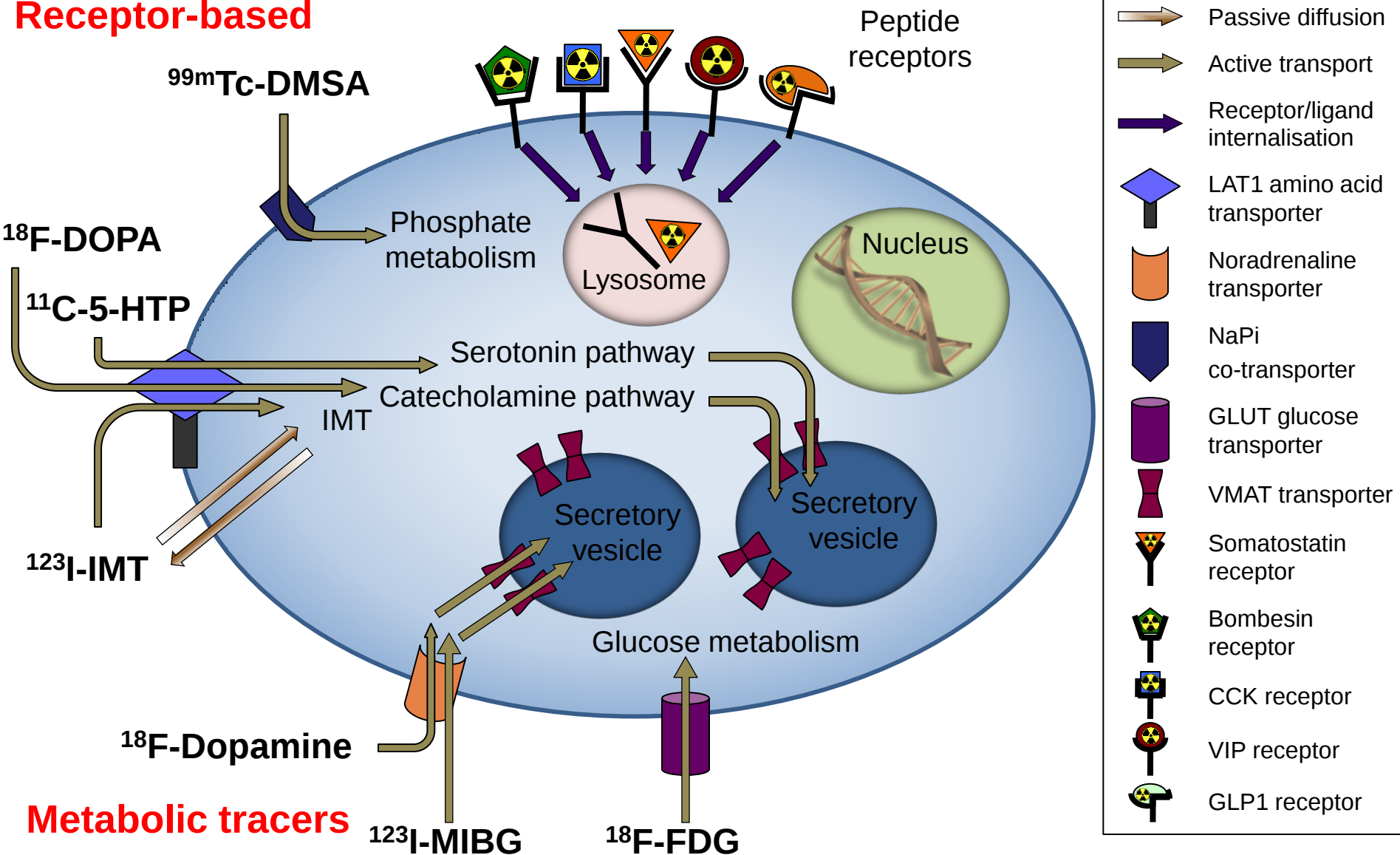
PET/MRI



PET/MRI

Molecular targets for GEP-NET imaging

Receptor-based

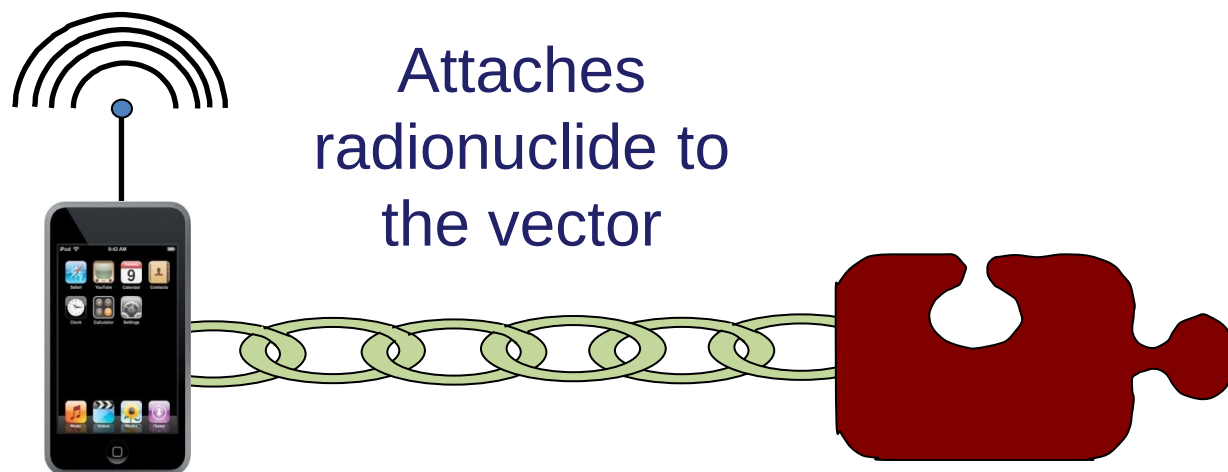


Classification of tracers available for NET imaging

- Peptide receptor based imaging
 - Somatostatin receptor (SSR)
 - Glucagon-like peptide 1 receptor (GLP-1)
- Metabolic tracers
 - Fluorodeoxyglucose (^{18}F -FDG)
 - Catecholamine and serotonergic precursors
 - Catecholamines
- Proliferation tracers
 - Fluorodeoxythymidine (^{18}F -FLT)

Radiopharmaceutical

For molecular imaging



Attaches
radionuclide to
the vector

Radionuclide

Emits externally
detectable radiation
upon decay

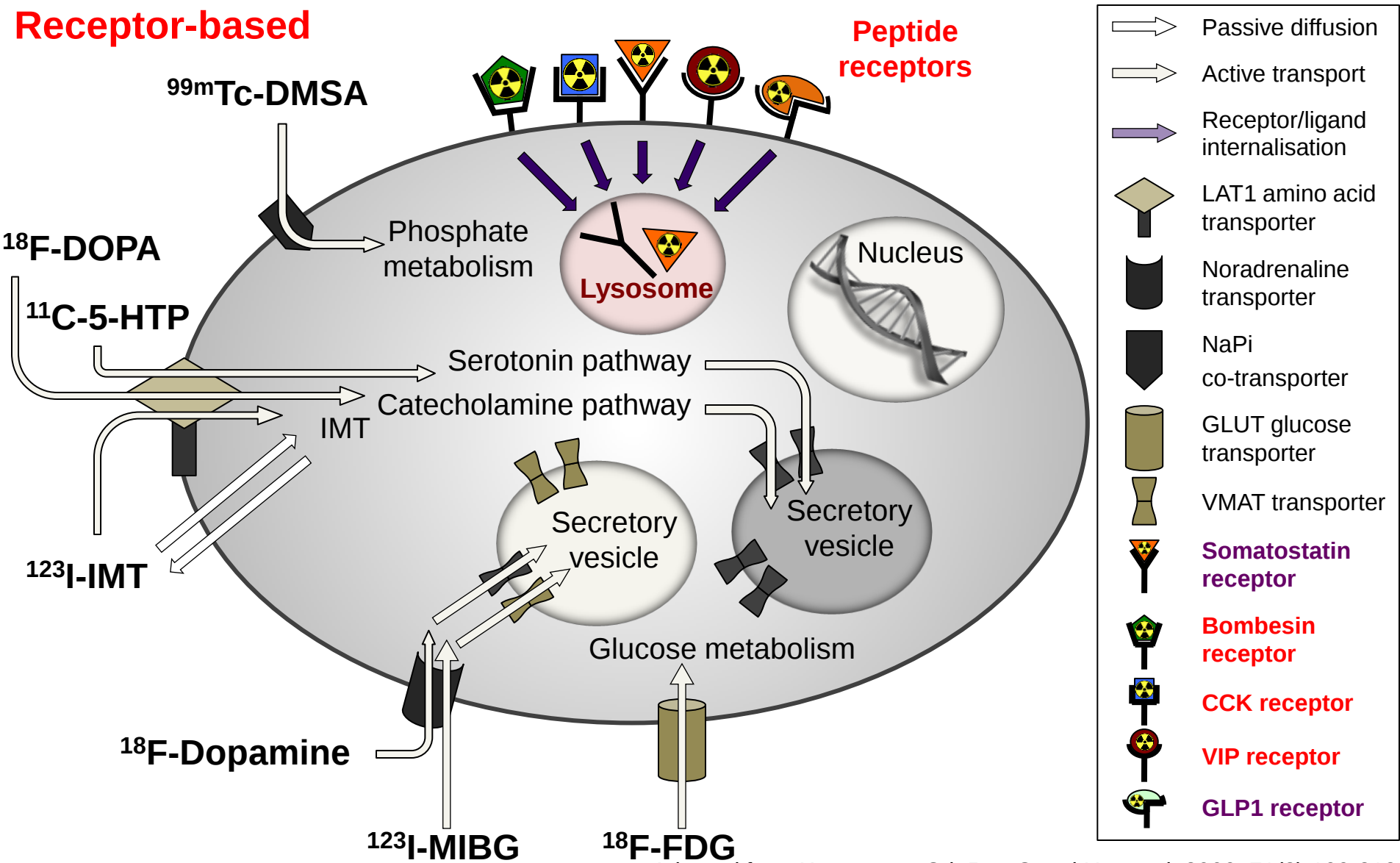
Linker

Vector molecule

Is responsible for a specific
molecular interaction with the target
(receptor, transporter, enzyme,...)

Peptide Receptors

Receptor-based



Somatostatin Receptor (SSTR)

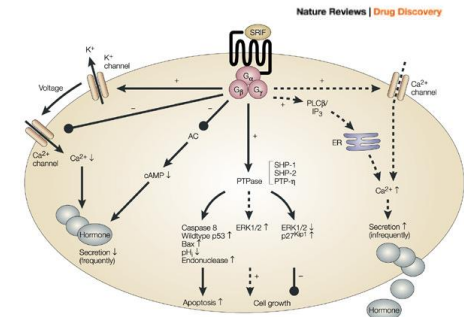
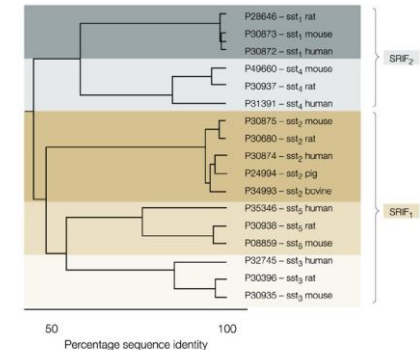
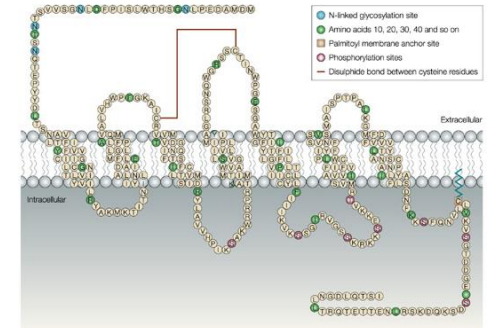
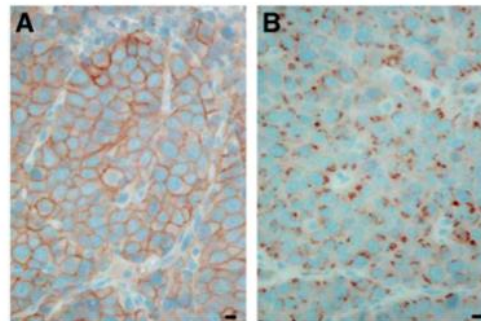
- Seven transmembrane G-coupled receptor
- Six human subtypes
 - SSTR1
 - SSTR2 (2A & 2B)
 - SSTR3
 - SSTR4
 - SSTR5



Vector

Receptor

- Function
 - ↓ secretions
 - Endocrine
 - Exocrine
 - ↓ Cell growth
 - ↑ Apoptosis

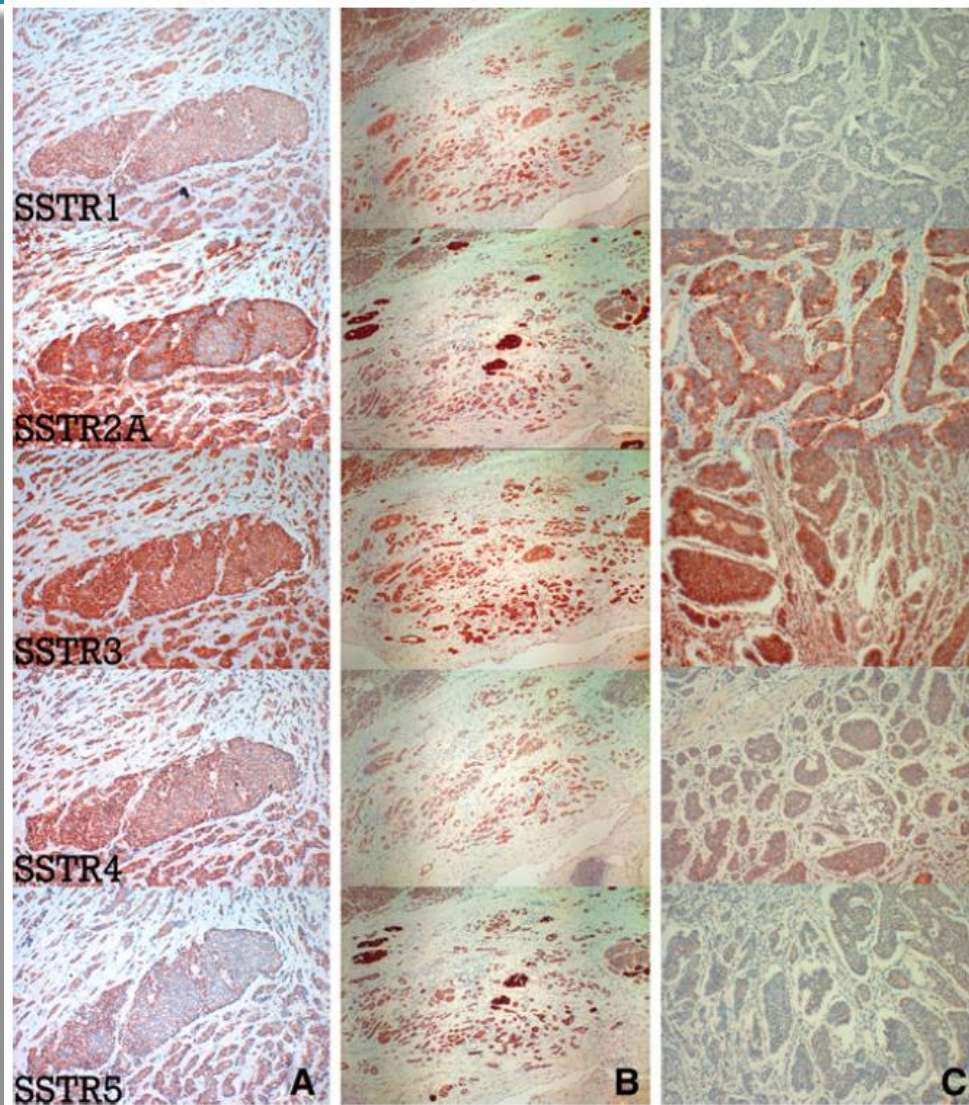


- Internalise upon agonist binding / recycle

Weckbecker, 2003, Nat Rev Drug Disc; 2(12):999-1017

Waser, 2009, J Nucl Med; 50(6):936-41

Overexpression of SSTR subtypes on NET



48%

86%

87%

50%

46%

- cytoplasmic staining
 - SSTR1
 - SSTR3
 - SSTR5
- membrane bound
 - SSTR2A

N=34

NET LN+ NET ileum pNET

SSTR overexpressing tumortypes

NET

Other tumour entities

- **Carcinoid:**
 - Thymus
 - Bronchus
 - Esophagus
 - Stomach
 - Small bowel
 - Appendix
 - Large bowel
 - Unknown primary
- **Pancreatic NET**
 - Gastrinoma
 - Insulinoma
 - Glucagonoma
 - VIPoma
 - ACTHoma
 - Somatostinoma
 - Non-functioning

GEP-NET

- Medullary thyroid carcinoma
- Neuroblastoma
- Pheochromocytoma
- Paraganglioma
- Small-cell lung cancer
- Pituitary gland tumours
- Merkel cell tumours
- Meningeoma
- Renal cell carcinoma
- GIST

The somatostatin receptor as a molecular target in NET

- Overexpression correlates with **differentiation status**
- **No correlation with hormonal** function of tumor
- SSTR target of **pharmacological** and **radionuclide** therapy – SRS as *predictive* marker



Diagnostic agents for SSR

Radionuclide + Chelator + Somatostatin analogue



^{111}In Indium

$^{99\text{m}}\text{Tc}$ Technetium

^{68}Ga Gallium

^{18}F Fluorine

DTPA

DOTA

NOTA

HYNIC

Octreotide

Tyr³-octreotide

Tyr³-octreotate

Naph-octreotide

DIAGNOSTIC COMBINATIONS:

- ^{111}In -DTPA-octreotide (pentetreotide) (**Octreoscan®**)
- ^{68}Ga -DOTA, Tyr³-octreotide (^{68}Ga -DOTA**TOC**)
- ^{68}Ga -DOTA, Tyr³-octreotate (^{68}Ga -DOTA**TATE**)
- ^{68}Ga -DOTA, [Phe¹-1-Nal³]-octreotide (^{68}Ga -DOTA**NOC**)

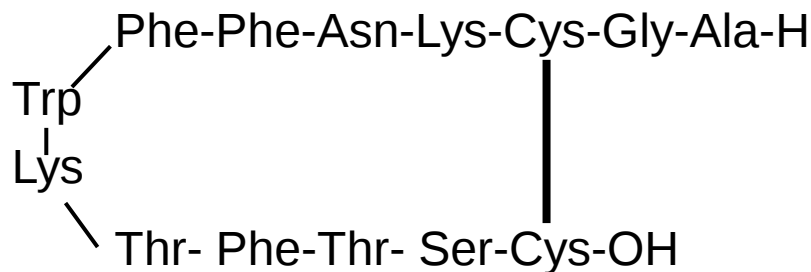
SPECT

PET

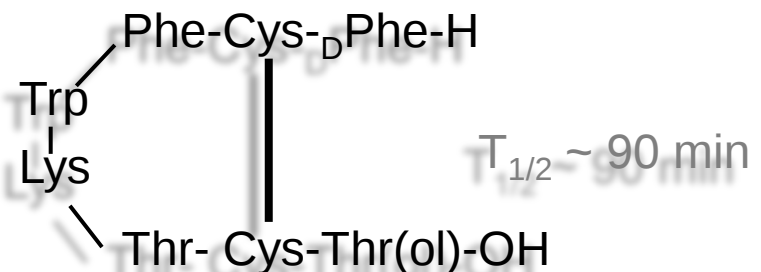
Vector molecule for SSTR

- Somatostatin: plasma $T_{1/2}$ ~1 to 3 min
- Chemical modification needed

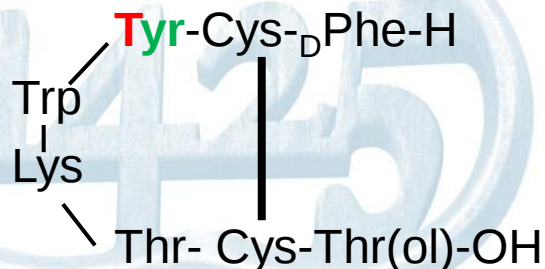
Somatostatin (SS14), 14 amino acids



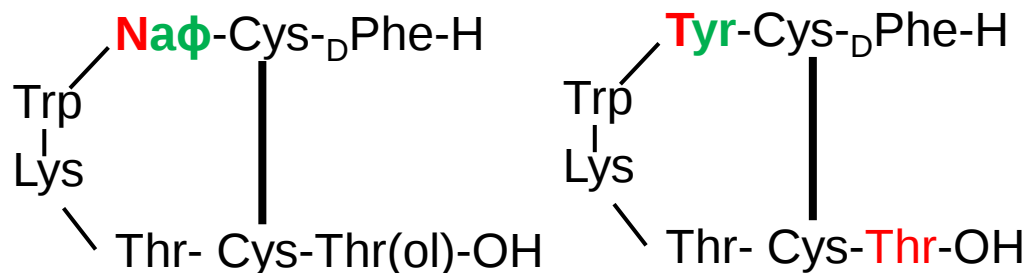
Octreotide, 8 amino acids



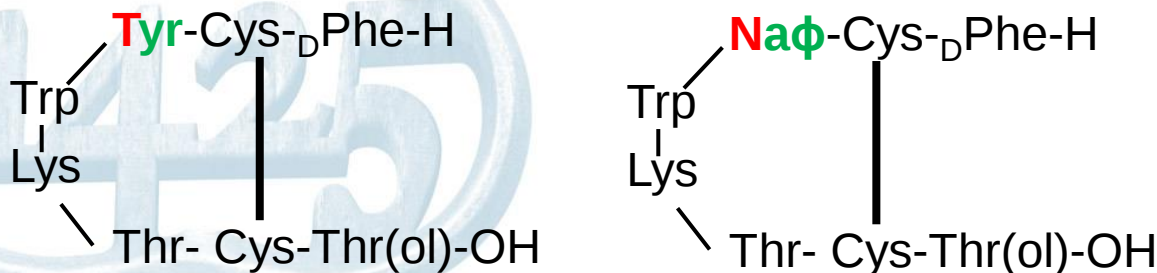
Tyr³-Octreotide, 8 amino acids (**TOC**)



Tyr³-Octreoate, 8 amino acids (**TATE**)



Naphtalene³-Octreotide, 8 amino acids (**NOC**)



Radioisotope – Gallium-68

- Gallium-68 (^{68}Ga)
- Positron emitter
- Generator product (germanium-68)
- No cyclotron needed for production ($\neq ^{18}\text{F}$)
- Metal



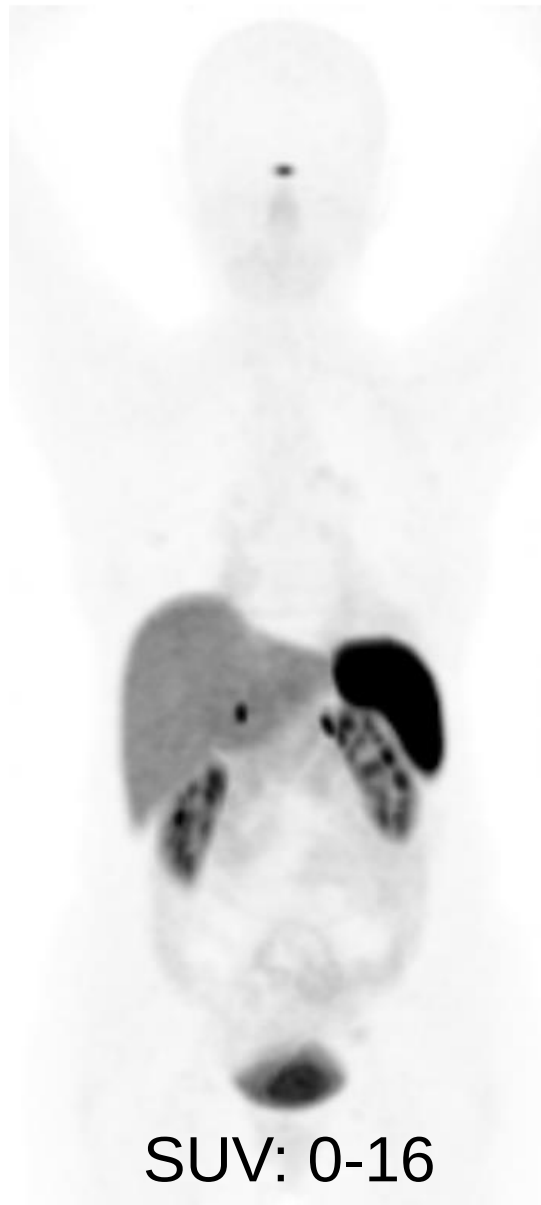
Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Period																			
1	H																	2 He	
2	Li	Be											B	C	N	O	F	Ne	
3	Na	Mg											Al	Si	P	S	Cl	Ar	
4	K	Ca		21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
5	Rb	Sr		39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
6	Cs	Ba	*	71 Lu	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
7	Fr	Ra	**	103 Lr	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Uut	114 Uuq	115 Uup	116 Uuh	117 Uus	118 Uuo

