



Most frequent confusions in NEN management

Wednesday, 3 June 2025, 18:00 – 19:10 CEST

Disclosure Statement

Eva Tiensuu Janson (Moderator) has no conflicts of interest to disclose.

The Aim and Concept

- ✓ Transferring research to education and teaching is a major goal at ENETS.
- ✓ Webinars are free of charge and can be accessed by all.
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Live poll question: Getting to know the audience

In which medical discipline are you trained or currently working?

Tonight's faculty



Eva TIENSUU JANSON

Uppsala University Hospital
Sweden
Endocrinology



Valentina AMBROSINI

Univ. of Bologna, IRCCS Azienda
Ospedaliero Universitaria di Bologna, Italy
Nuclear Medicine



**Marie-Louise
VAN VELTHUYSEN**

Erasmus MC
Leiden, The Netherlands
Pathology



Damiano CARUSO

Sapienza University of Rome
Italy
Radiology



Julien HADOUX

Institut Gustave Roussy,
Villejuif, France
Oncology

Tonight's agenda

Moderator: Eva TIENSUU JANSON, SWE

18:00 – 18:05 Opening – **Eva TIENSUU JANSON, SWE**

18:05 – 18:15 Immunohistochemistry and functioning status – **Marie-Louise VAN VELTHUYSEN, NED**

18:15 – 18:25 PET imaging and WHO status – **Valentina AMBROSINI, ITA**

18:25 – 18:35 Conventional imaging – **Damiano CARUSO, ITA**

18:35 – 18:45 Primary location – **Julien HADOUX, FRA**

18:45 – 19:05 Discussion

19:05 – 19:10 Closing comments – **Eva TIENSUU JANSON, SWE**

Most frequent confusions in NEN – Immunohistochemistry and functioning status

Pathology perspective

Marie-Louise van Velthuysen

Pathologist, Erasmus Medical Centre, Erasmus University, Rotterdam, the Netherlands

DISCLOSURE SLIDE

I have no conflicts/disclosures to declare



Ursus Werli

Source of confusions in NEN pathology

- ✓ Evolving classification
- ✓ Differences in nomenclature in different organs and in time
- ✓ Interpretation of immunohistochemical markers
- ✓ Lack of knowledge on differential diagnosis



Source of confusions in NEN pathology

- ✓ Evolving classification
 - ✓ High-grade versus Low-grade (NEC versus NET) (2000, 2010, 2017)
 - ✓ Grading of NET, based on proliferation (but different cut-of in gep-NET vs lung-NEN)
 - ✓ (2004, 2010, 2017)
 - ✓ Gobletcell carcinoma (former gobletcell carcinoid) now recognised as non-NEN
- ✓ Differences in nomenclature in different organs

WHO 2019 GEP - NEN

Grade	Mitosis / 2mm ²	Ki-67 %/500-2000 nuclei
NET G1	<2	< 3
NET G2	2-20	3-20
NET G3	>20	>20
NEC (SC/LC)	>20	>20

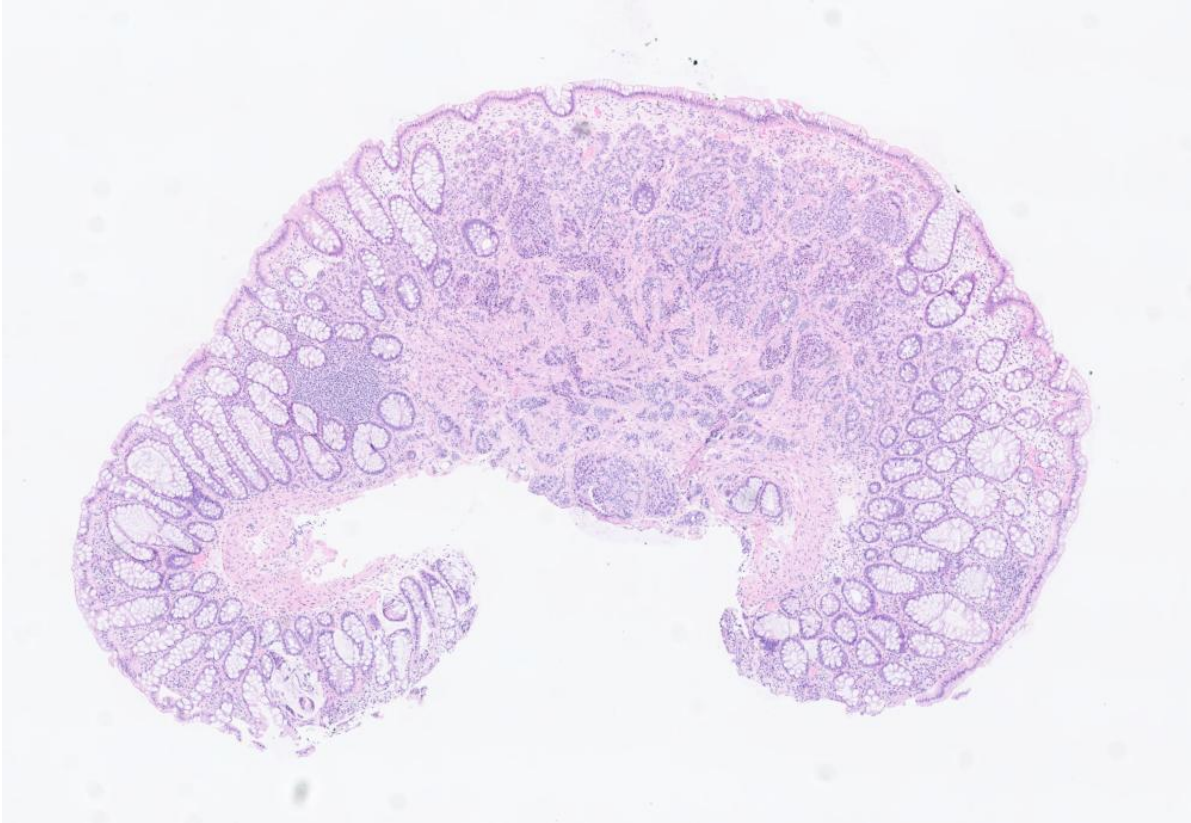
WHO Lung 2021

Grade	Mitosis / 2mm ²
Typical carcinoid	<2
Atypical carcinoid	2-10
“super carcinoid”	>10
LCNEC, SCLC	>10