*Lanthanoids

**Actinoids

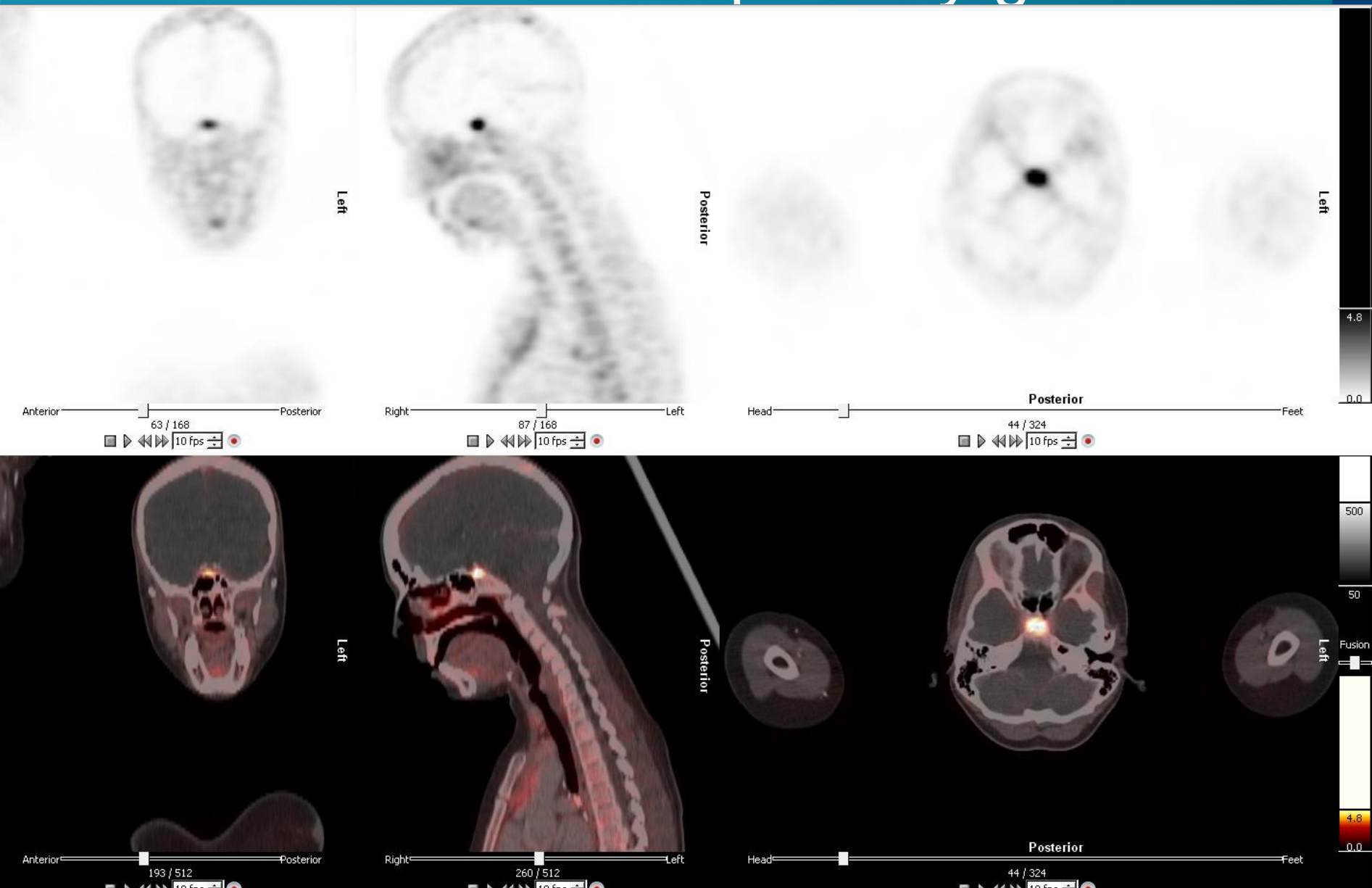


^{68}Ga -DOTATOC: normal biodistribution

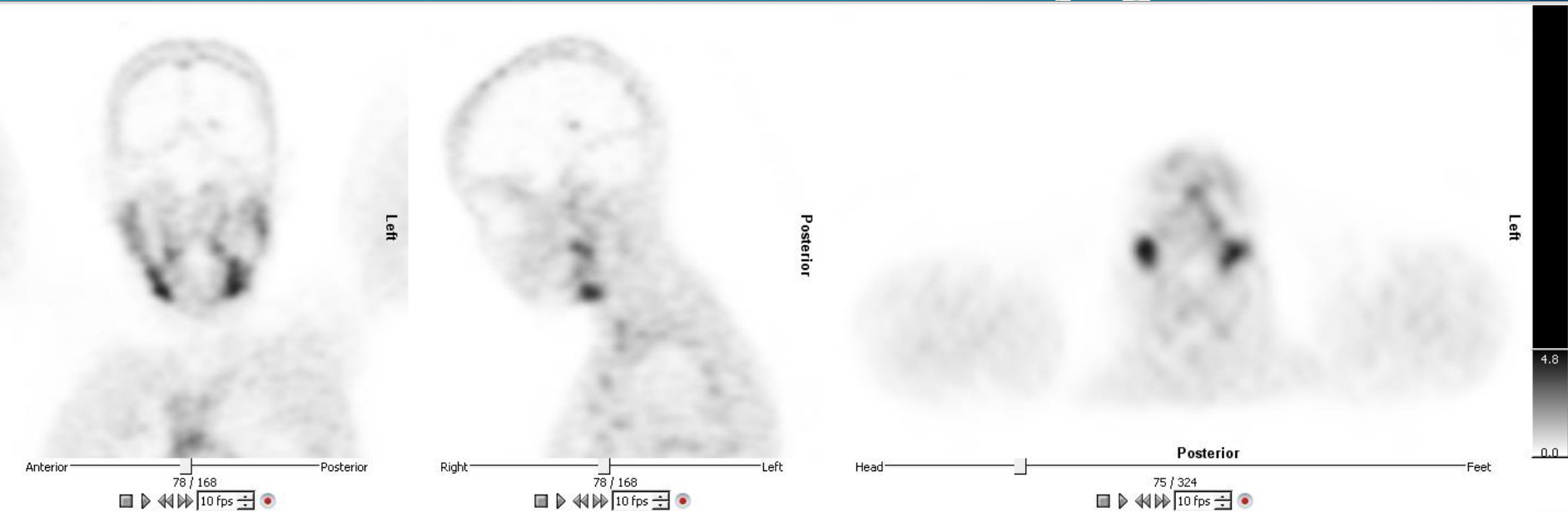


- High uptake:
 - Spleen
 - Adrenals
 - Pituitary gland
 - Kidney
 - Bladder
- Moderate:
 - Liver
 - Pancreas (head/uncinate process)
 - Bowel
 - Inflammatory LN
- Low:
 - Lung
 - Brain
 - Muscle

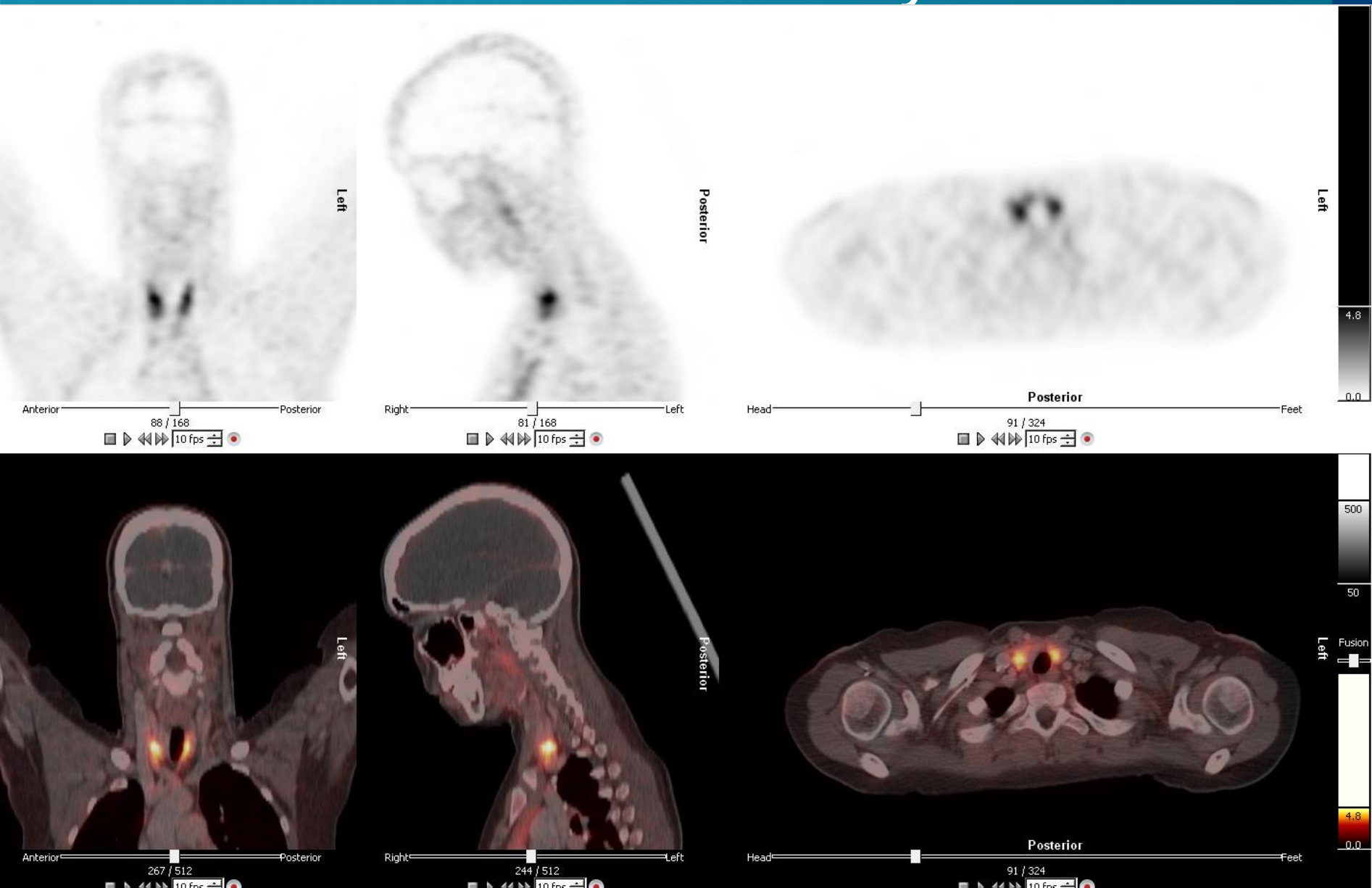
^{68}Ga -DOTATATE normal biodistribution: pituitary gland



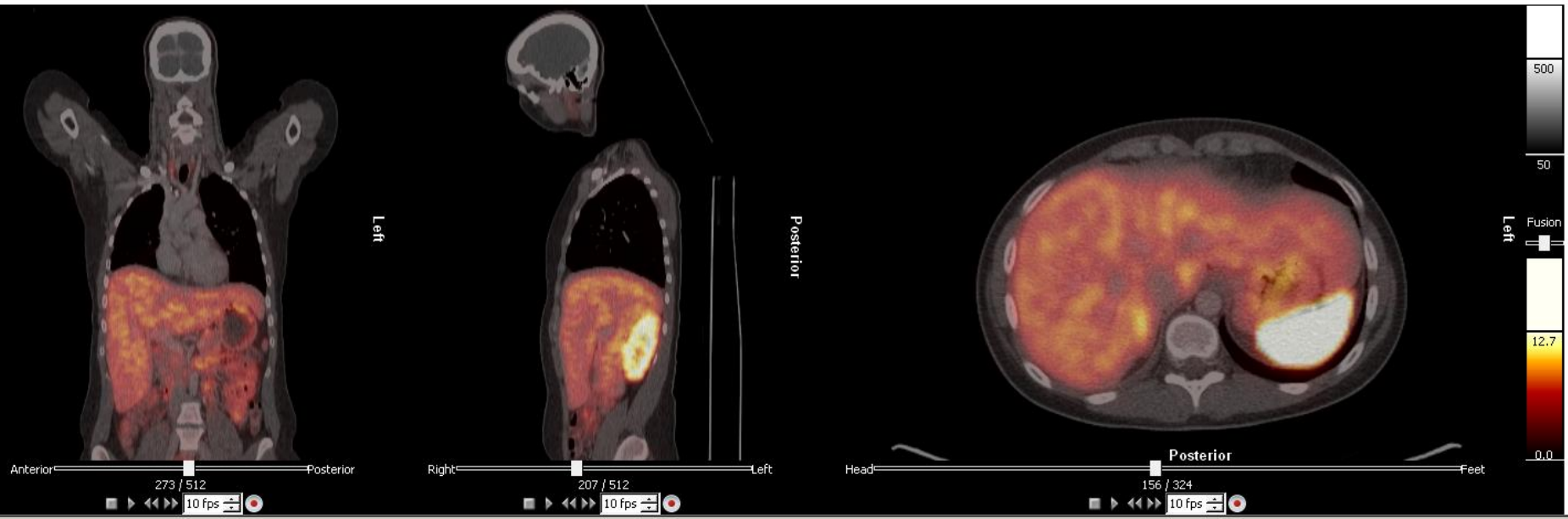
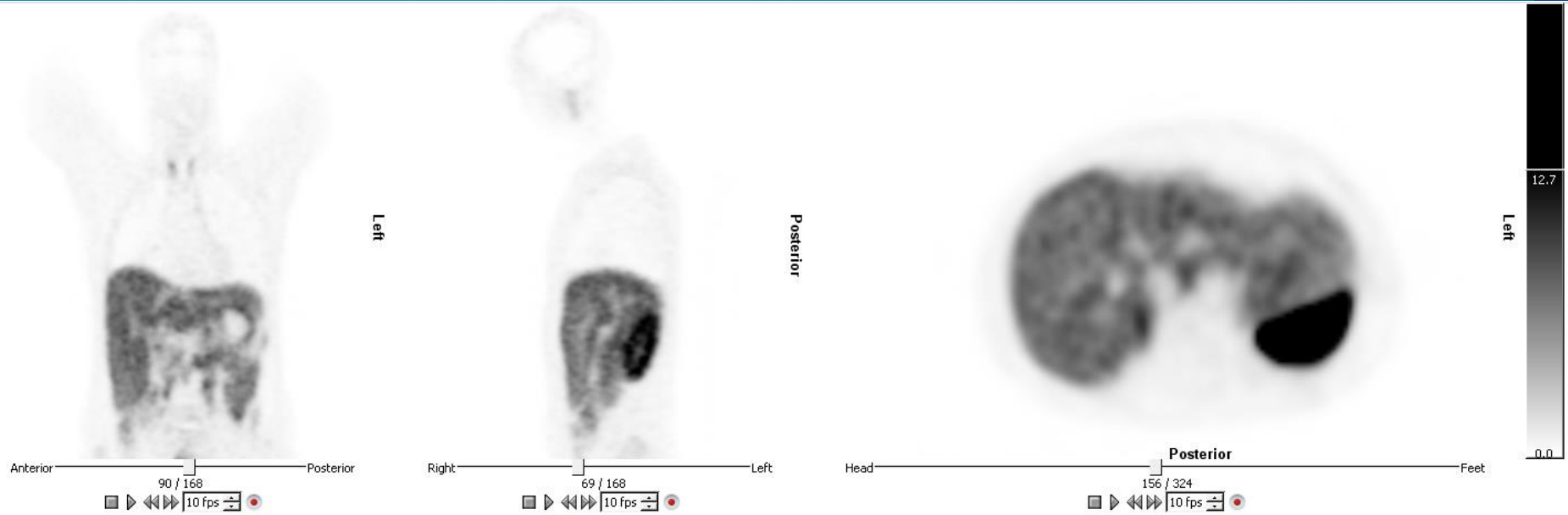
^{68}Ga -DOTATATE normal biodistribution: salivary glands



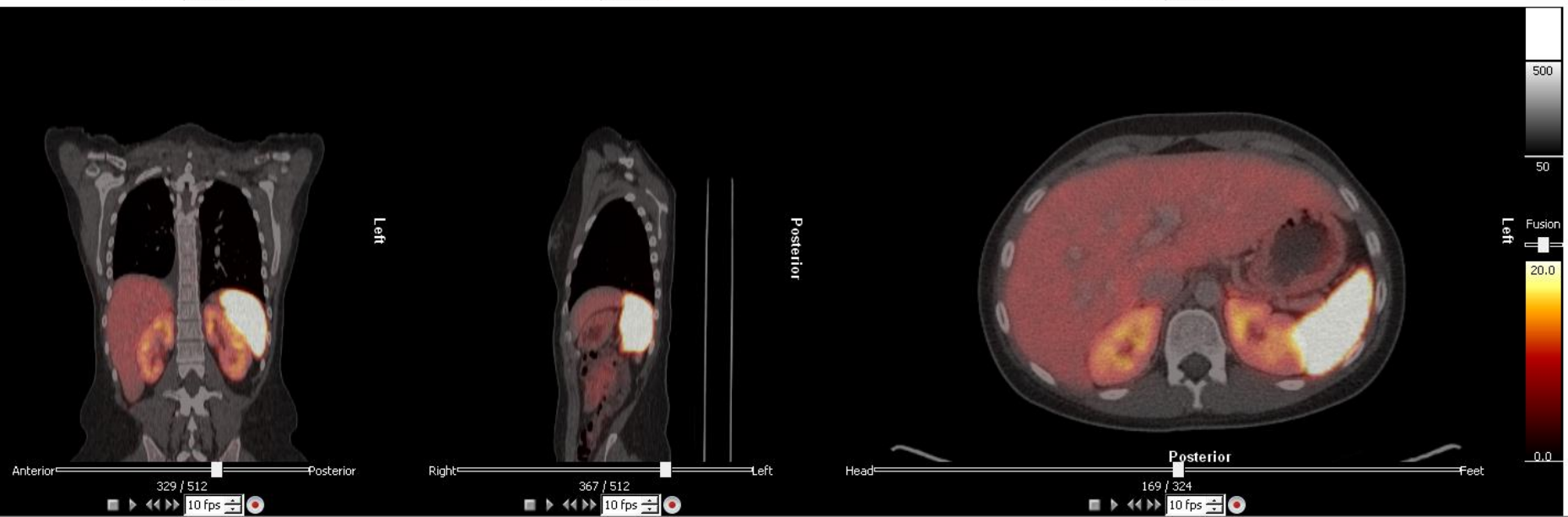
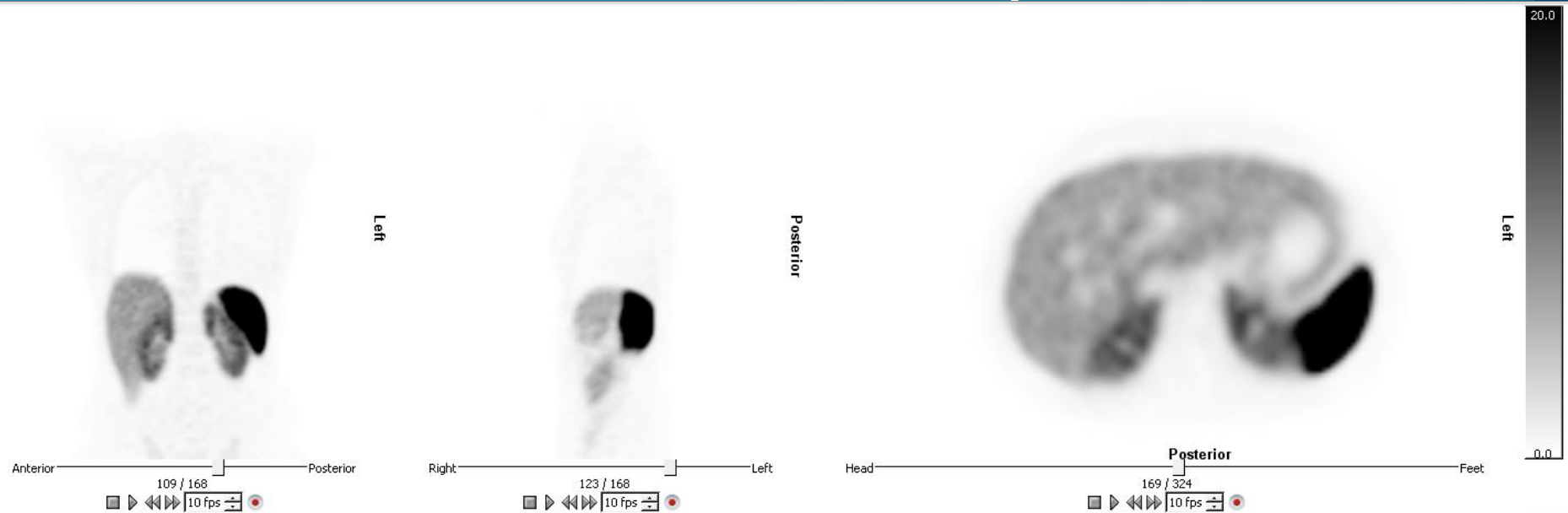
^{68}Ga -DOTATATE normal biodistribution: thyroid



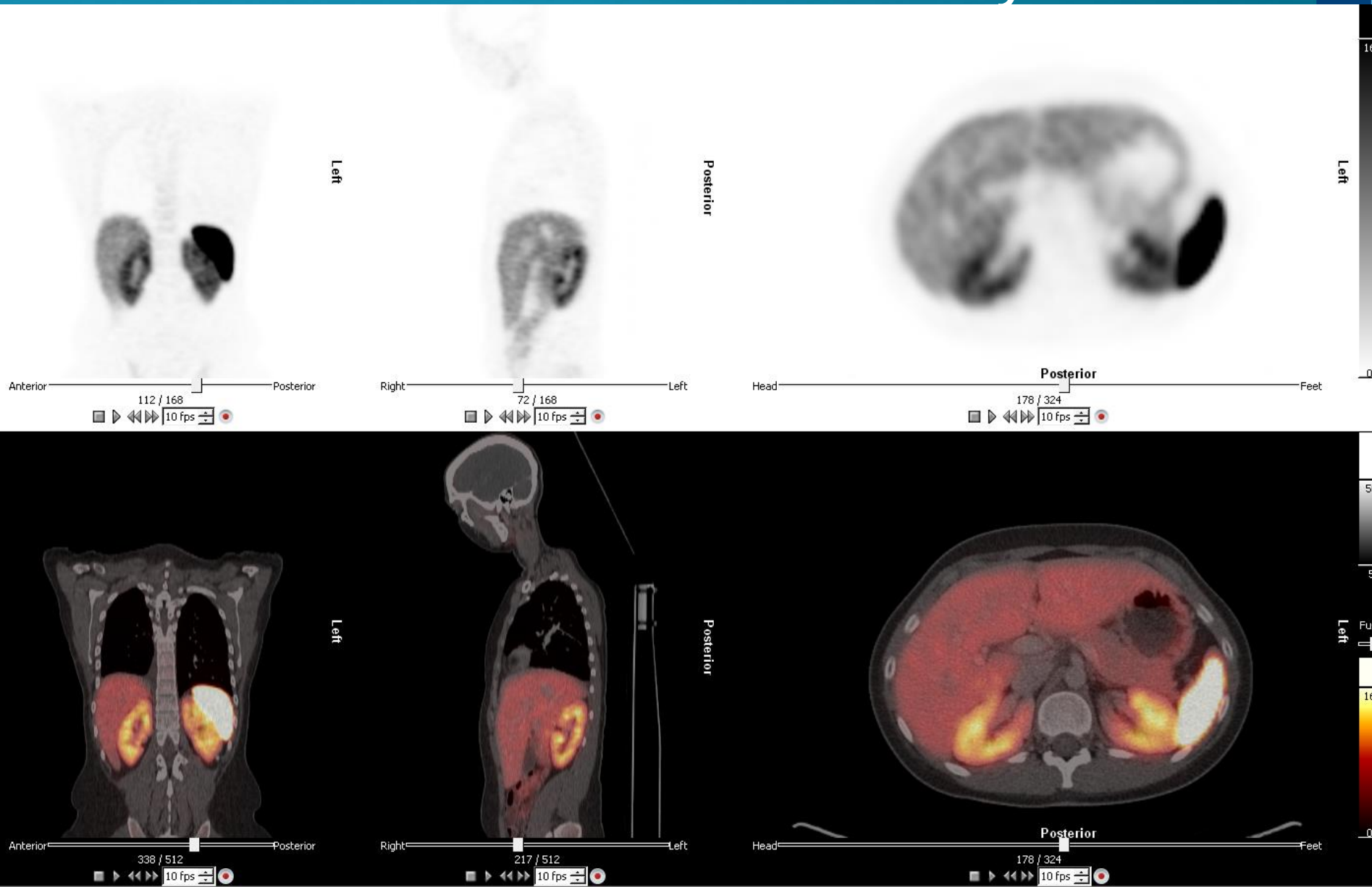
^{68}Ga -DOTATATE normal biodistribution: liver



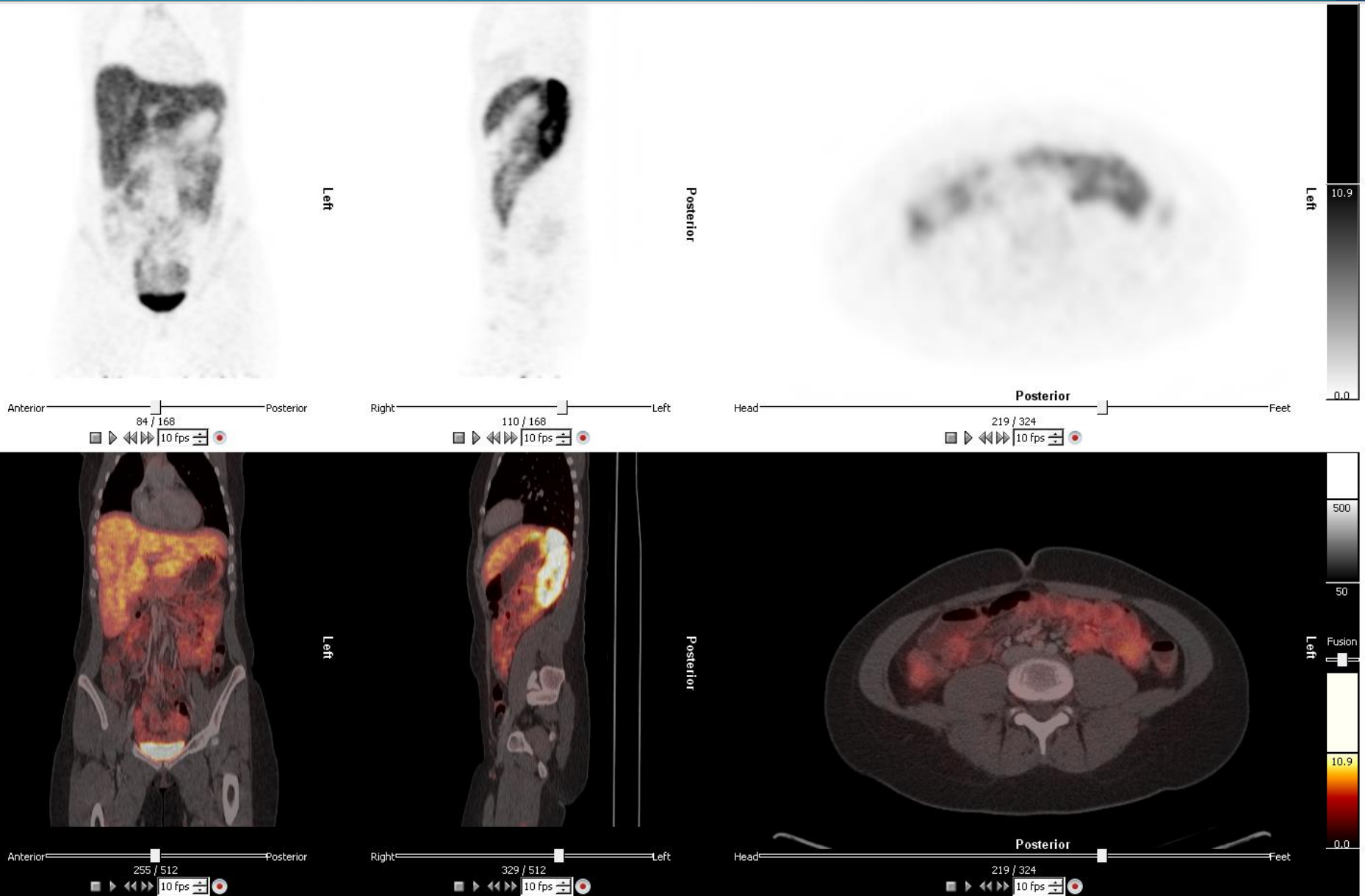
^{68}Ga -DOTATATE normal biodistribution: spleen



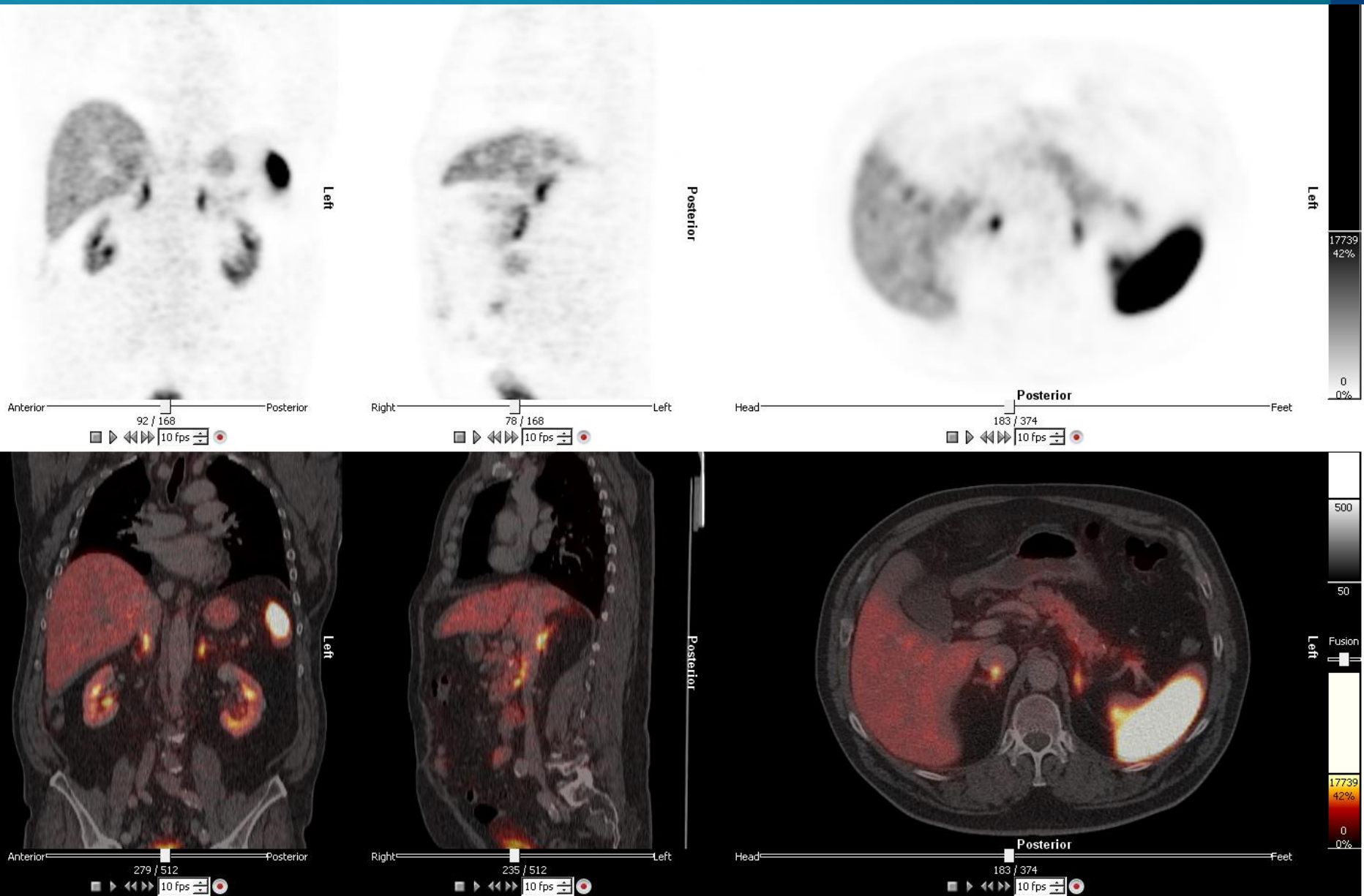
^{68}Ga -DOTATATE normal biodistribution: kidney



^{68}Ga -DOTATATE normal biodistribution: bowel

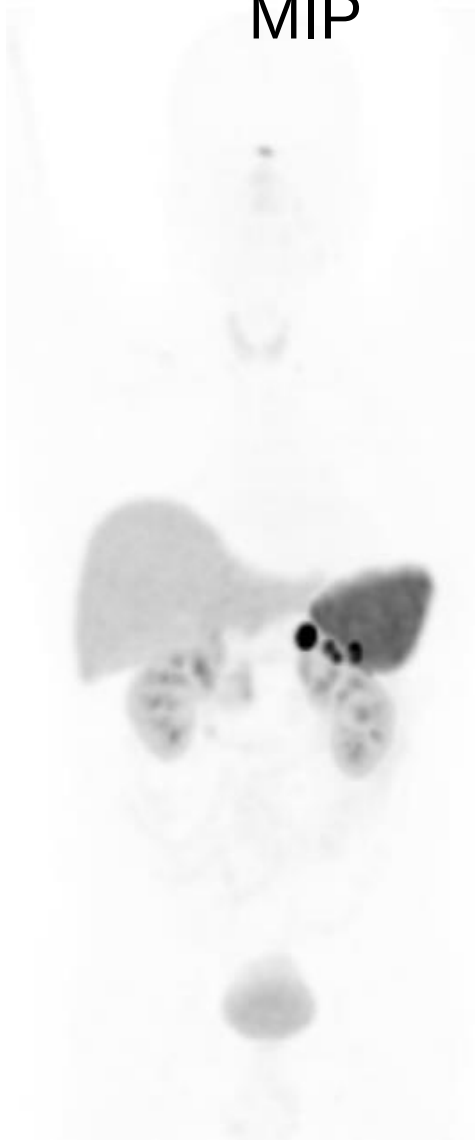


^{68}Ga -DOTATOC normal biodistribution: adrenal



^{68}Ga -DOTATOC PET/CT is highly sensitive for small tumors

MIP



MEN 1

Smallest lesion is 10 mm, but it is hotter than the spleen!



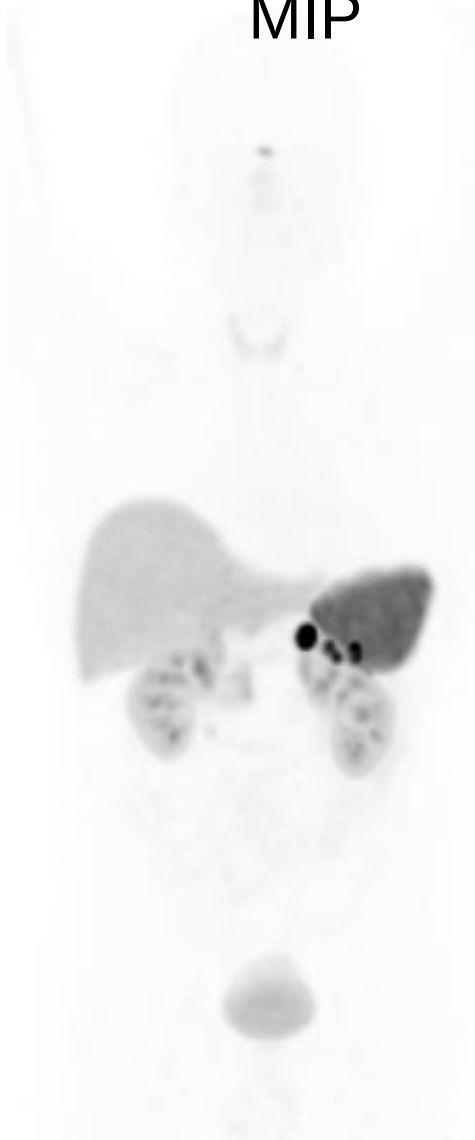
Transverse



Transverse
CT & Fusion

^{68}Ga -DOTATOC PET/CT is highly sensitive for small tumors

MIP

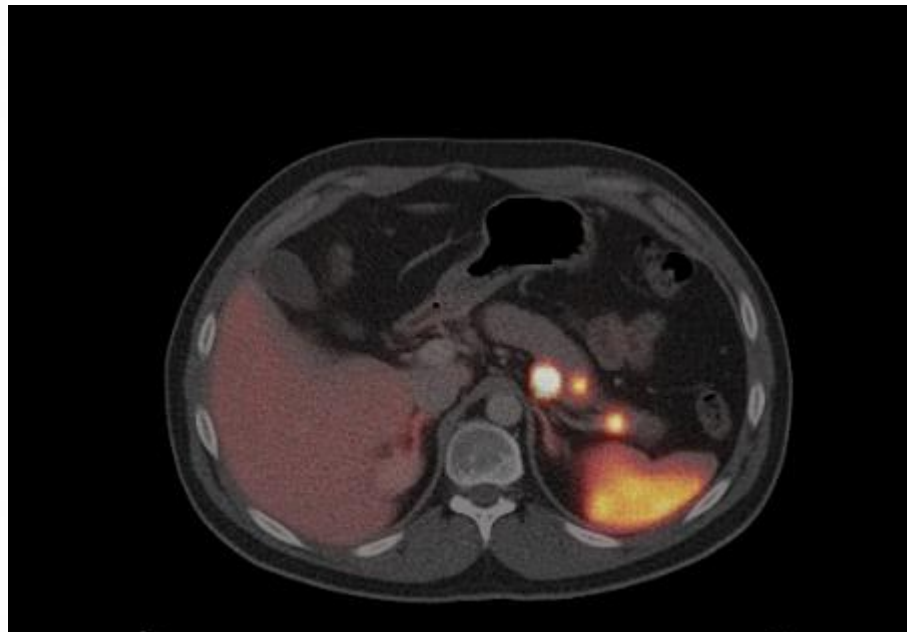


MEN 1

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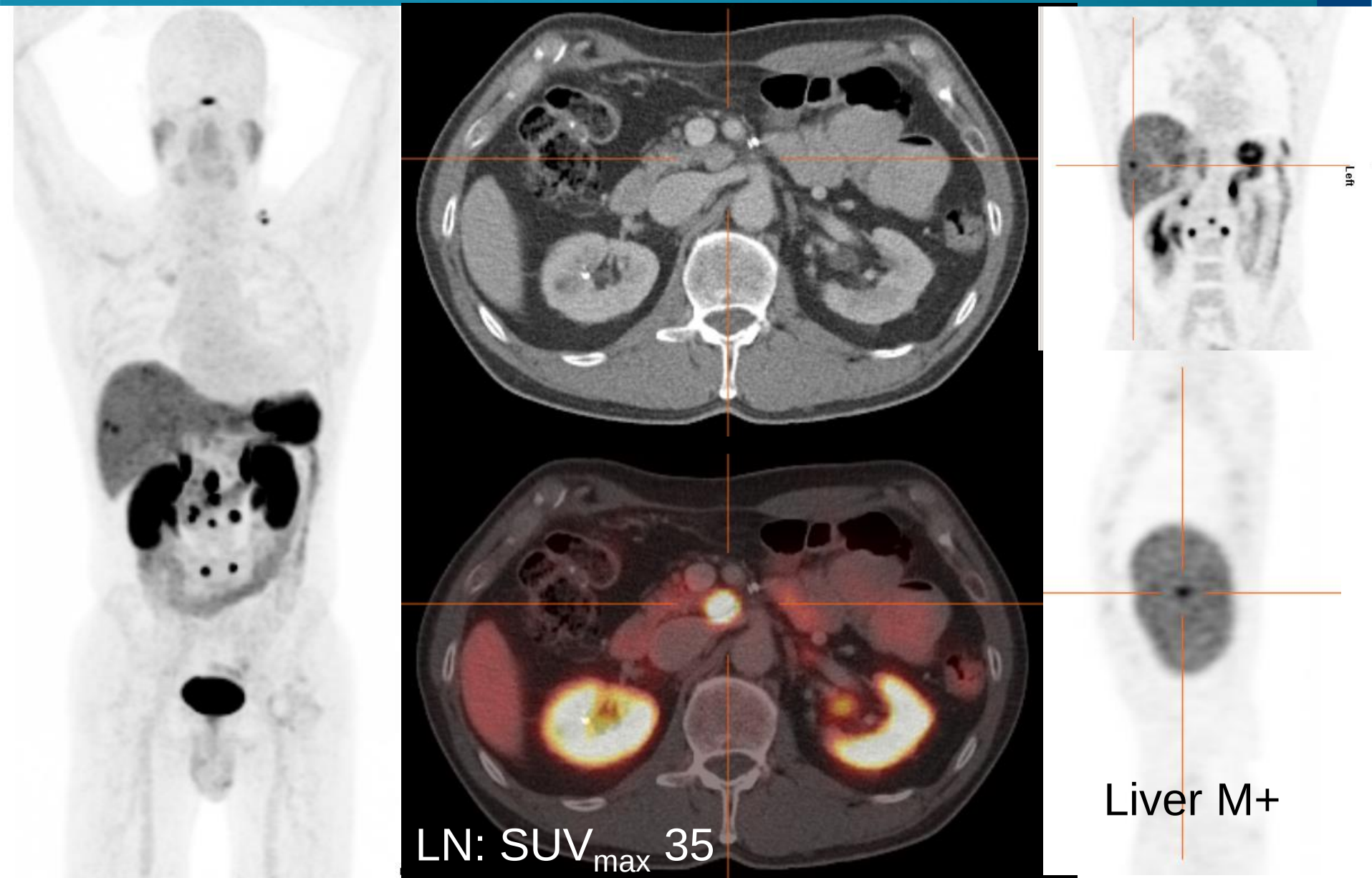


Transverse

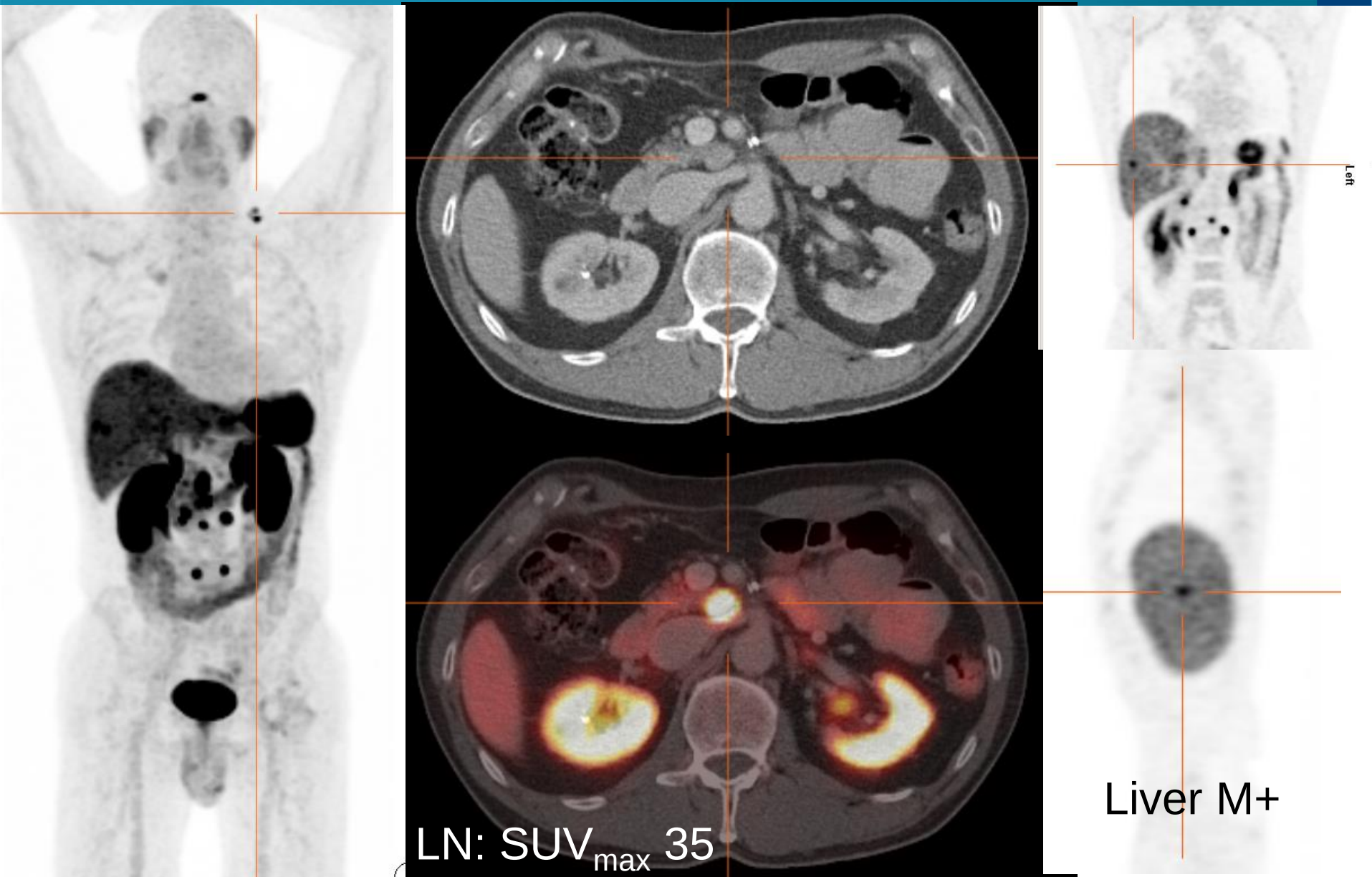


Transverse
CT & Fusion

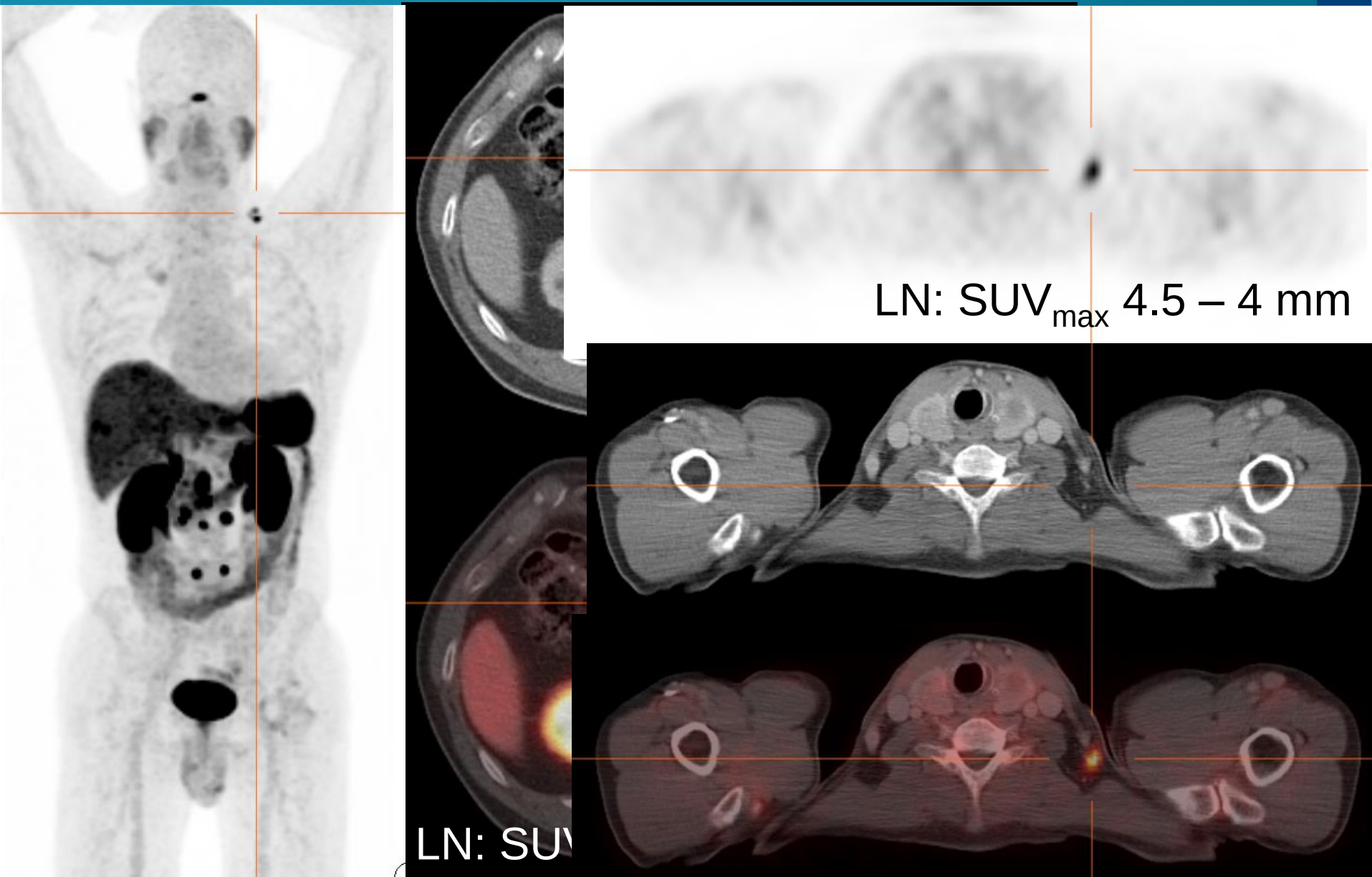
^{68}Ga -DOTATATE: detection of small lesions



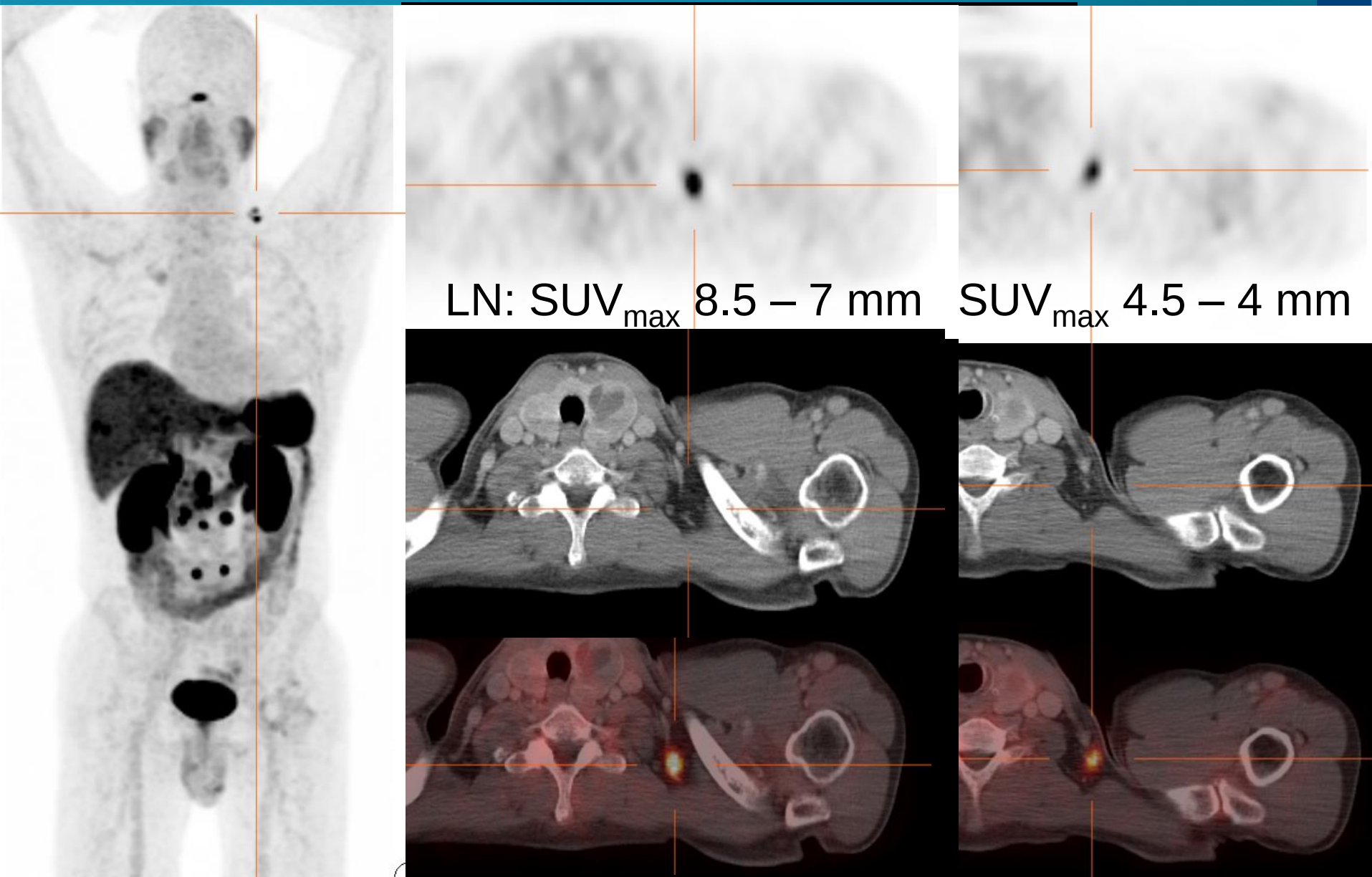
^{68}Ga -DOTATATE: detection of small lesions