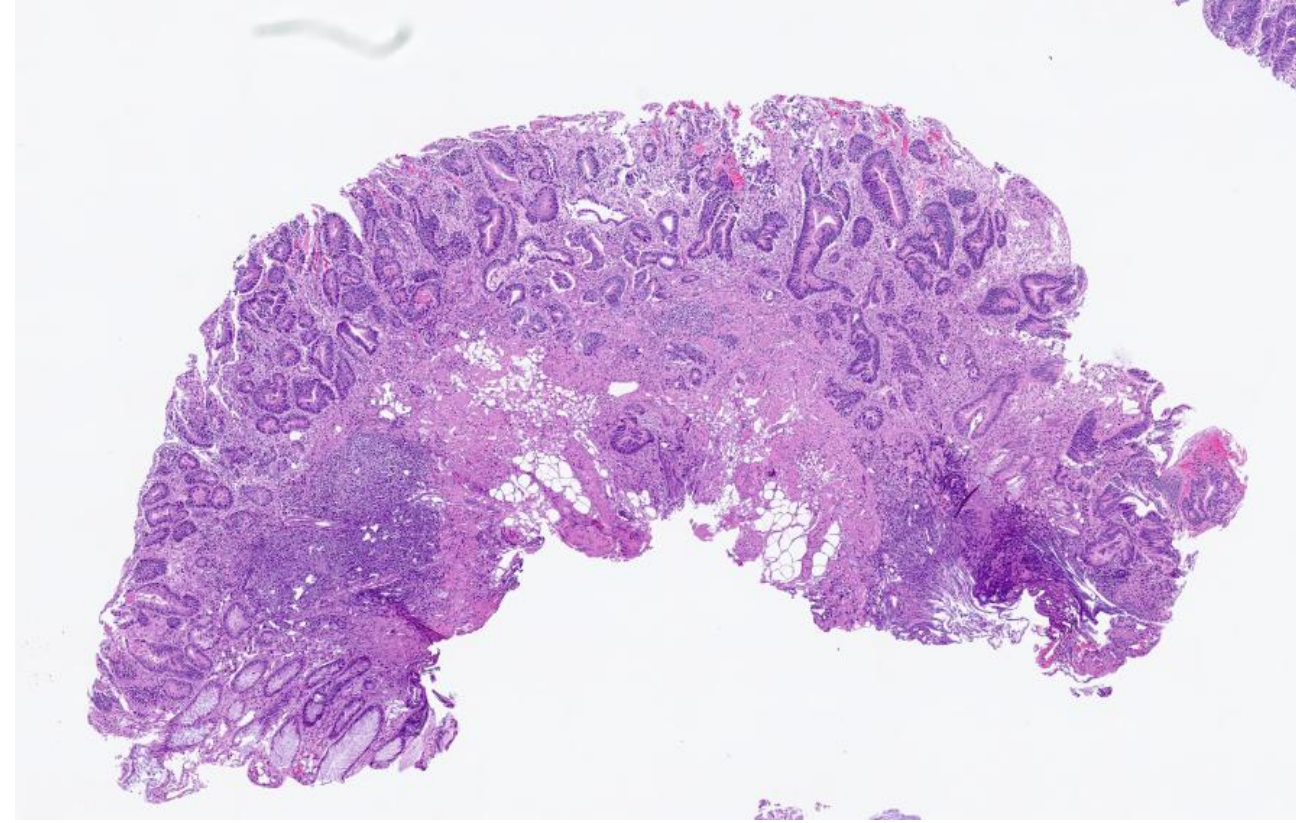
Source of confusions in NEN pathology

- ✓ Evolving classification
- ✓ Differences in nomenclature in different organs
- ✓ Interpretation of immunohistochemical markers
 - ✓ Which markers are required for diagnosis?
 - ✓ When is a tumour neuroendocrine?