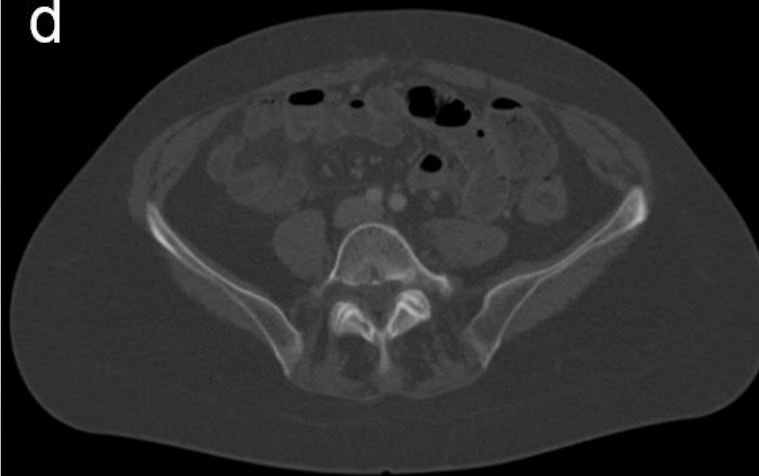
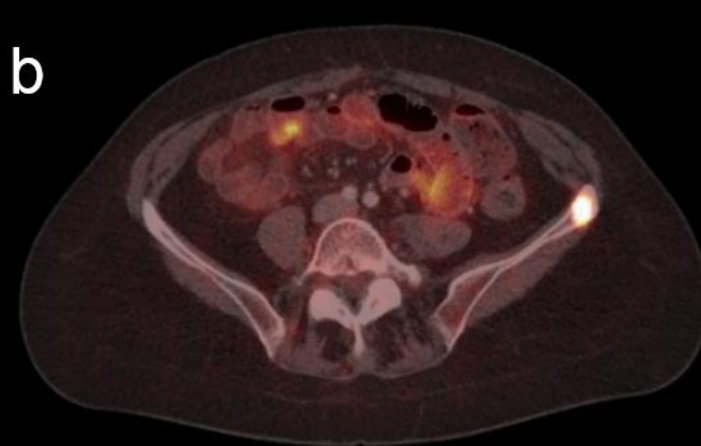


^{68}Ga -DOTATATE: detection of small lesions



^{68}Ga -DOTATATE: detection of small lesions





Contribution of **SSTR** radionuclide imaging

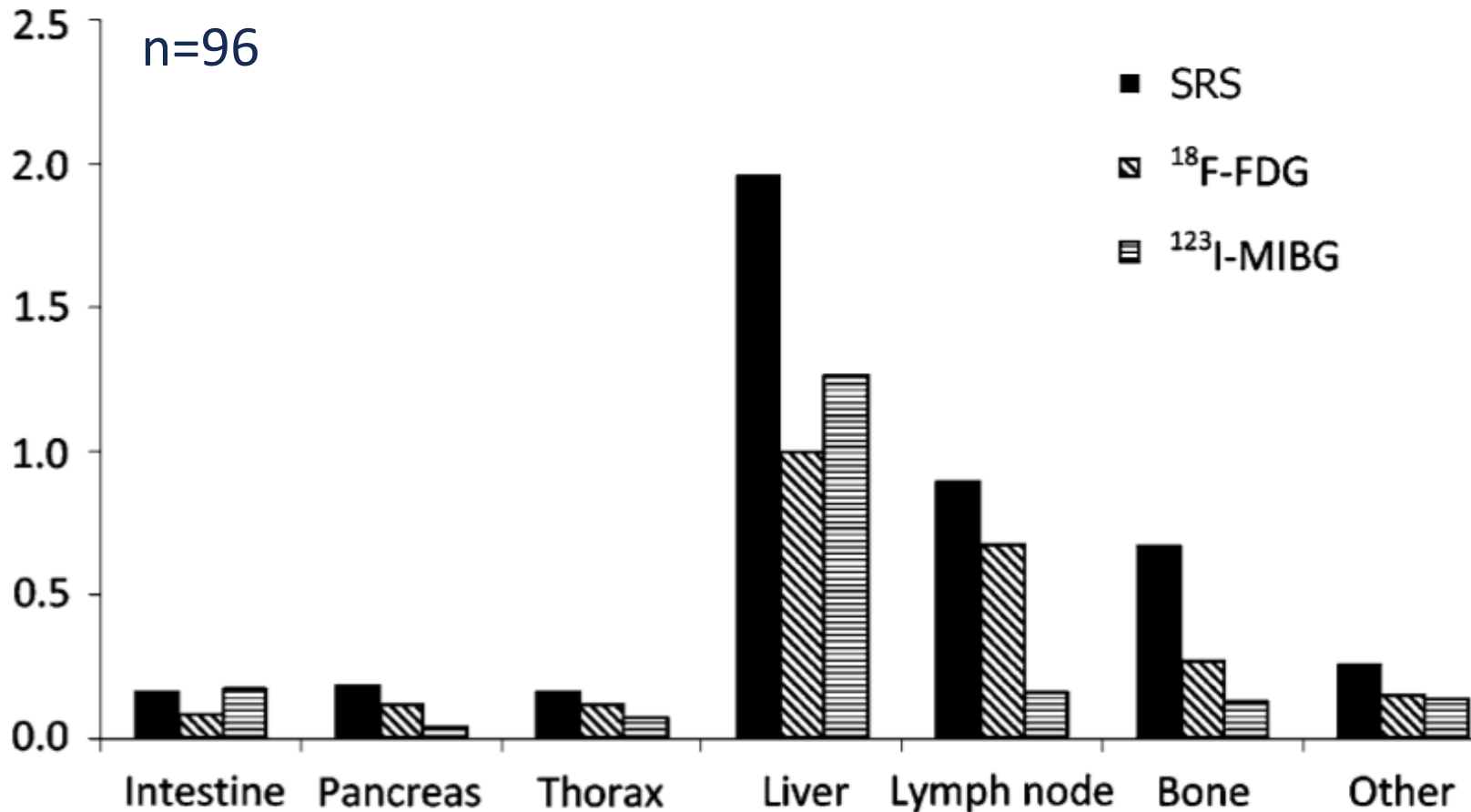
- **Sensitive** and **specific** detection of tumoral lesions, including very small lesions (G1&G2):
 - Diagnosis of NET in cases of clinical suspicion
 - lesion on morphological imaging
 - hormonal symptoms
 - ↑ serum chromogranin A
 - Pre-operative staging
 - Post-operative staging
 - Suspicion of recurrence
 - Advanced therapy planning: liver surgery, debulking, SIRT, liver Tx, ...
- **Molecular characterization** of tumoral lesions:
 - **Predictive** biomarker for cold somatostatin analogue (**SSA**) treatment
 - **Predictive** biomarker for peptide receptor radionuclide therapy (**PRRT**)

2012 ESMO guidelines for NET management

Table 10. Summary of recommendations

- The diagnosis of NET should be confirmed by histopathology (CgA, synaptophysin Ki-67).
- The current classification and staging systems should be applied in the clinic.
- Somatostatin receptor imaging besides standard imaging (CT and MRI) is part of standard of care.
- Resection of locoregional disease in patients with small intestinal NET (carcinoids) is recommended.
- Somatostatin analog therapy is first-line therapy in all functional NET and small intestinal NET G1/G2.
- Everolimus and sunitinib are registered for pancreatic NETs based on two phase III randomized trials.
- Temozolomide alone or in combination with capecitabine is promising for treatment of pancreatic NETs.

SRS (^{111}In -Pentetreotide) detects more NET lesions than FDG or MIBG



SRS > FDG > MIBG

Liver MIBG $\approx$ FDG

SRS (^{111}In -Pentetreotide) has higher sensitivity for NET than FDG or MIBG

N=96 All NET subtypes, except colonic (FDG > ^{111}In -Pentetreotide)

TABLE 5. Sensitivity of Functional Imaging Results Based on Origin of Tumor

Origin of tumor	SRS	^{123}I -MIBG	^{18}F -FDG
Ileal neuroendocrine (<i>n</i> = 45)	91% (41)	71% (32)	36% (16)
Pancreaticoduodenal neuroendocrine (<i>n</i> = 29)	90% (26)	31% (9)	79% (23)
Neuroendocrine of lung (<i>n</i> = 7)	86% (6)	57% (4)	71% (5)
Colonic neuroendocrine (<i>n</i> = 6)	67% (4)	17% (1)	83% (5)
Unknown or rare origin (<i>n</i> = 9)	89% (8)	44% (4)	78% (7)
Total	89% (85)	52% (50)	58% (56)

Data in parentheses are numbers of patients.

Total Sensitivity

SRS: 89%

MIBG: 52%

FDG: 58%

SRS (^{111}In -Pentetreotide) has higher sensitivity for NET than FDG or MIBG

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TABLE 6. Functional Imaging Results Based on Proliferation Index

Ki67 value	SRS		^{123}I -MIBG		^{18}F -FDG	
	Positive	Negative	Positive	Negative	Positive	Negative
<2%	87% (40)	13% (6)	48% (22)	52% (24)	41% (19)	59% (27)
2%–15%	96% (25)	4% (1)	73% (19)	27% (7)	73% (19)	27% (7)
>15%	69% (9)	31% (4)	46% (6)	54% (7)	92% (12)	8% (1)

Data in parentheses are numbers of patients.

For Ki67 >2% and 2%-15%, but not for >15% (FDG > ^{111}In -Pentetreotide)

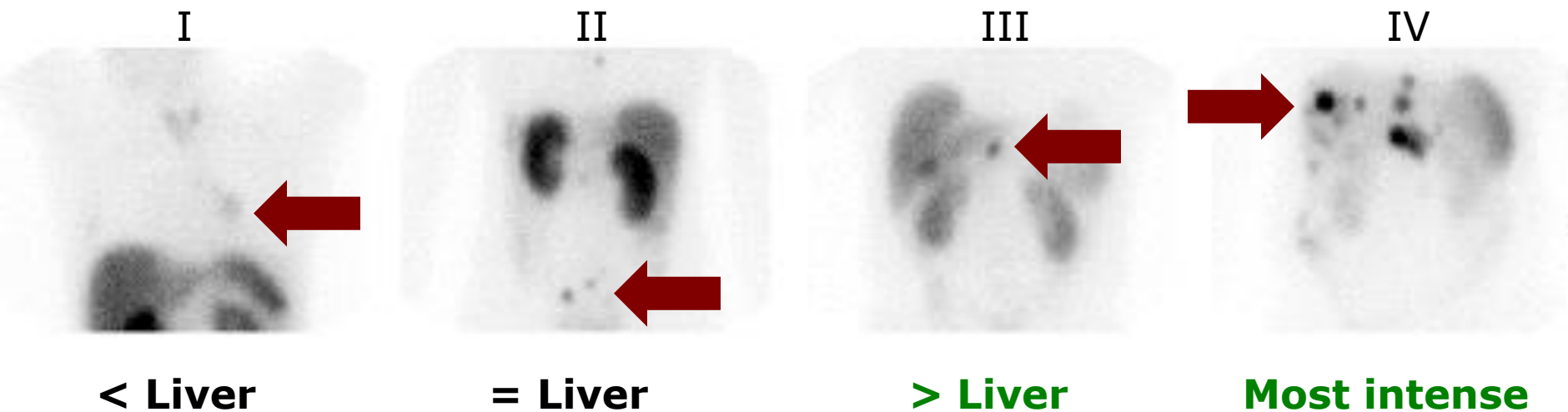
41% of grade 1 patients are positive on FDG!

Binderup, 2010, J Nucl Med; 51(5):704-12

Semi-quantitative determination of SSR expression with ^{111}In -pentetreotide

Krenning scale

Visual comparison of uptake in tumor versus normal organs



Cold somatostatin analogues can slow tumor growth... in SSTR scintigraphy + patients

PROMID

SSTR scintigraphy

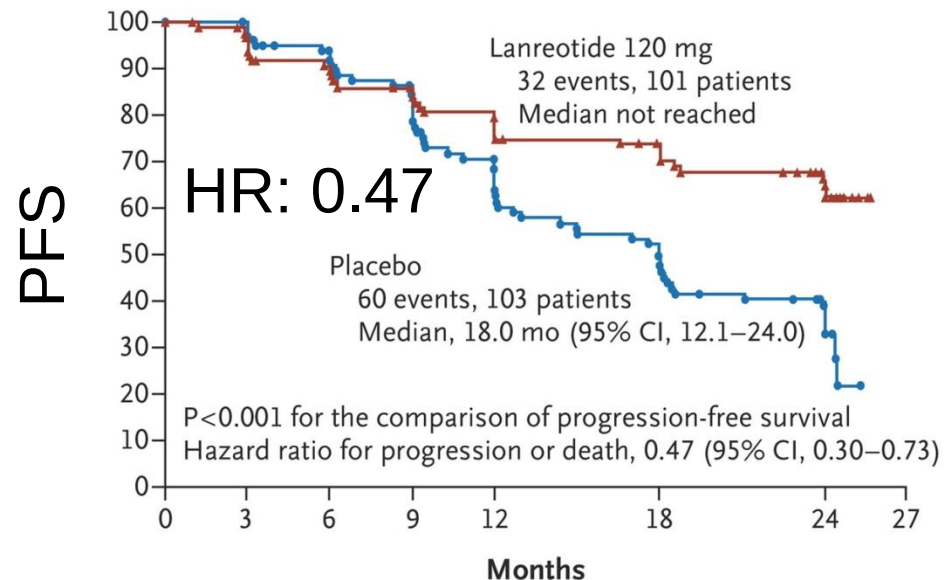
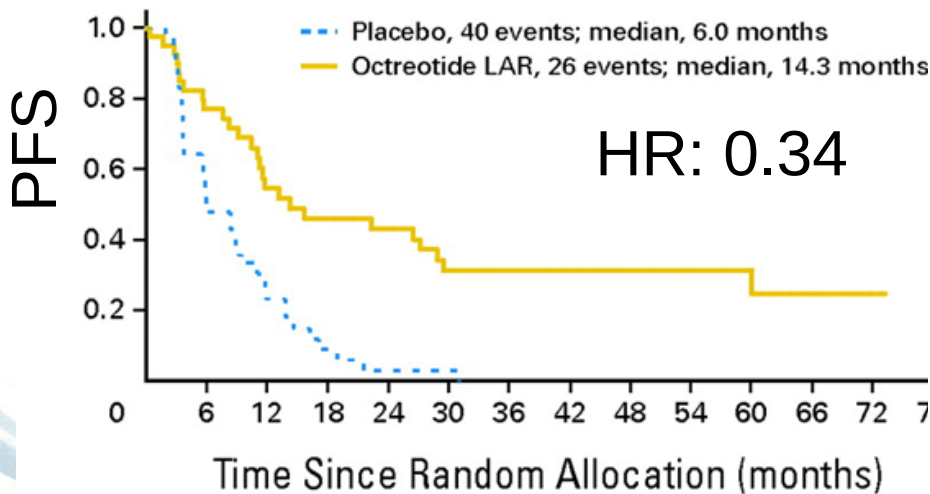
CLARINET

in 73/85 patients (86%)

- **Positive:** 63/85 (**74%**; **86%** w. scan)
- **Negative:** 10/85 (12%; 14% w. scan)
- **Unknown:** 12/85 (14%)

Inclusion criterium: target lesion grade 2 or higher on SSTR scintigraphy (Krenning scale)

100% SSTR positive



Rinke, 2009, J Clin Oncol;
2009;27:4656-4663

Caplin ME, 2014, New Engl J Med; 371:224-233.

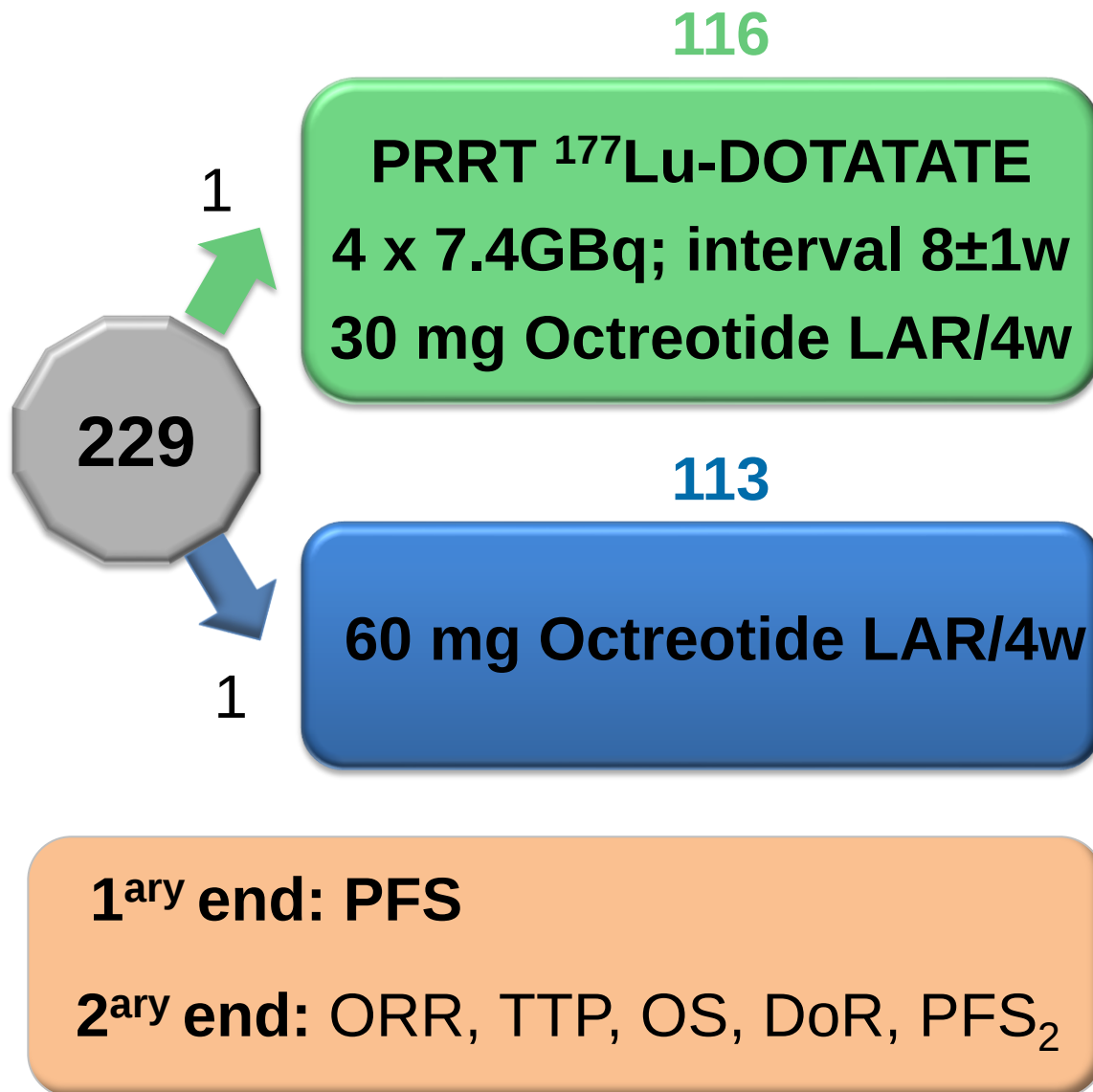
NETTER-1

Metastatic NET (midgut)

- RECIST progression on fixed dose SSA
- Ki67 <20% (Gr 1/2)
- **SRS + all lesions**
- Adequate GFR, blood, liver
- No prior PRRT

Stratification

- Fixed dose SSA: <6 months vs >6 months
- **SRS uptake score**



SRS: ^{68}Ga -peptide PET is superior to conventional scintigraphy (^{111}In -Pentetreotide)

Comparison ^{111}In -Pentetreotide, ^{68}Ga -DOTATOC, CT (n=84)

- Sensitivity:
 - ^{68}Ga -DOTATOC 97%
 - ^{111}In -Pentetreotide 52%
 - CT 61%
- Better performance for small lesions in LN and bone

Gabriel, 2007, J Nucl Med; 48(4):508-18

Comparison ^{111}In -Pentetreotide, ^{68}Ga -DOTATOC, CT (n=27)

- Sensitivity:
 - ^{68}Ga -DOTATOC 100%
 - ^{111}In -Pentetreotide 66%
 - CT or MRI 73%
- ^{68}Ga -DOTATOC finds more lesions in lung and bones

Buchmann, 2007, Eur J Nucl Med Mol Imaging;34(10):1617-26 2007

Comparison of ^{68}Ga -DOTA-peptide PET vs. ^{111}In -pentetreotide

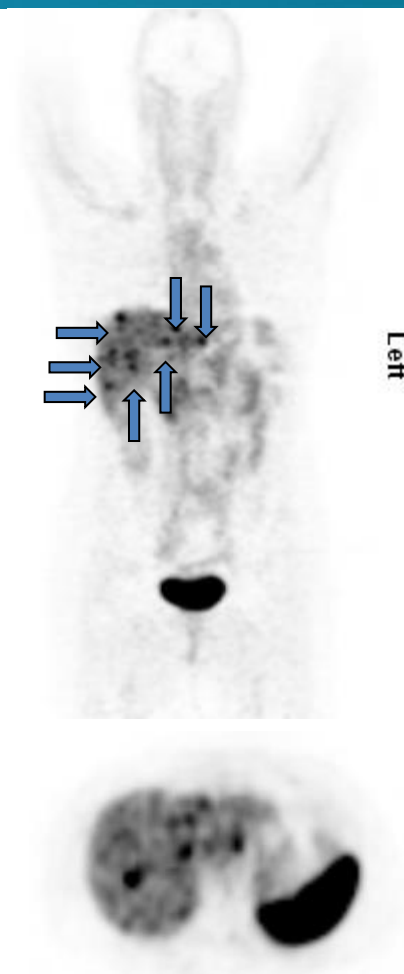
Author	Year	n	^{68}Ga -Peptide	Level (Patient /lesion)	Sensitivity ^{111}In -pentetreotide	Sensitivity ^{68}Ga -peptide	Δ Sens
Gabriel	2007	84	-TOC	Patient	52.0%	97.0%	45.0%
Buchmann	2007	27	-TOC	Region	66.0%	100.0%	34.0%
Srirajaskanthan	2010	51	-TATE	Lesion	11.9%	74.3%	62.4%
Van Binnebeek	2016	53	-TOC	Lesion	60.0%	99.9%	39.9%
Deppen	2016	78	-TATE	Patient	72.0%	96.0%	24.0%
Sadowski	2016	131	-TATE	Lesion	30.9%	95.1%	64.2%
TOTAL		424		Range	12-72%	74-100%	24-64%

Gabriel, 2007, J Nucl Med; 48(4):508-18; **Buchmann**, 2007, Eur J Nucl Med Mol Imaging; 34(10):1617-26; **Srirajaskanthan**, 2010, J Nucl Med; 51:875-82; **Van Binnebeek**...Deroose, 2016 Eur Radiol; 26(3):900-9; **Deppen**, 2016, J Nucl Med; 57: 708-14; **Sadowski**, 2016, J Clin Oncol; 34(6): 588-96

^{111}In -Pentetreotide vs. ^{68}Ga -DOTATOC PET/CT



^{111}In -Pentetreotide:
Planar WB and SPECT
24 hour PI

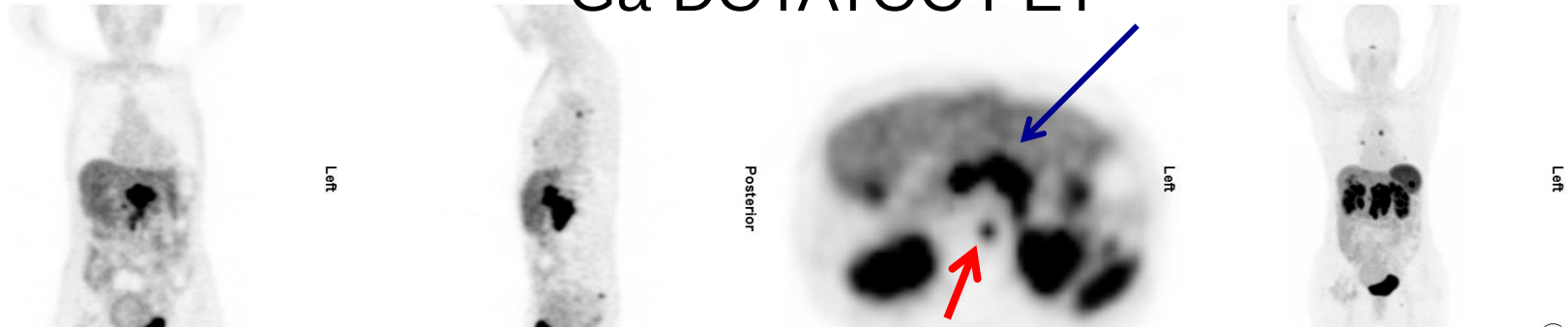


^{68}Ga -DOTATOC PET/CT:
MIP and transverse section
30 min PI

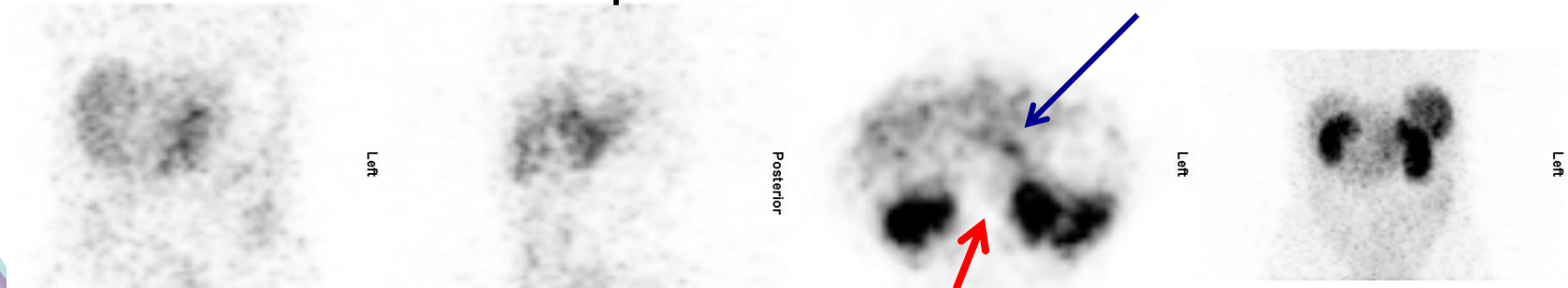


Incremental lesions

^{68}Ga -DOTATOC PET



^{111}In -pentetreotide SPECT



Retroperitoneal **lymph node aggregate**: uptake intense on PET – moderate on SPECT