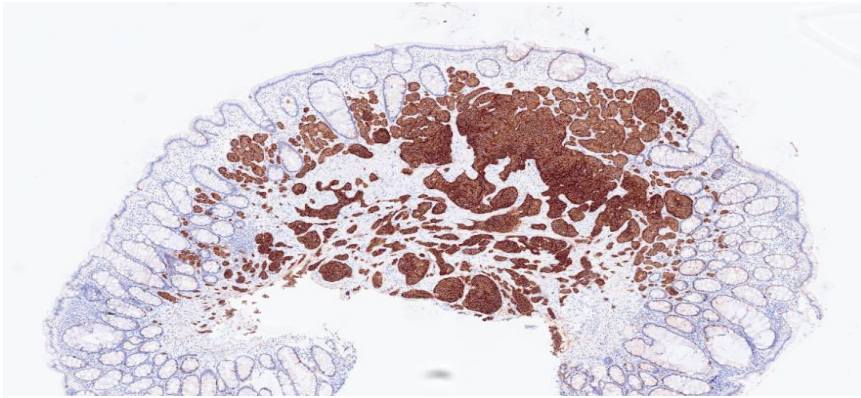
Rectal biopsy, 69y male



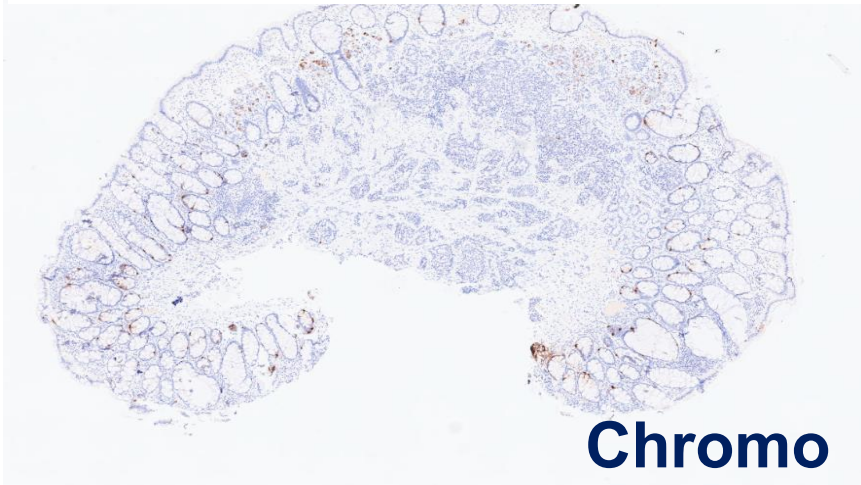
Rectal biopsy, 64y male



Rectal biopsy, 69y

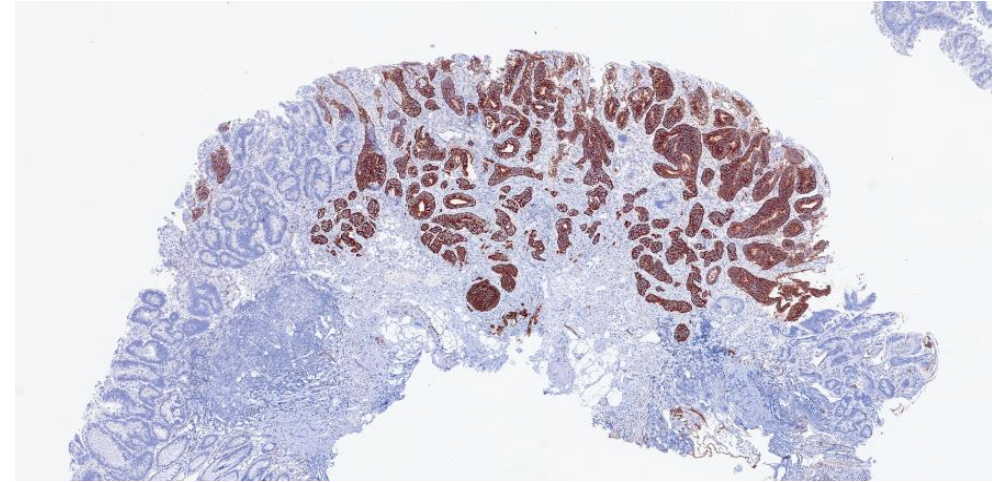


NET