Retroperitoneal focal **lymph node**: strong PET uptake, but no uptake whatsoever on SPECT = **'incremental PET lesion'**

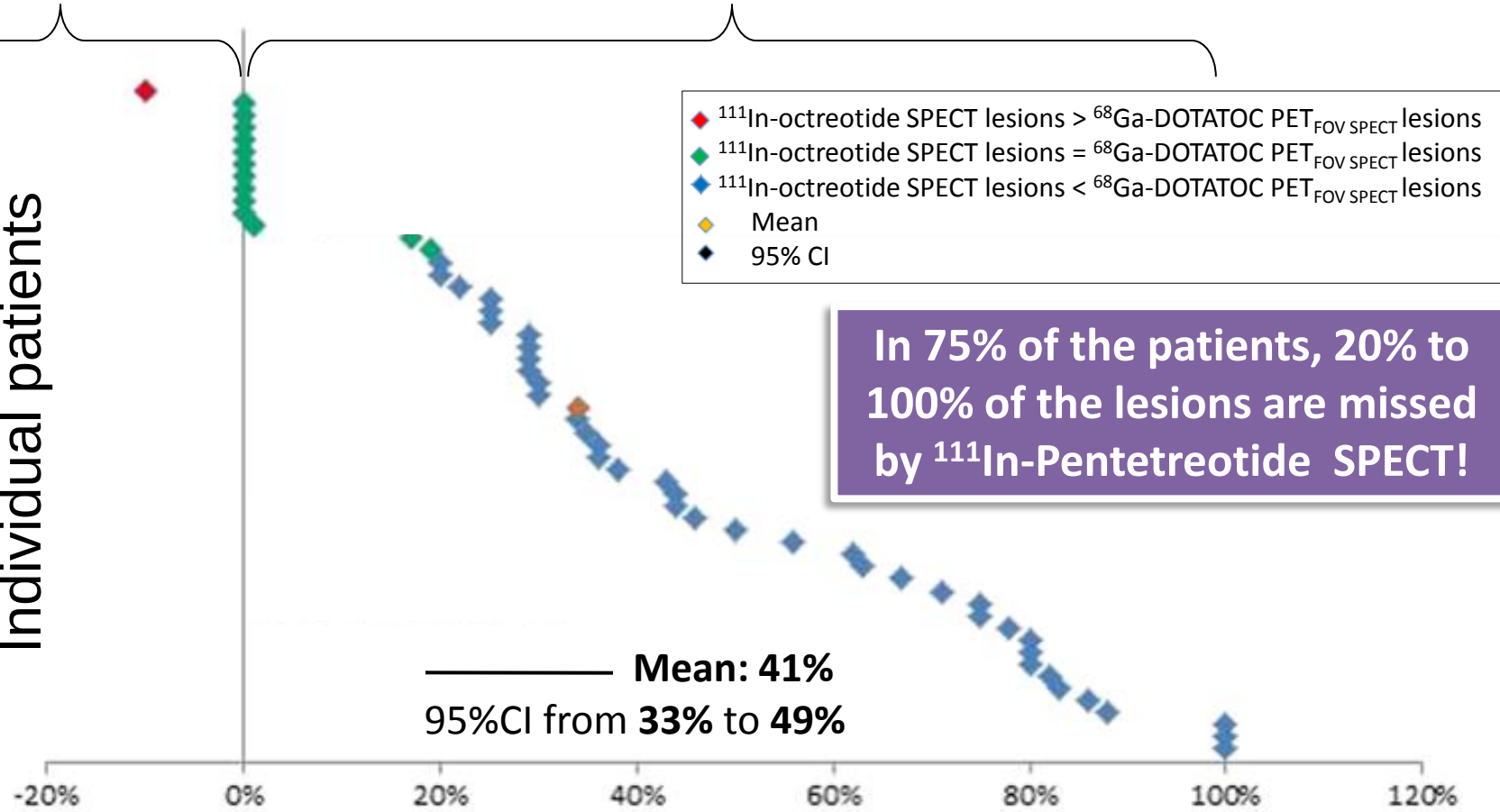
^{111}In -Pentetreotide vs. ^{68}Ga -DOTATOC PET/CT: Number of incremental lesions on PET_{FOV SPECT} vs SPECT

N=53

^{111}In -Pentetreotide detects incremental lesions

^{68}Ga -DOTATOC detects incremental lesions

Individual patients



Proportion of lesions that are incremental on one modality

Comparison of ^{68}Ga -DOTATATE PET/CT vs. ^{111}In -pentetreotide SPECT: largest series on record

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ORIGINAL REPORT

Comparison ^{111}In -Pentetreotide, ^{68}Ga -DOTATATE, CT (n=131)

- Sensitivity:
 - ^{68}Ga -DOTATATE 95.1%
 - ^{111}In -Pentetreotide SPECT/CT 30.9%
 - CT 45.3%
- ^{68}Ga -DOTATATE PET/CT induced **change in management** in **43** of 131 patients (**32.8%**)
- In patients with **carcinoid symptoms** and negative biochemical testing:
 - ^{68}Ga -DOTATATE PET/CT: positive in **65.2%**
 - **40%** of these were anatomic imaging and ^{111}In -pentetreotide SPECT/CT **negative**

^{68}Ga -DOTATOC $\approx$ ^{68}Ga -DOTATATE

- n=40
- Lesions detected:

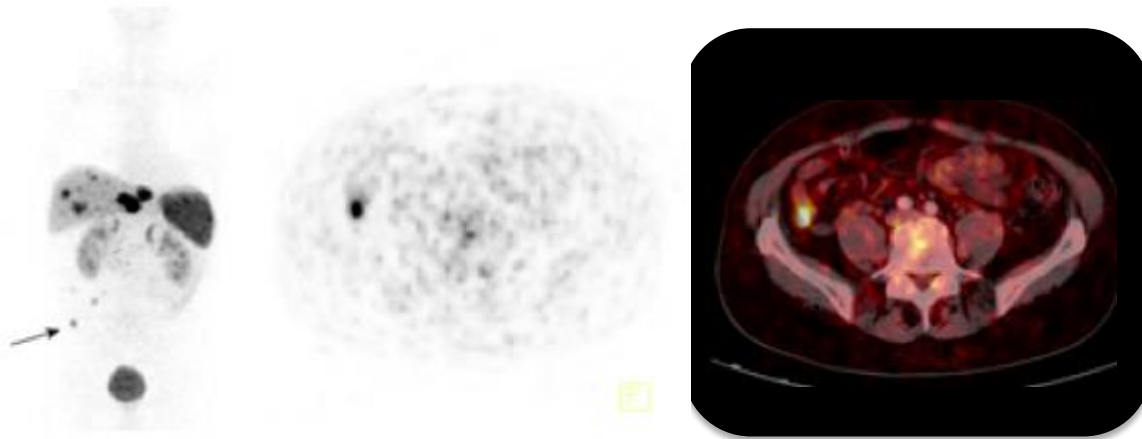
– ^{68}Ga -DOTATOC:	262	SUV_{max} 20.4 $\pm$ 14.7
– ^{68}Ga -DOTATATE:	254 (97%)	16.0 $\pm$ 10.8

TABLE 2
Tumor Uptake

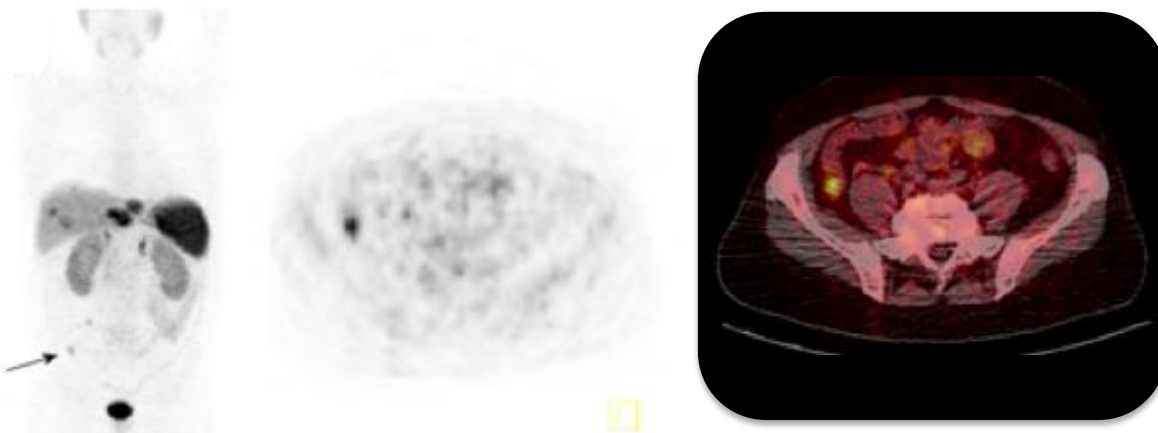
Group	No. of patients	^{68}Ga -DOTATATE						^{68}Ga -DOTATOC					
		Native SUVmax		Normalized SUVmax for liver		Normalized SUVmax for muscle		Native SUVmax		Normalized SUVmax for liver		Normalized SUVmax for muscle	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
All	40	16.0	10.8	2.0	2.2	8.6	7.5	20.4	14.7	2.2	1.5	10.3	6.6
Hepatic metastases	34	19.2	11.3	2.4	2.7	10.0	8.6	22.9	12.7	2.5	1.4	11.6	6.4
Bone metastases	17	10.6	8.7	1.4	1.2	6.2	5.1	13.5	12.3	1.7	1.5	7.8	6.3
Lymphatic metastases	24	15.4	9.6	1.8	1.8	8.2	6.7	21.1	16.5	2.2	1.7	10.0	6.7
Pulmonary metastases	5	9.8	5.5	0.8	0.4	4.4	2.5	14.0	8.4	1.1	0.6	5.5	3.0
Primary tumor	11	18.4	12.3	2.5	2.3	11.6	8.5	32.8	22.0	2.7	1.8	14.9	7.5

Very similar findings in ^{68}Ga -DOTATOC vs ^{68}Ga -DOTATATE

^{68}Ga -DOTATOC



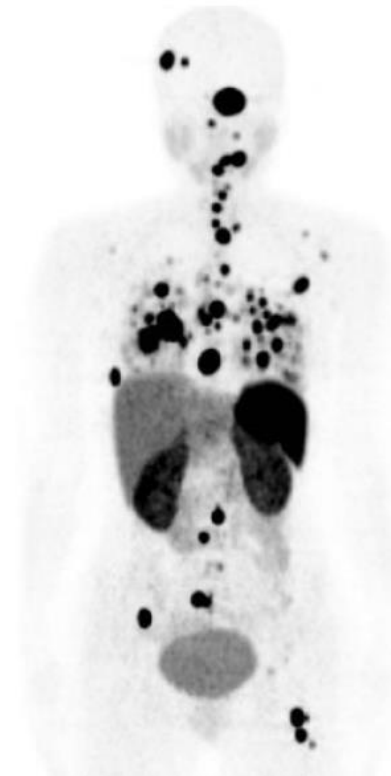
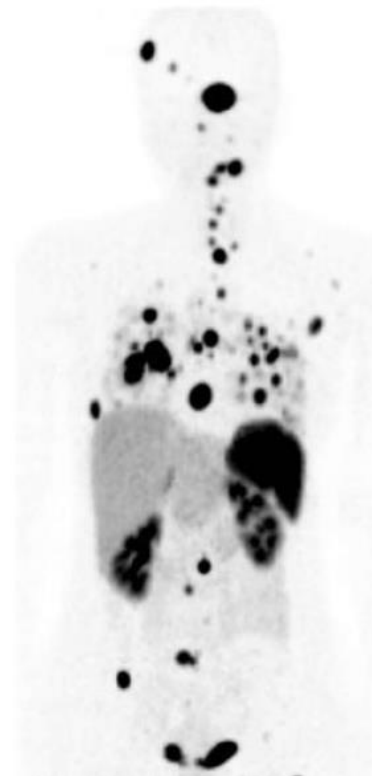
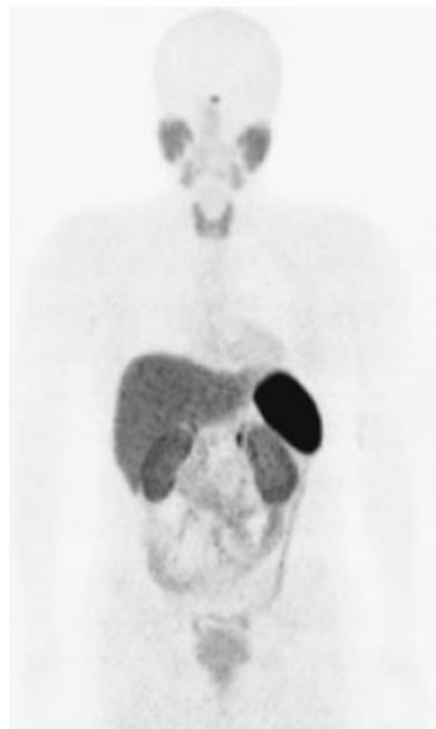
^{68}Ga -DOTATATE



^{68}Ga -DOTANOC vs ^{68}Ga -DOTATATE

Normal Biodistribution

Metastatic NET



^{68}Ga -DOTANOC

^{68}Ga -DOTATATE

^{68}Ga -DOTANOC

^{68}Ga -DOTATATE

^{68}Ga -DOTANOC vs ^{68}Ga -DOTATATE

- n=20
- Lesions detected:

			SUV_{max}
– ^{68}Ga -DOTANOC:	116	(89%)	24.5 ± 20.3
– ^{68}Ga -DOTATATE:	130		29.9 ± 26.4 ($p < 0.001$)

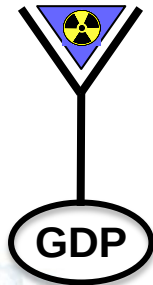
Clinical impact of ^{68}Ga -DOTA-peptide PET/CT vs ^{111}In -Pentetreotide

- Detection of **smaller** lesions
- Detection of lesions with only **light to moderate** SSR expression
- Detection of **more** lesions
 - $\Rightarrow$ No change in therapy
 - $\Rightarrow$ Change in therapy in substantial fraction of patients e.g.:
 - Additional liver metastases $\Rightarrow$ change in liver directed therapy
 - Extra-hepatic metastases (refrain from SIRS, refrain from liverTx)
- “One stop shop” – **90 minutes** door to door, including diagnostic CT (^{111}In -pentetreotide: 2 day procedure)
- Be **careful** with **direct comparison** between ^{111}In -pentetreotide and ^{68}Ga -DOTA-peptide PET
 - More lesions does not necessarily mean clinical progression!

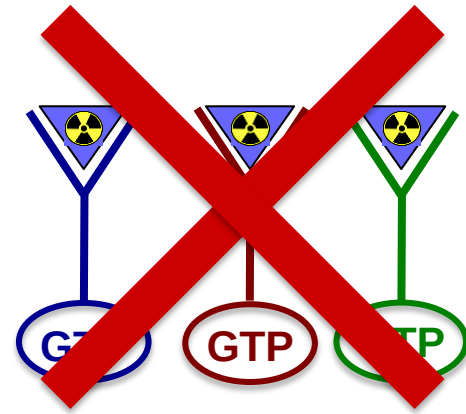
Differential binding of SSTR agonists and antagonists



SSTR Agonist



Activated receptor state
Bound to **GDP**



Inactivated receptor state
Bound to **GTP**

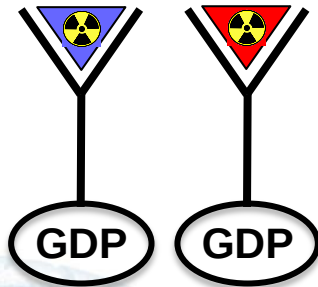
Differential binding of SSTR agonists and antagonists



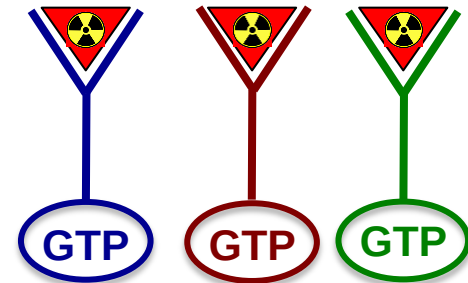
SSTR Agonist



SSTR Antagonist



Activated receptor state
Bound to **GDP**



Inactivated receptor state
Bound to **GTP**

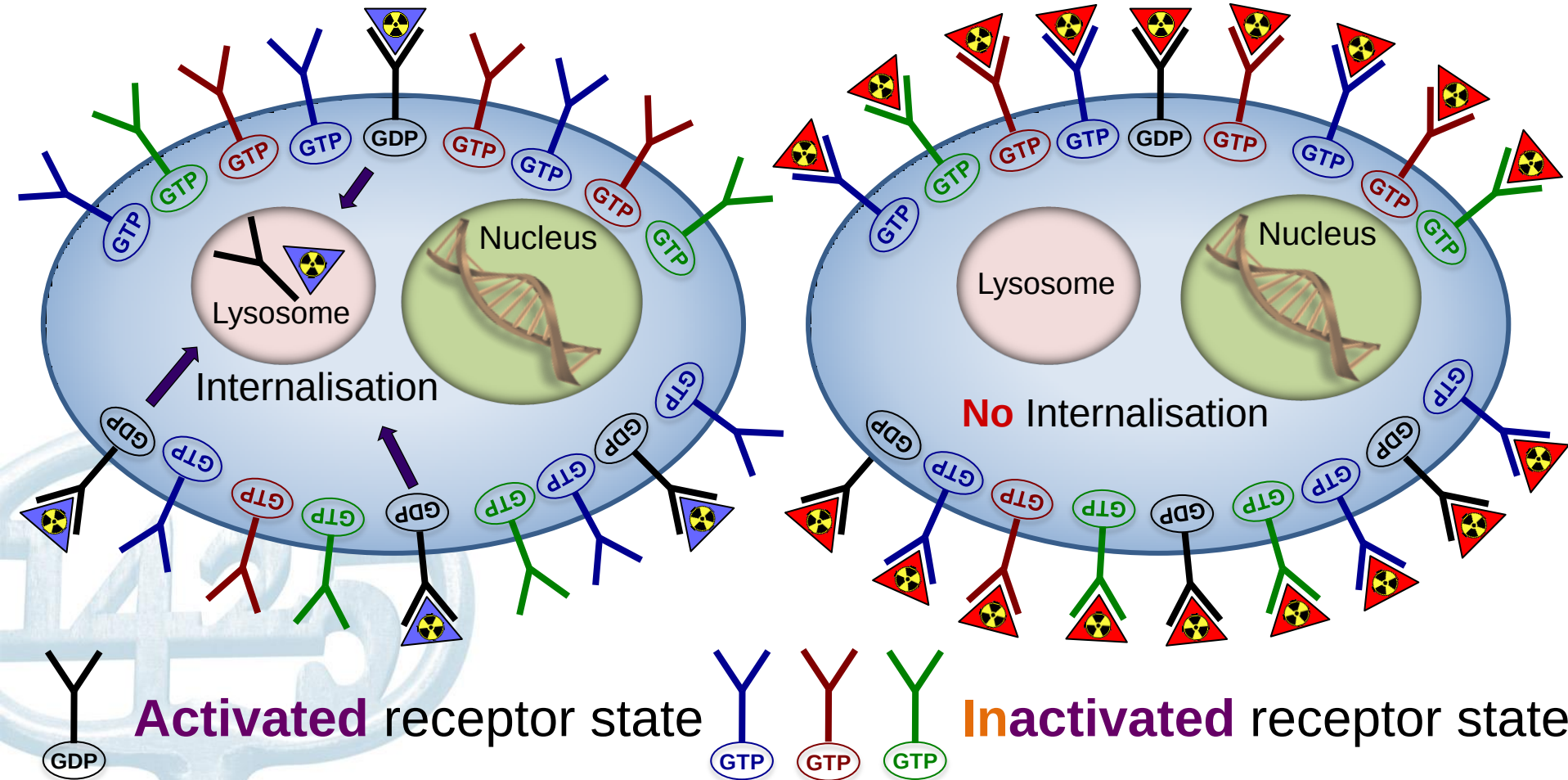
Differential binding of SSTR agonists and antagonists



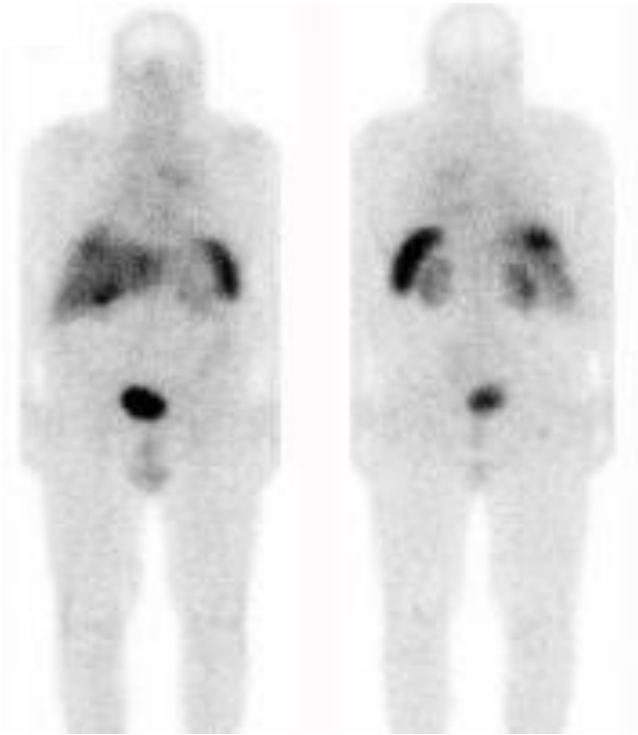
SSTR Agonist



SSTR Antagonist



Imaging somatostatin receptor expression with SSTR **ant**agonists

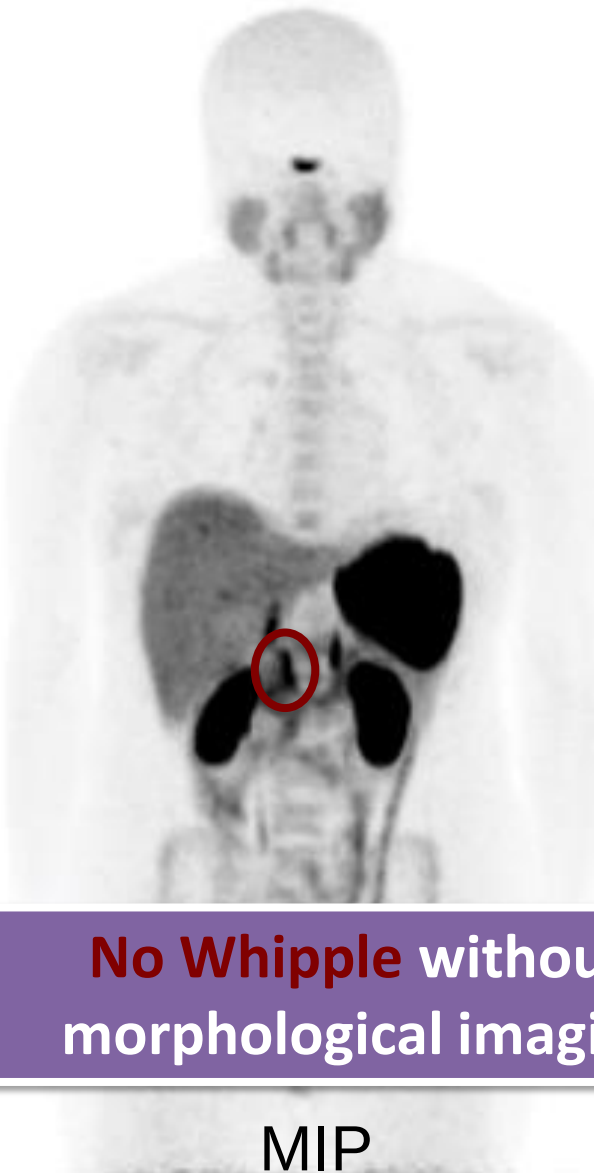


^{111}In -pentetreotide (Octreoscan®)
(**A**gonist)



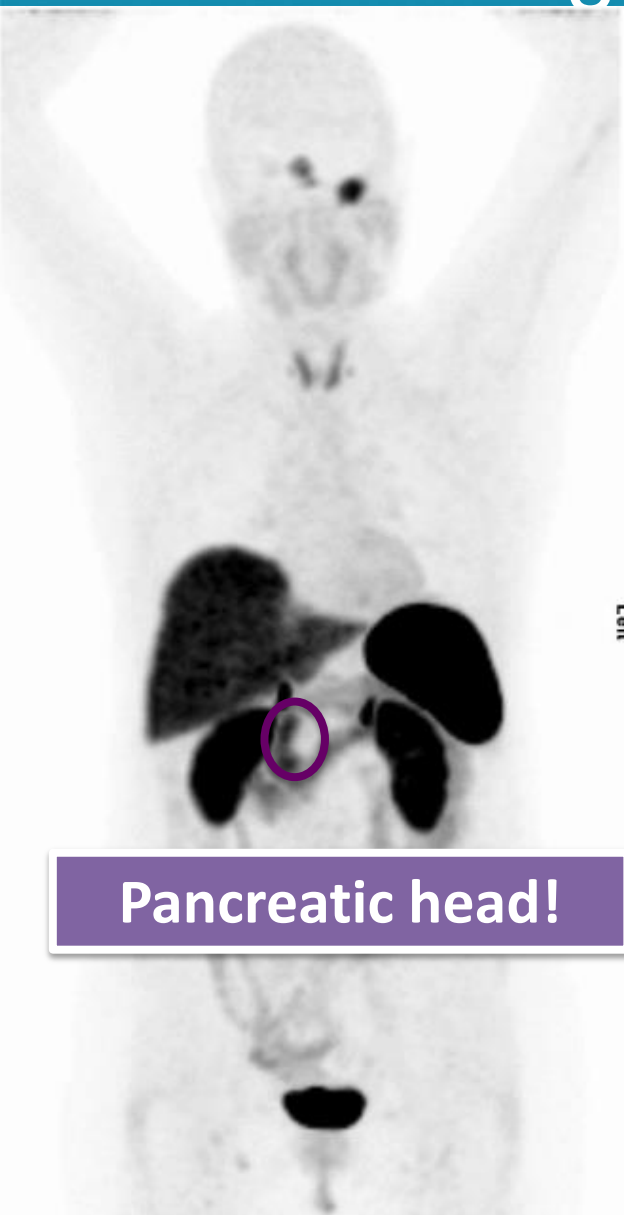
^{111}In -DOTA-BASS
(**Ant**agonist)

Pitfall: increased **physiological** uptake in pancreatic head and uncinate process

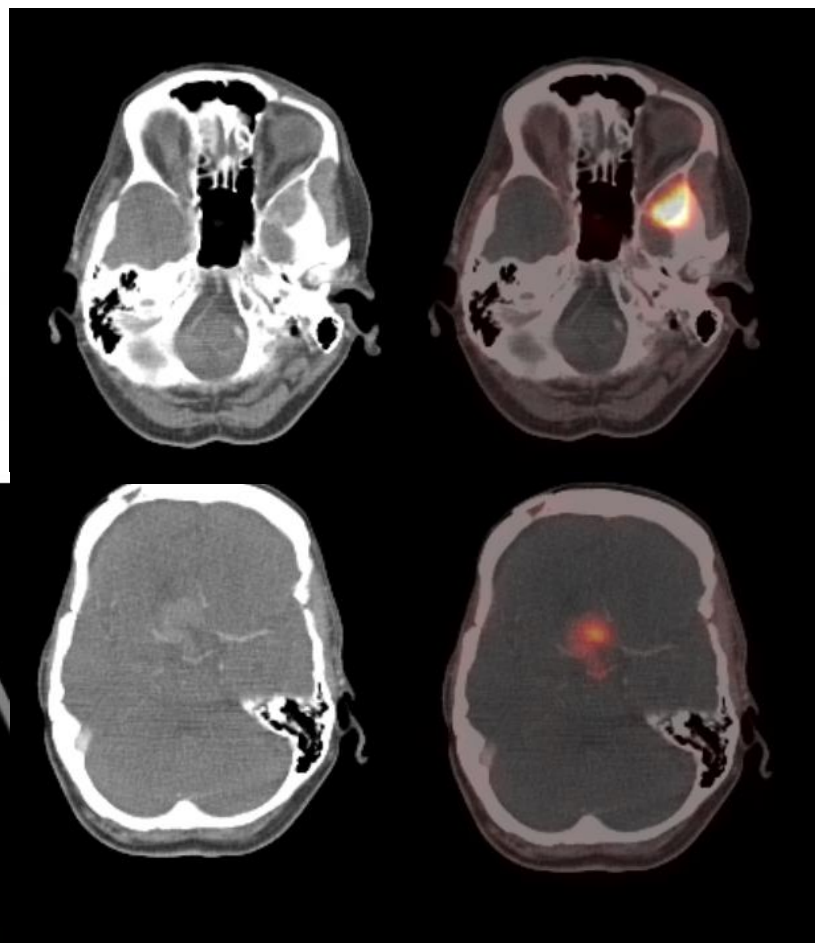


No Whipple without cytological or morphological imaging confirmation

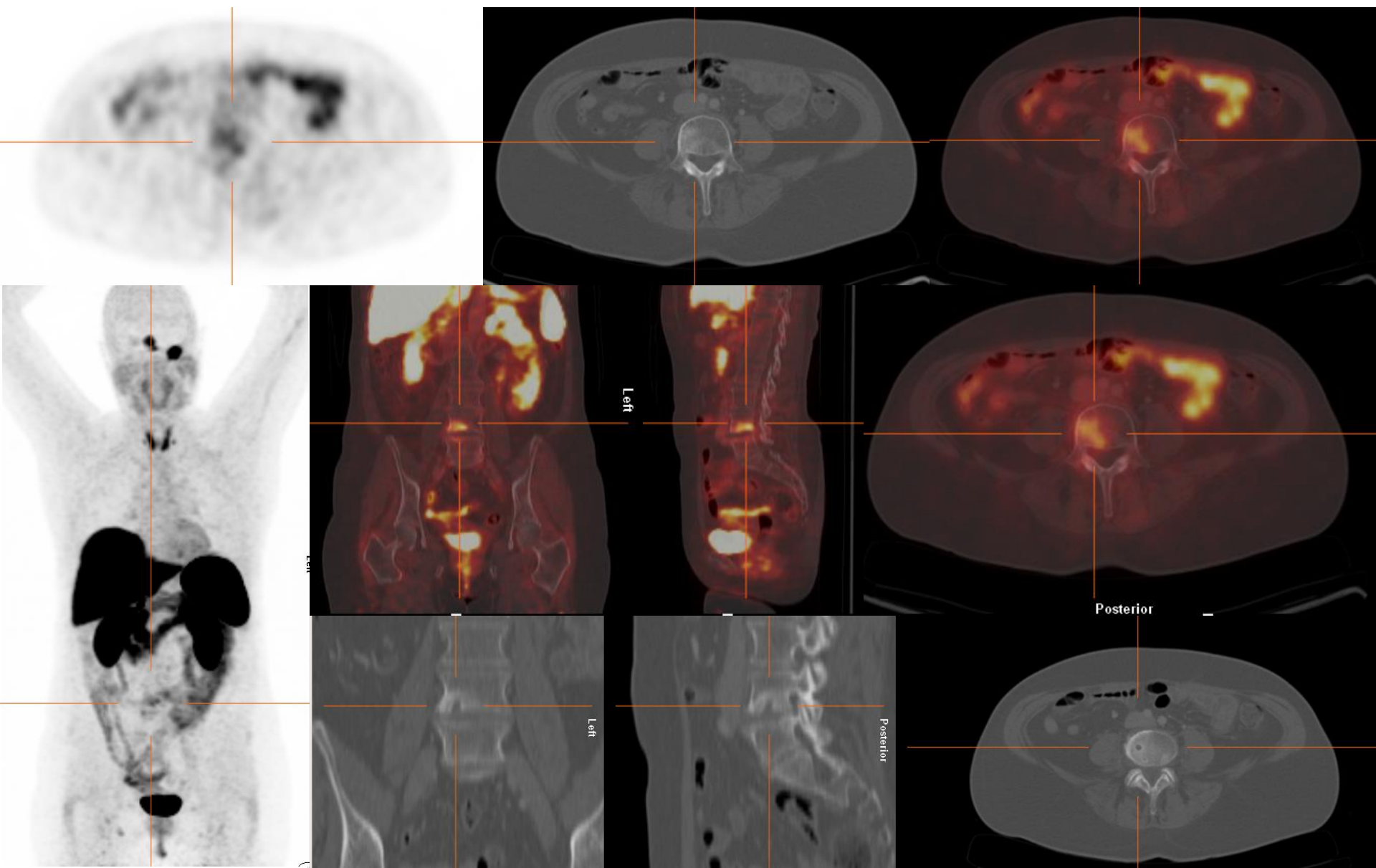
Pitfall: SSR expression on meningeoma (^{68}Ga -DOTATATE)



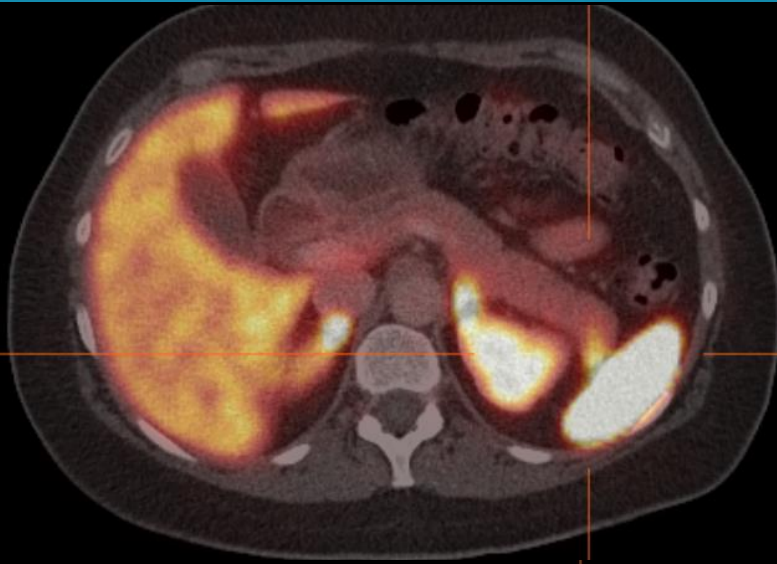
Pancreatic head!



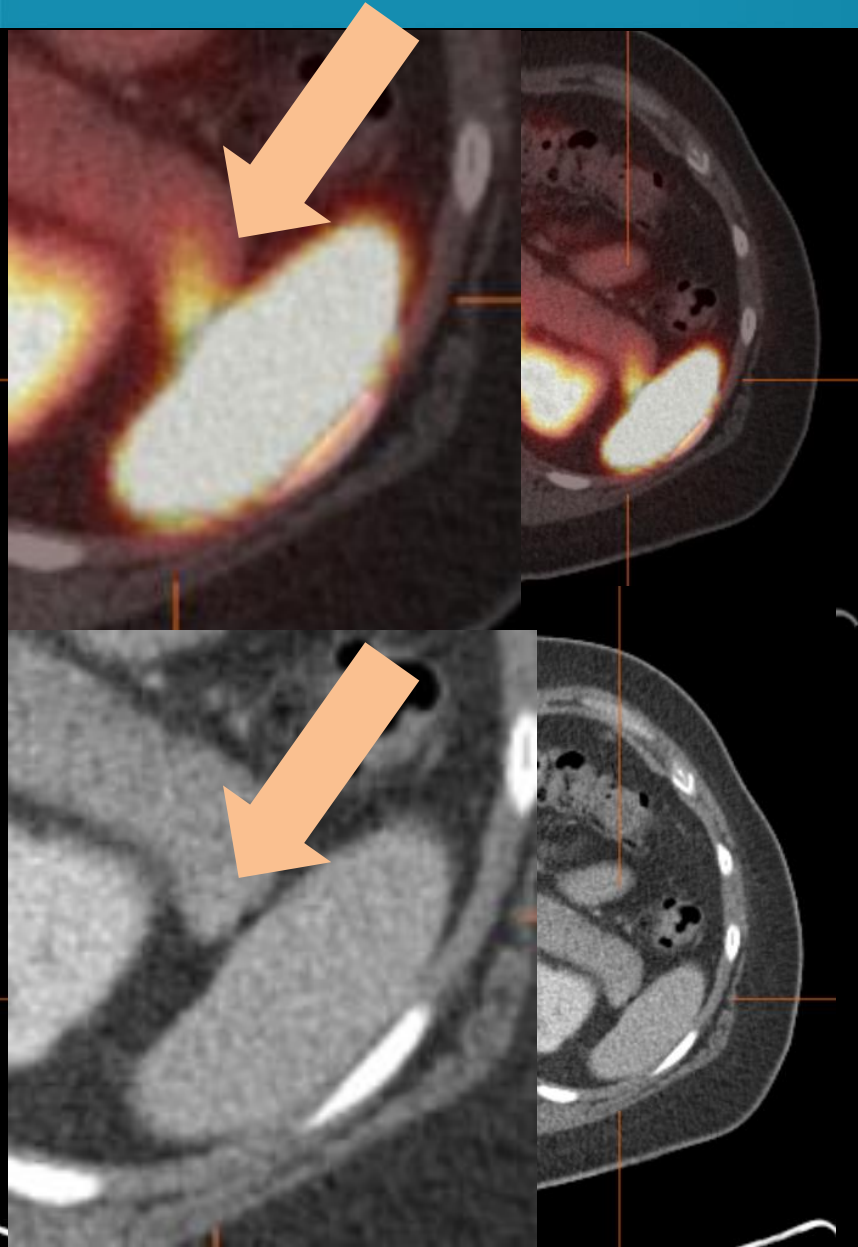
Pitfall: inflammatory uptake in degenerative osteoarthritis (^{68}Ga -DOTATATE)



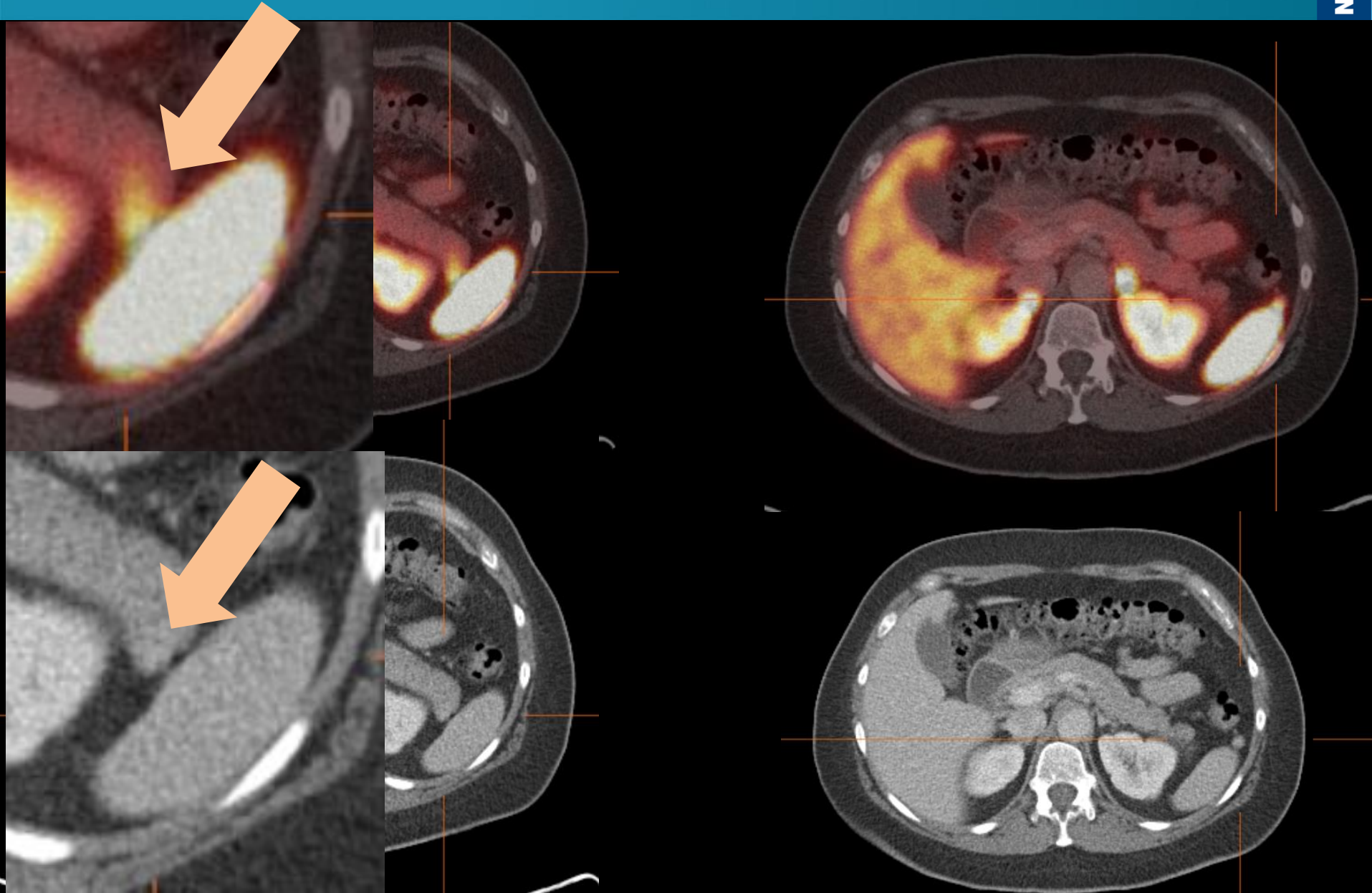
Pitfall: Accessory spleen and probable intrapancreatic accessory spleen on ^{68}Ga -DOTATOC



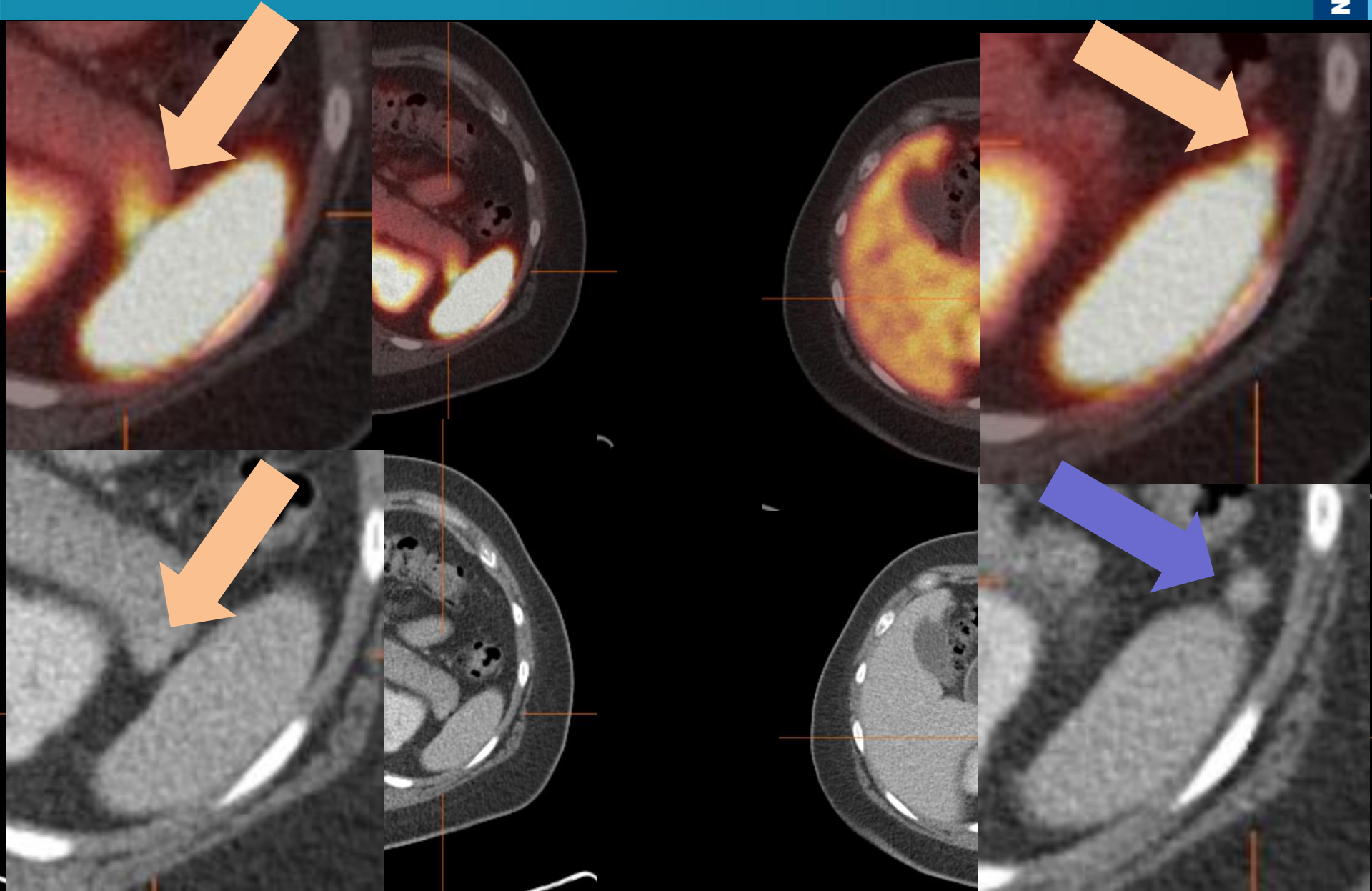
Pitfall: Accessory spleen and probable intrapancreatic accessory spleen on ^{68}Ga -DOTATOC



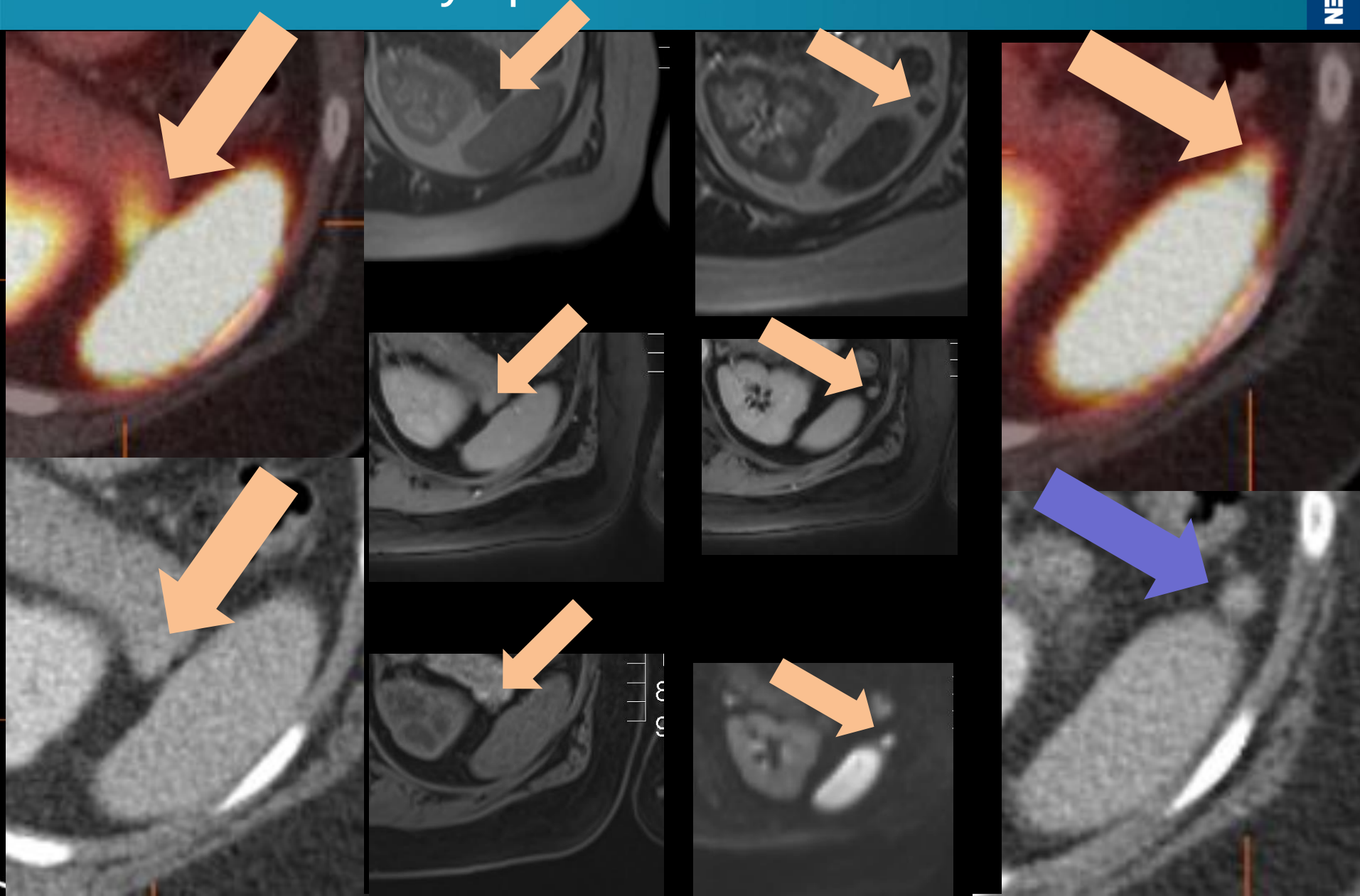
Pitfall: Accessory spleen and probable intrapancreatic accessory spleen on ^{68}Ga -DOTATOC



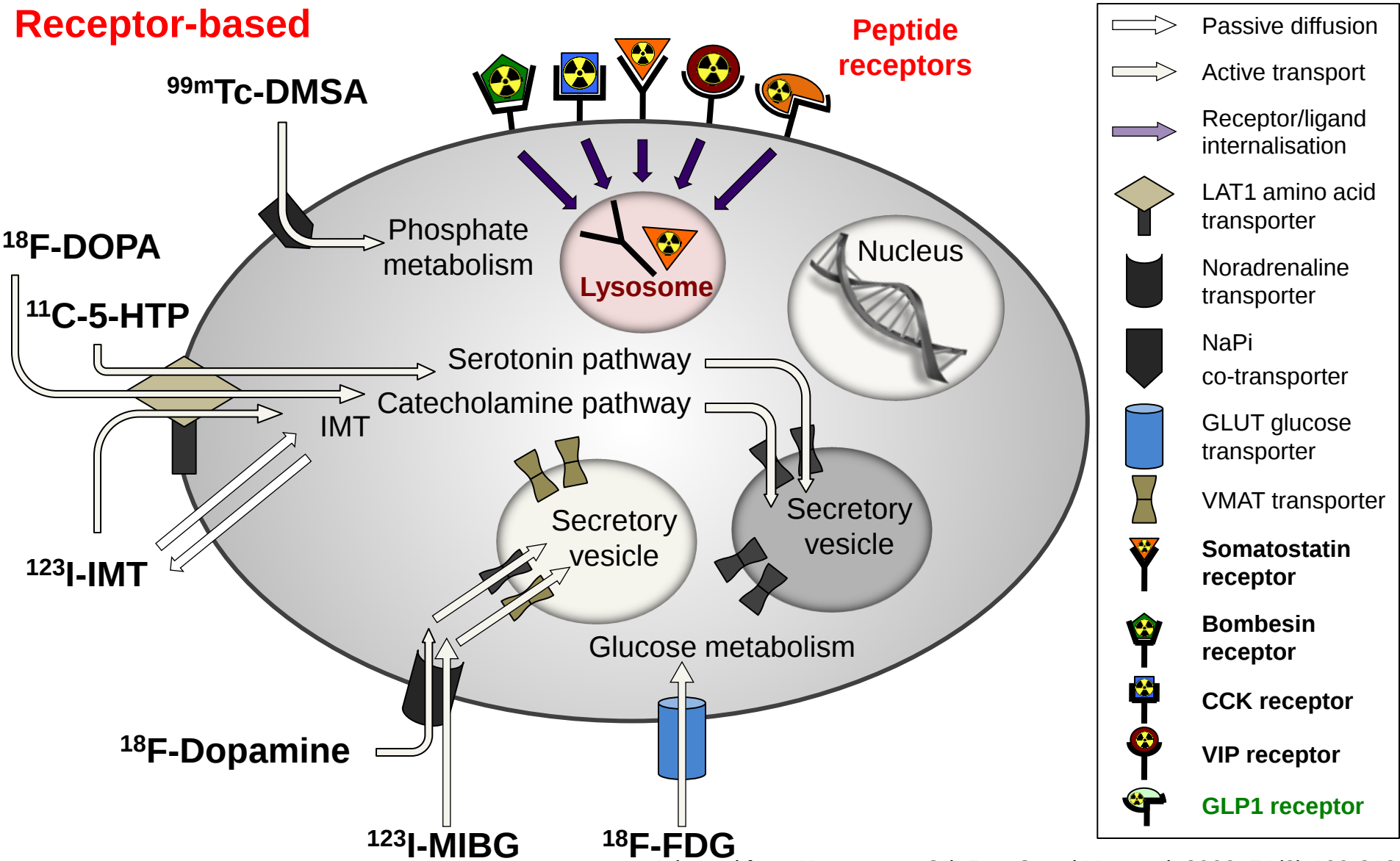
Pitfall: Accessory spleen and probable intrapancreatic accessory spleen on ^{68}Ga -DOTATOC



Pitfall: Accessory spleen and probable intrapancreatic accessory spleen on ^{68}Ga -DOTATOC



Peptide Receptors – Glucagon-like peptide 1 receptor (GLP-1R)



Glucagon-like peptide 1 receptor (GLP-1R) ligands for SPECT

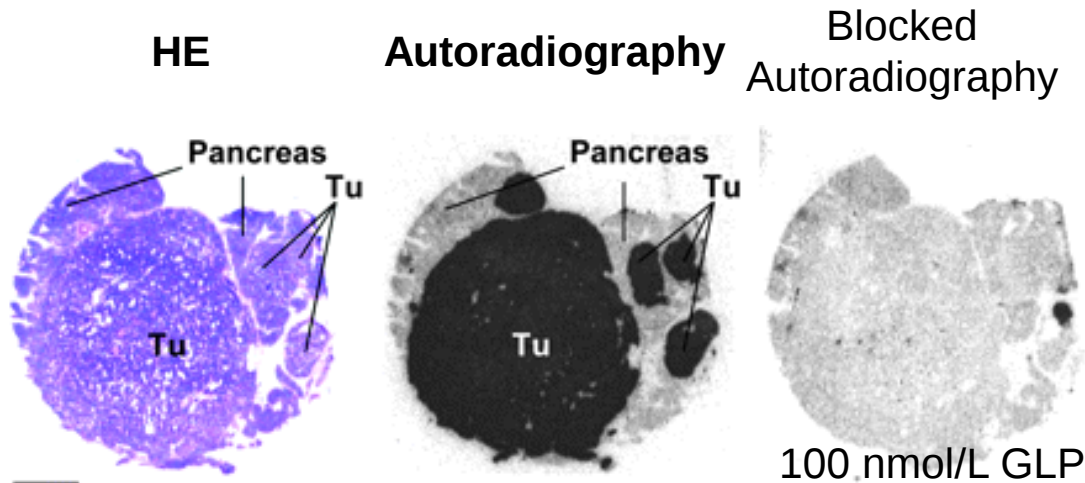
- Receptors for glucagon-like peptide 1 (GLP-1) are highly overexpressed in almost all insulinomas

Reubi, 2003, Eur J Nucl Med Mol Imaging;30(5):781-93

Korner, 2007, J Nucl Med;48(5):736-43

- [Lys⁴⁰(Ahx-DTPA-¹¹¹In)NH₂]exendin-4 pre-clinically validated tracer (RIP-Tag mouse model)

Wild, 2006, J Nucl Med;47(12):2025-33



Glucagon-like peptide 1 receptor (GLP-1R) ligands for SPECT

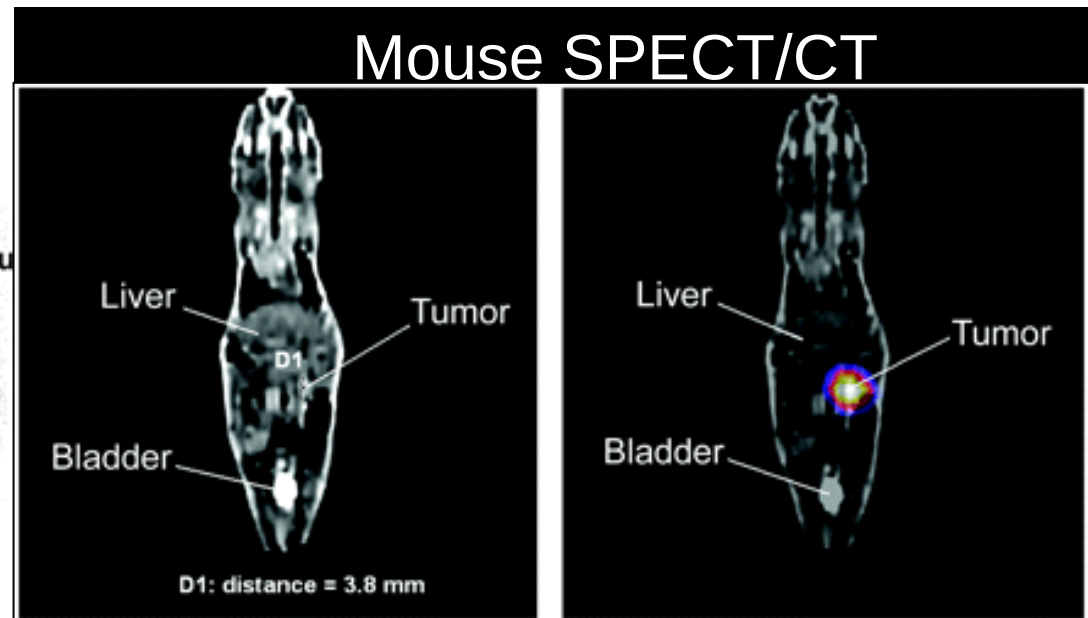
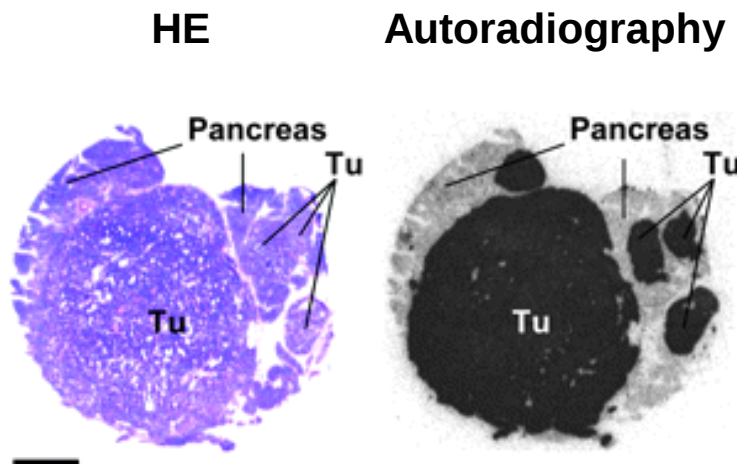
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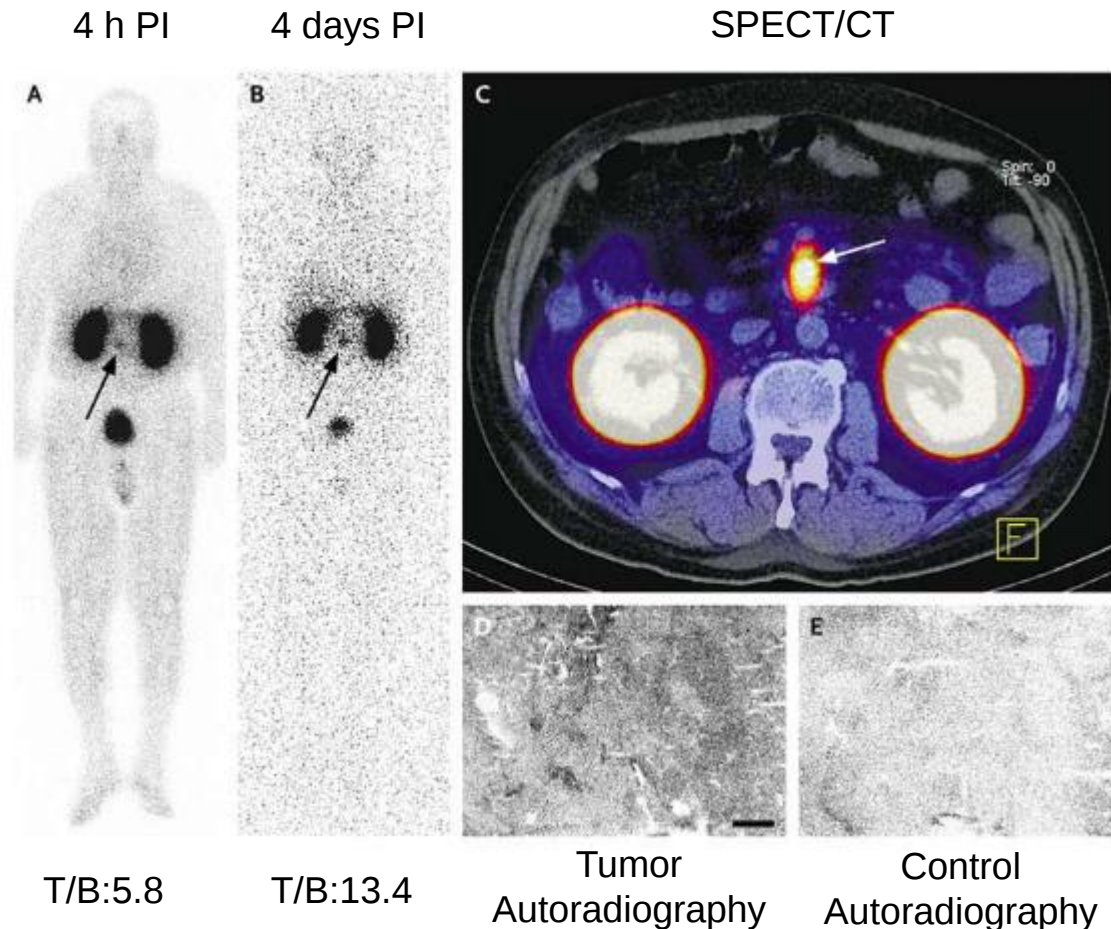
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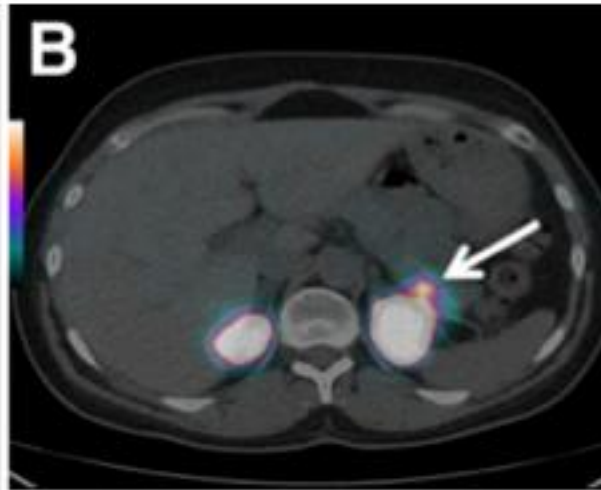
Glucagon-like peptide 1 receptor (GLP-1R) ligands for SPECT



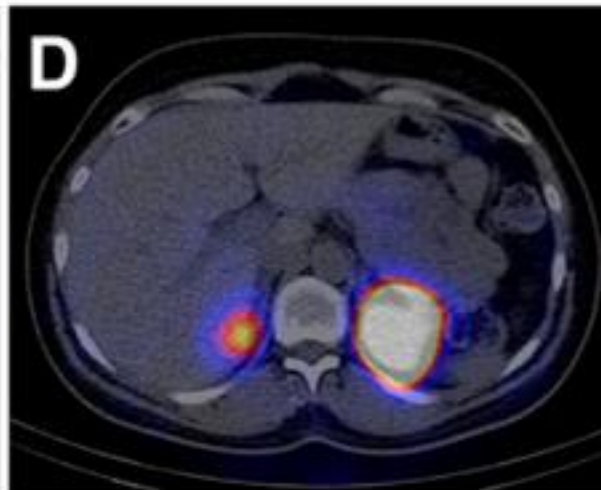
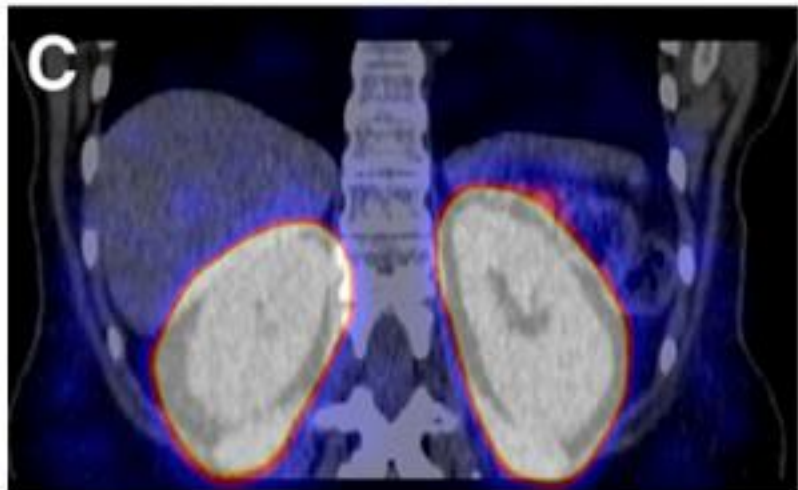
Man, 64 year
Neuroglycopenia
Endogenous
hyperinsulinism

SPECT/CT: small
nodule between the
duodenum and the
superior mesenteric
artery

Glucagon-like peptide 1 receptors (GLP-1R) ligands for PET (^{68}Ga -DOTA-exendin-4)

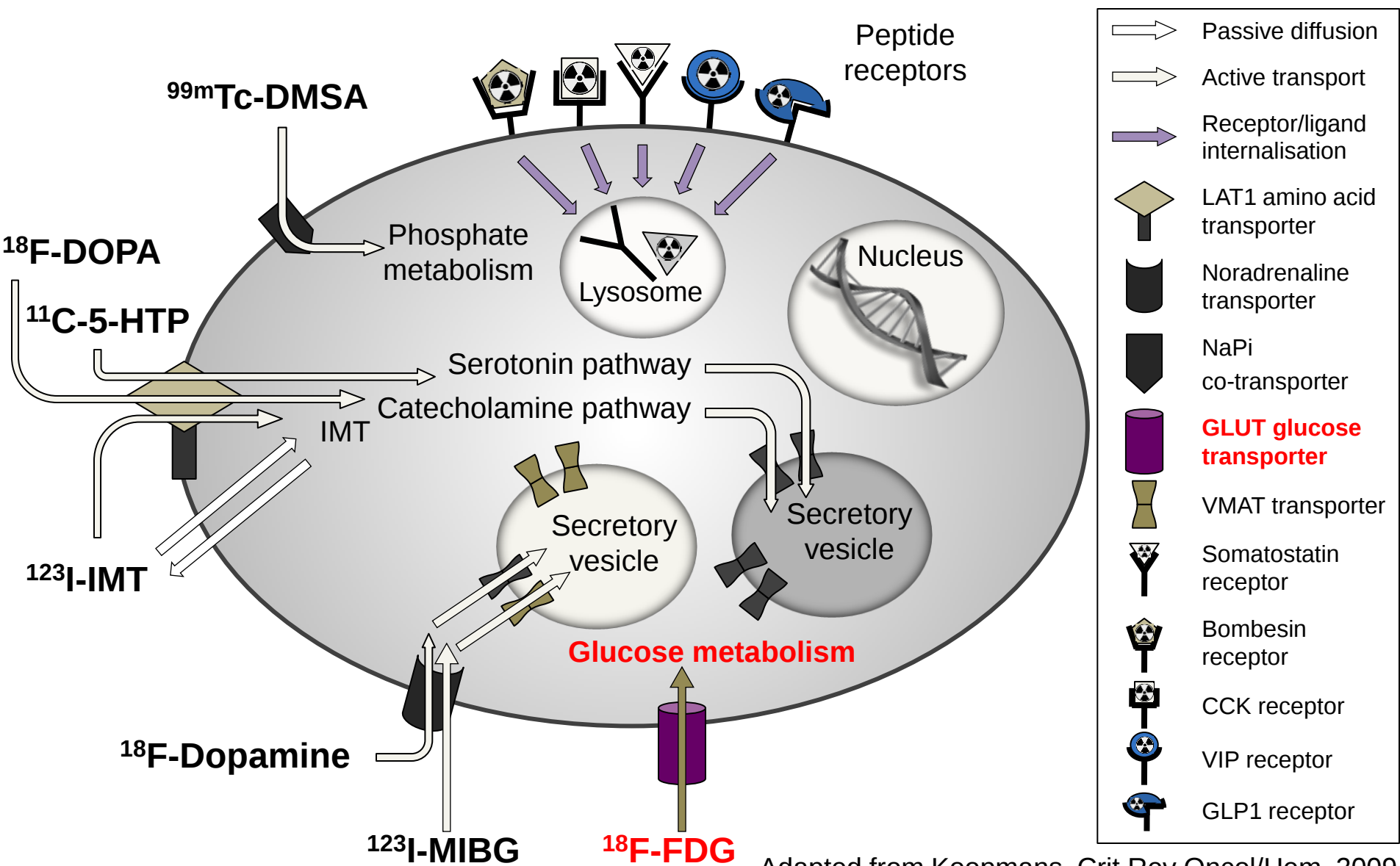


PET



SPECT

Glucose Metabolism – ^{18}F -FDG



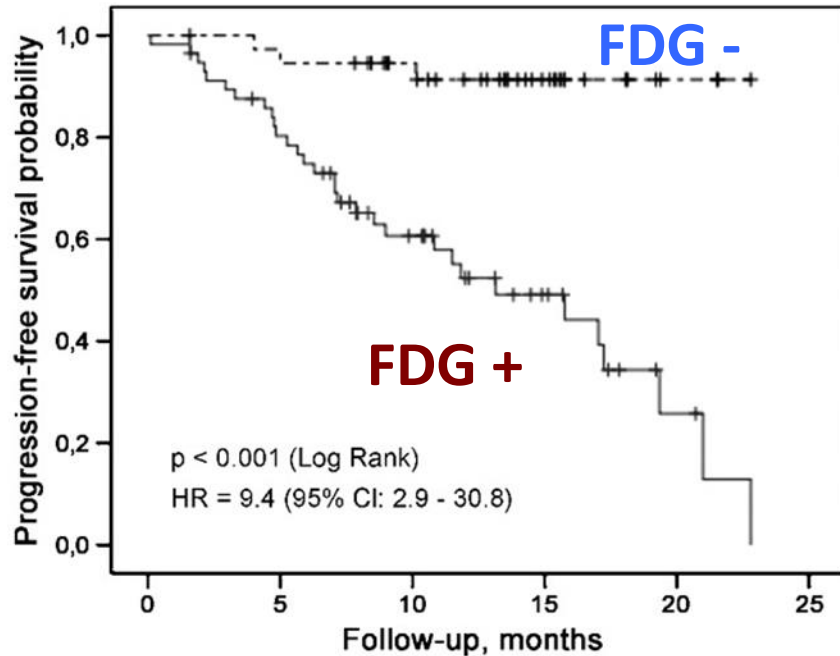
Adapted from Koopmans, Crit Rev Oncol/Hem, 2009

Contribution of ¹⁸F-FDG PET(/CT) imaging

- **Sensitive** detection of tumoral lesions, including small lesions (**G3**):
 - Staging
 - Suspicion of recurrence
 - Restaging
 - Therapy monitoring
- **Molecular characterization** of tumoral lesions:
 - **Prognostic** biomaker
 - **Guidance** for (re-)biopsy incase of clinical/morphological progression.

^{18}F -FDG PET detects patients with poor prognosis

PFS



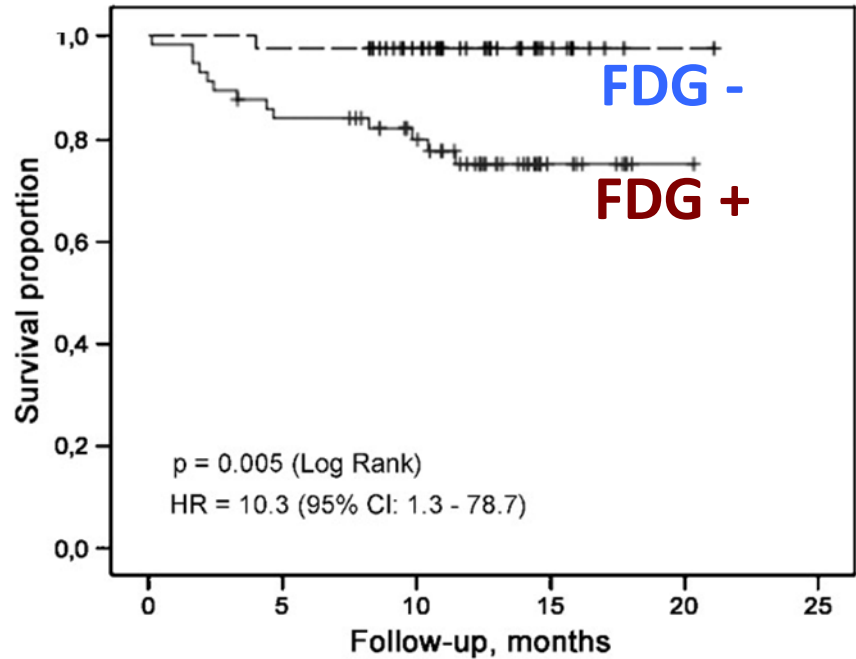
Hazard Ratio: 9.4

N=98

Sensitivity for FDG: 58%

Determines biological properties

OS



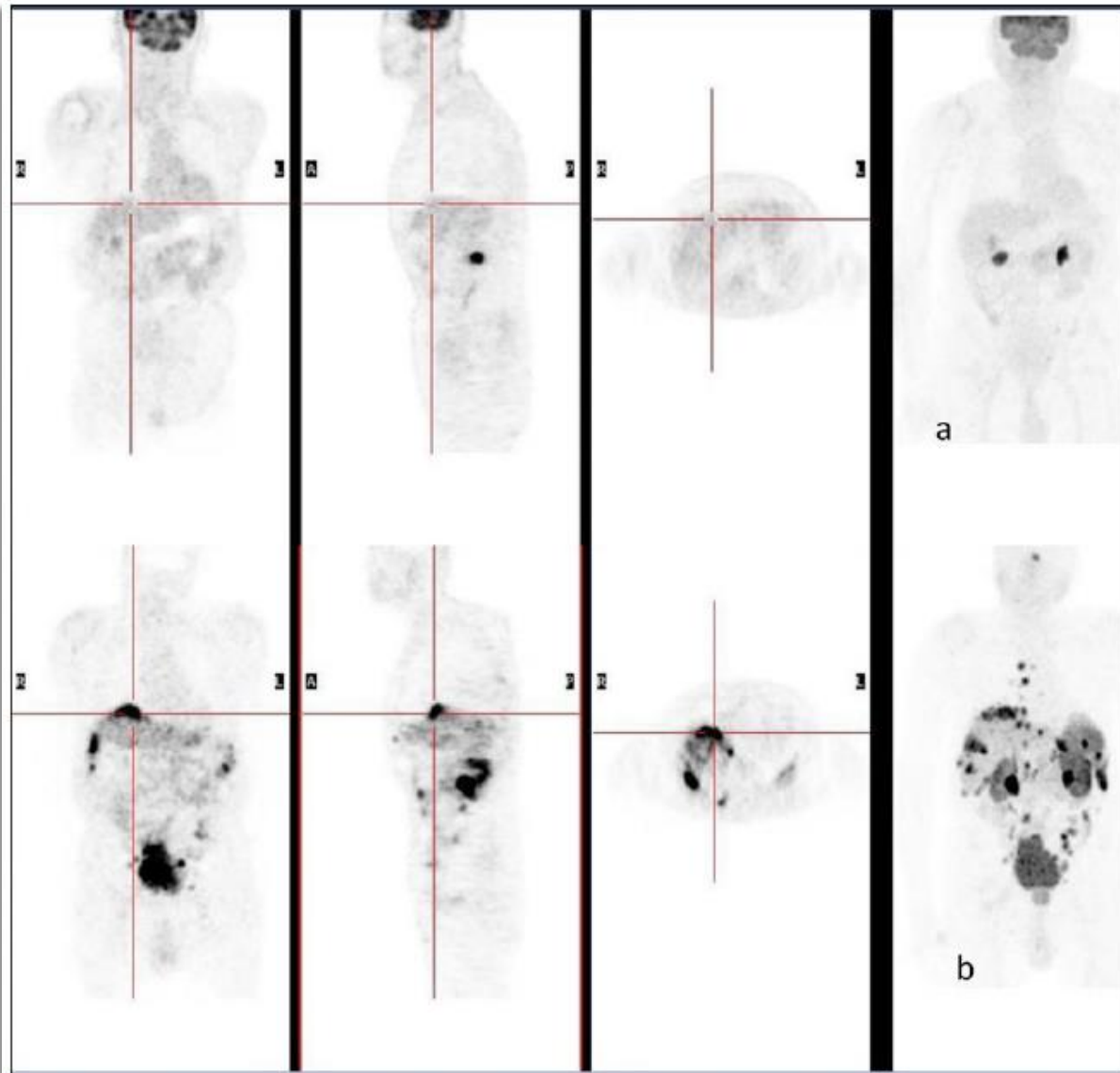
Hazard Ratio: 10.3

Role of ^{18}F -FDG PET/CT in patients treated with ^{177}Lu -DOTATATE for advanced differentiated NET

ileal NET
(grade 2, Ki67 9 %)

FDG -

^{68}Ga -DOTATOC +

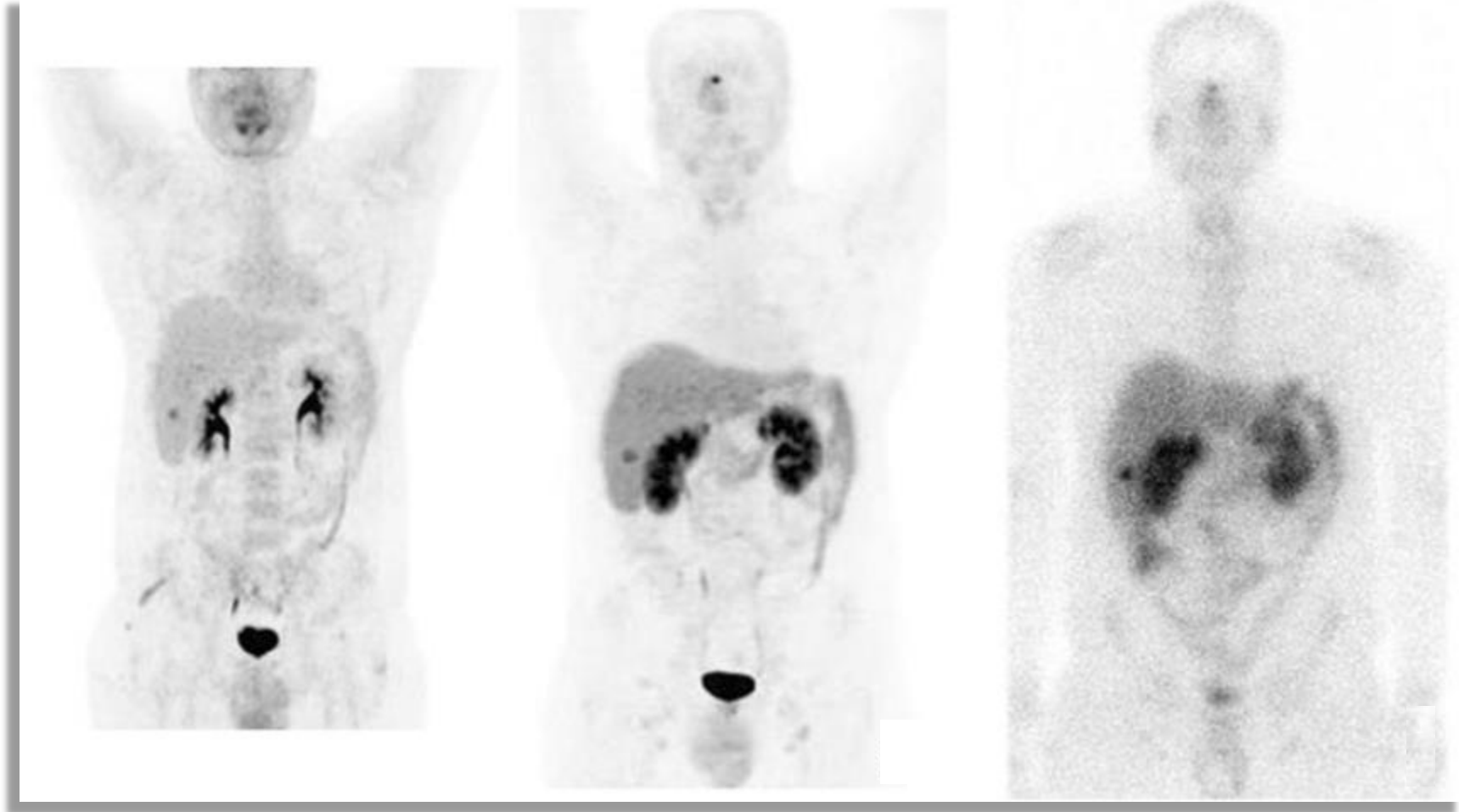


Role of ^{18}F -FDG PET/CT in patients treated with ^{177}Lu -DOTATATE for advanced differentiated NET

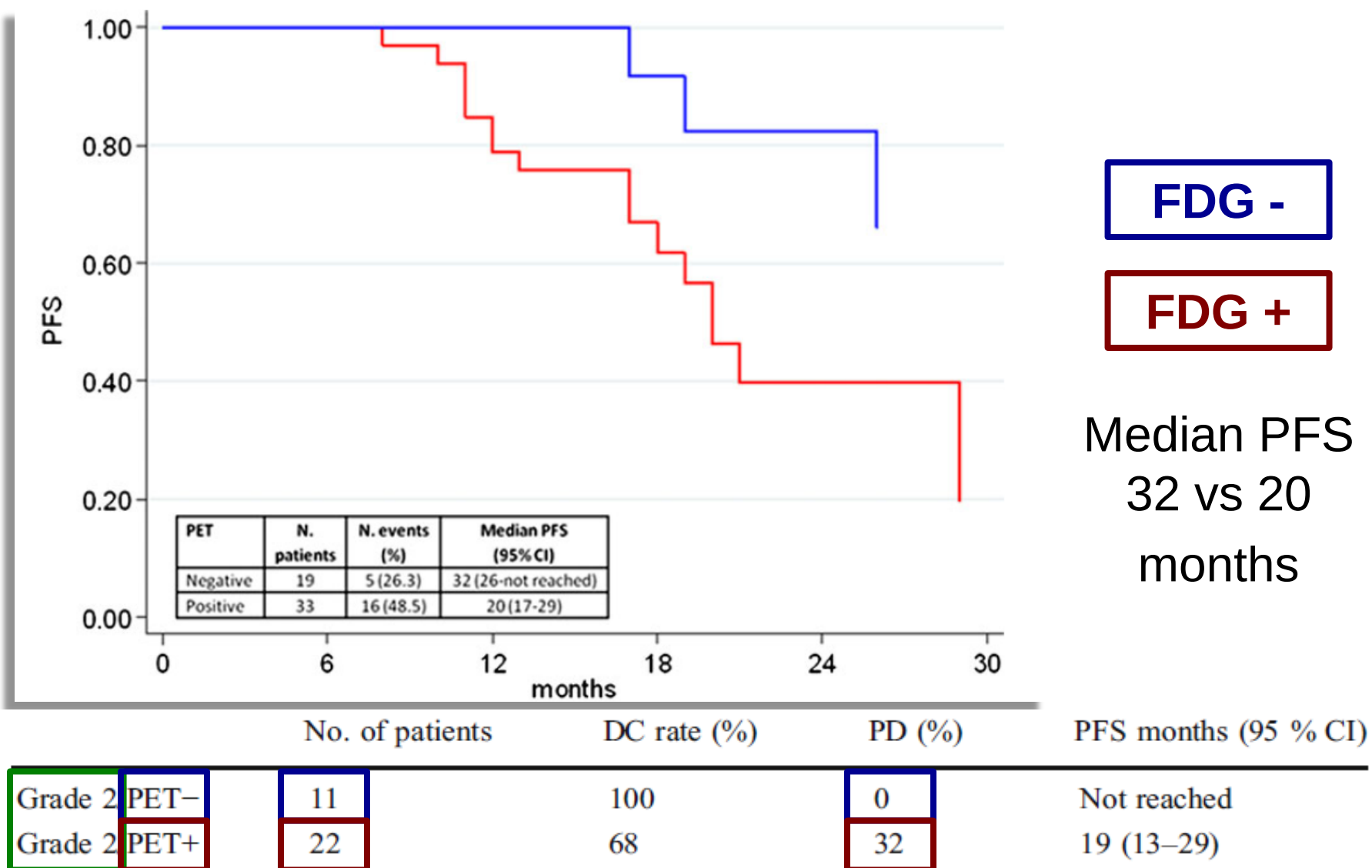
FDG +

^{68}Ga -DOTATOC +

^{177}Lu -DOTATATE +



^{18}F -FDG PET in patients treated with ^{177}Lu -DOTATATE PRRT for differentiated NET



Metabolic grading of NET with ^{18}F -FDG

Prognostic Stratification of Metastatic Gastroenteropancreatic Neuroendocrine Neoplasms by ^{18}F -FDG PET: Feasibility of a Metabolic Grading System

Samer Ezziddin¹, Linda Adler¹, Amir Sabet¹, Thorsten Dirk Pöppel², Florian Gräbells³, Ali Yüce⁴, Hans-Peter Fischer⁵, Birgit Simon⁶, Tobias Höller⁷, Hans-Jürgen Biersack¹, and James Nagarajah²

TABLE 3 T/L:Tumor/Liver
Definition of Pathologic and Metabolic Grading in This Study

Pathologic		Metabolic	
Grade	Ki-67 index	Grade	T/L SUV ratio*
pG1	$\leq 2\%$	mG1	< 1
pG2	3–20%	mG2	1–2.3
pG3	$> 20\%$	mG3	> 2.3

Metabolic grading of NET with ^{18}F -FDG

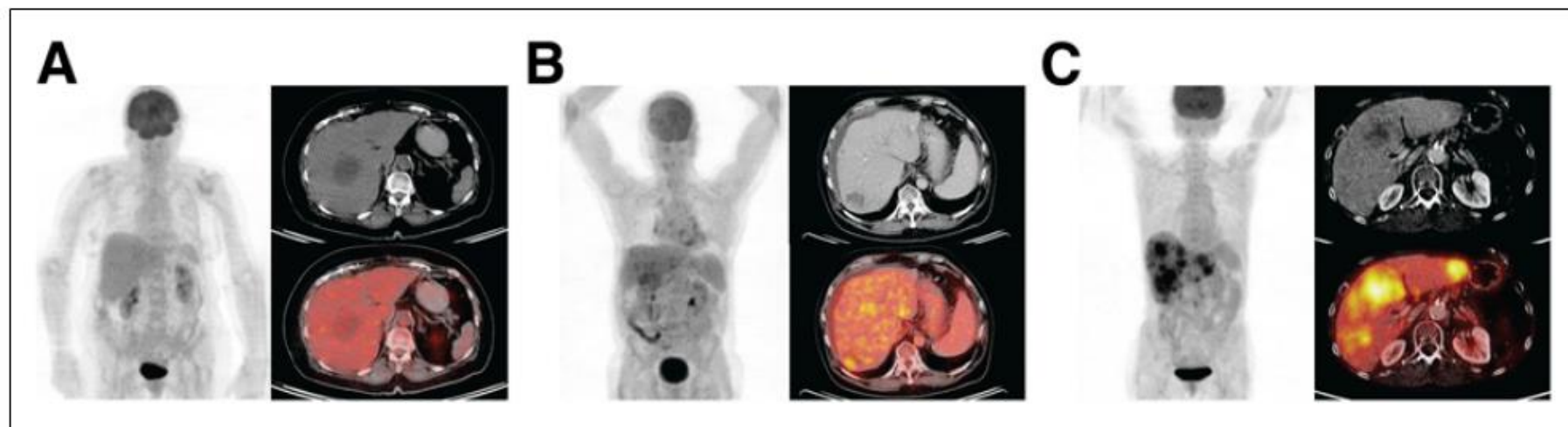
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mG1

mG2

mG3



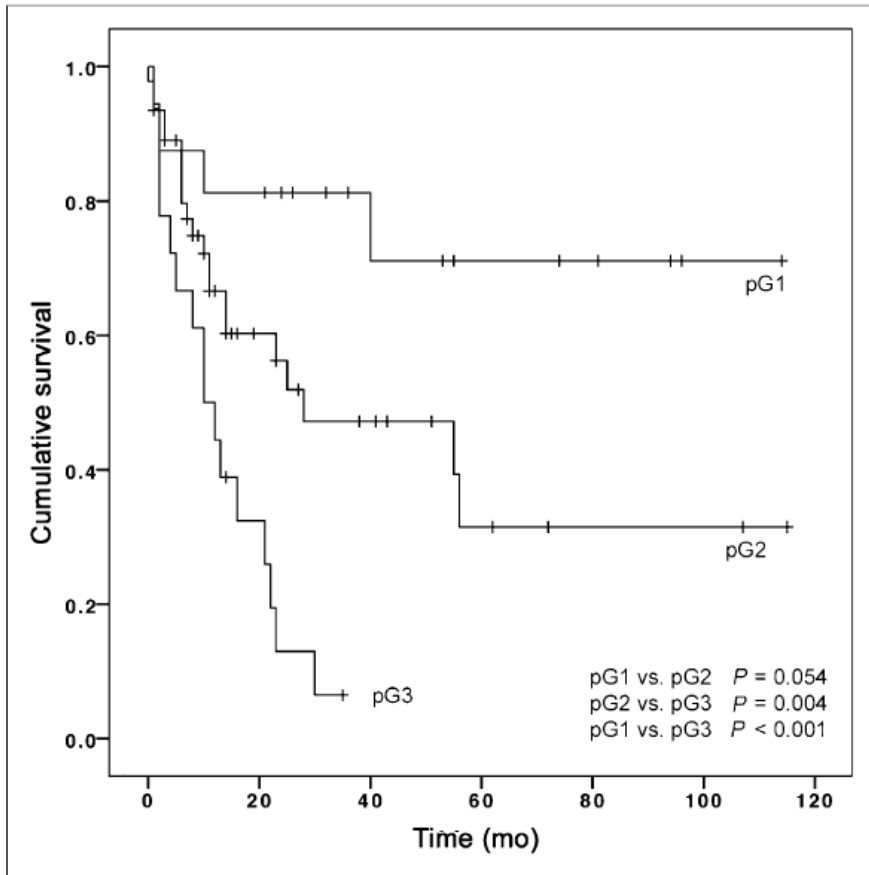
Ki67:10%

Ki67:1%

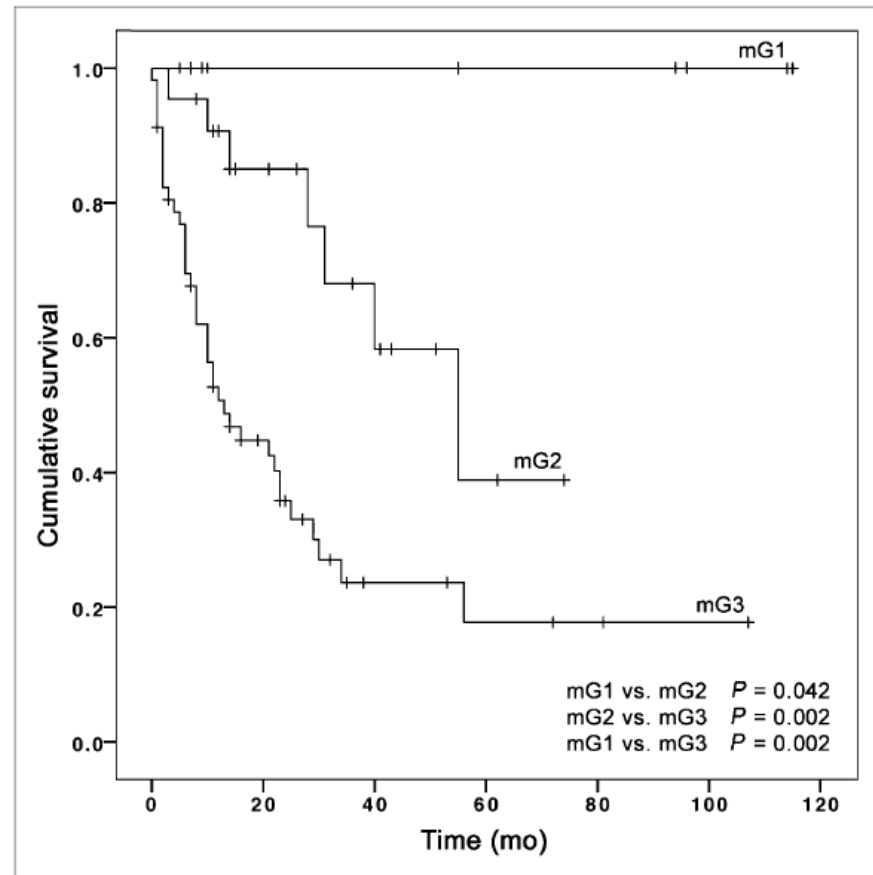
Ki67:20%

Metabolic grading of NET with ^{18}F -FDG

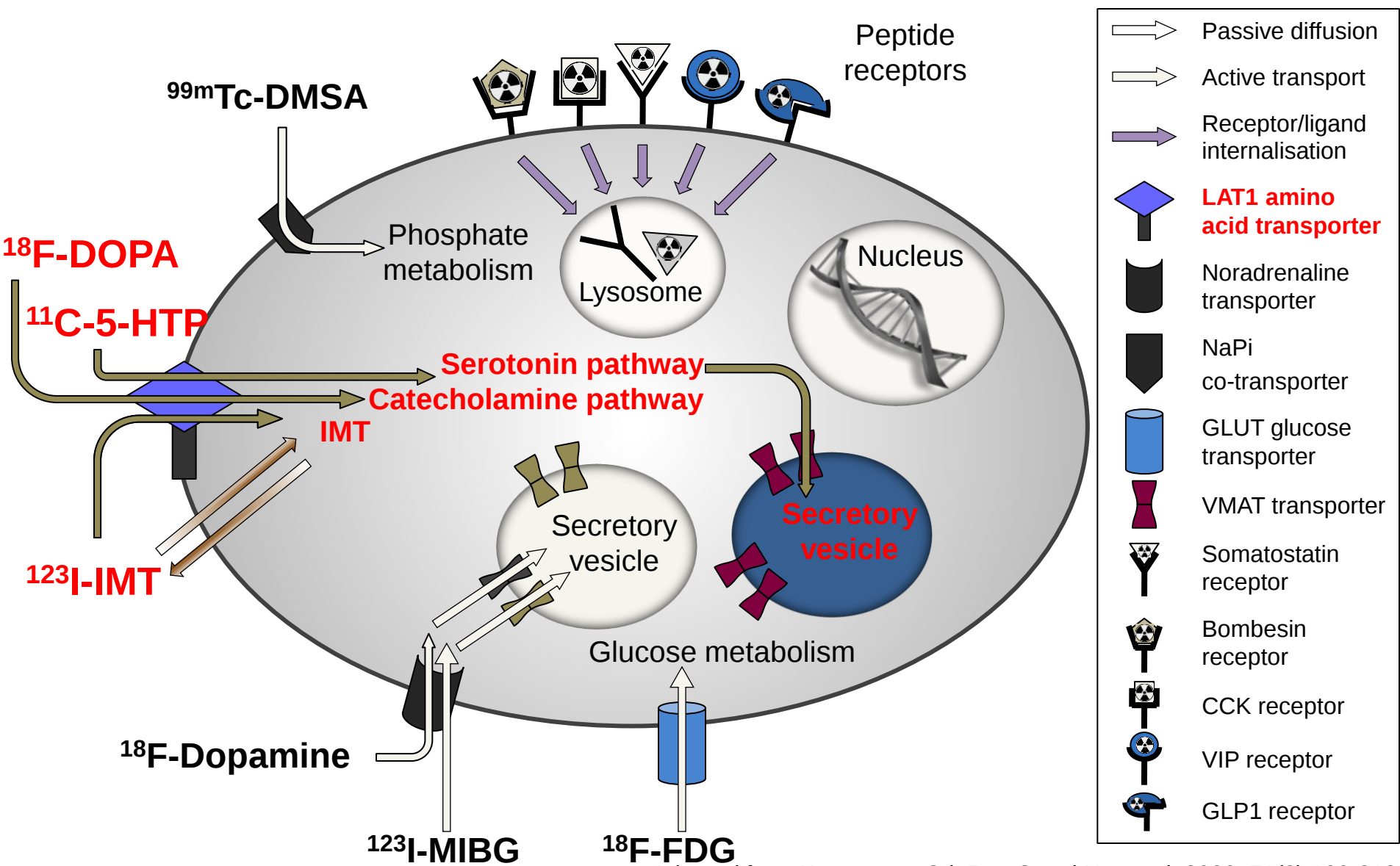
Pathological grading



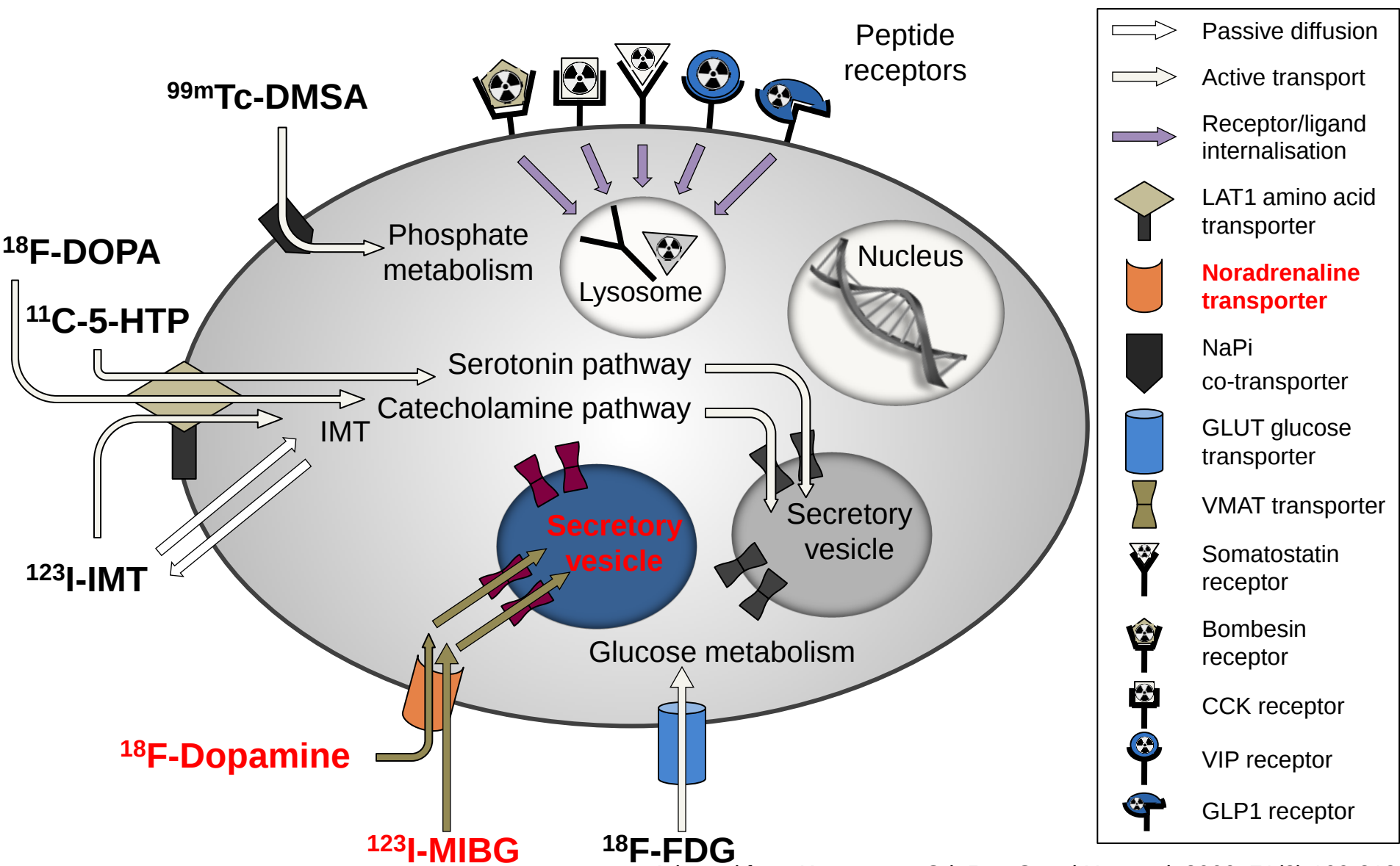
Metabolic grading



Radiolabelled Neurotransmitter Precursors



Radiolabeled Catecholamines



Take Home Messages

- **SSTR scintigraphy or PET**

- Sensitivity > 90% compared to conventional techniques
- Is part of standard management in a large fraction of NET patients
 - Time of diagnosis
 - During follow-up
- First choice in patients with grade 1 or 2 NET
- Can be useful in isolated tumor marker rise (chromogranin, 5-HIAA)
- ^{111}In -Pentetreotide: not gold standard (use of SPECT/CT strongly advised)
- ^{68}Ga -DOTA-peptides are the best tracers, should be used when available
- Pitfalls: uncinate process, other tumors (e.g. meningioma), spleen, inflammation
- Antagonists next step

- **^{18}F -FDG**

- First choice in patients with grade 3 NET for determination of tumor extent
- Offers prognostic information in patients with grade 1 or 2 NET
- Metabolic grading in metastatic patients?

- **^{18}F -DOPA/ ^{11}C -5-HTP/ ^{18}F -Dopamine**: other techniques inconclusive

Questions?

Leuven City Hall