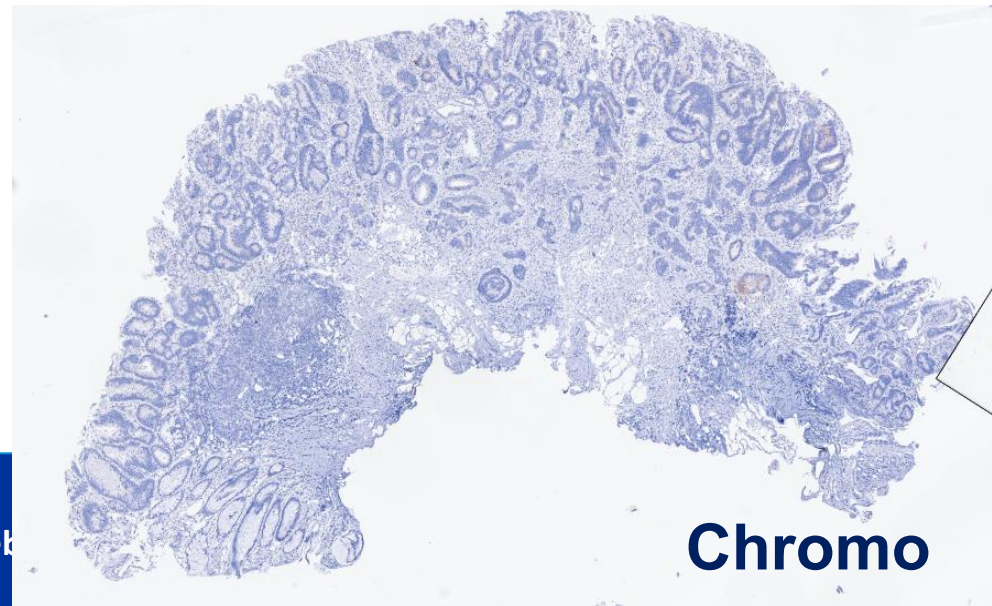


Chromo

Rectal biopsy, 64y male

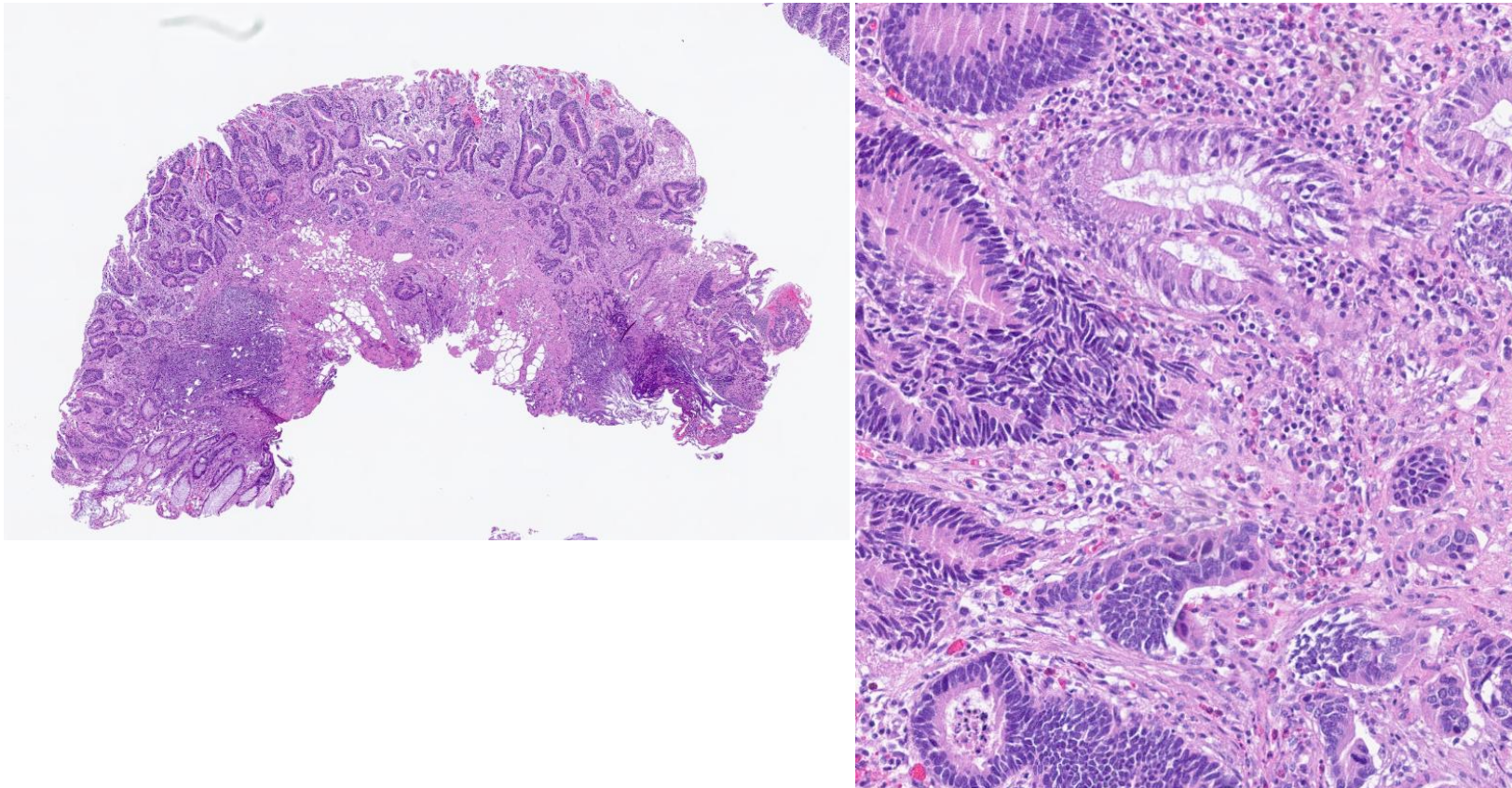


Carcinoma with NE-features



Chromo

Why is this case not a NEC but an adenocarcinoma with NE-features?



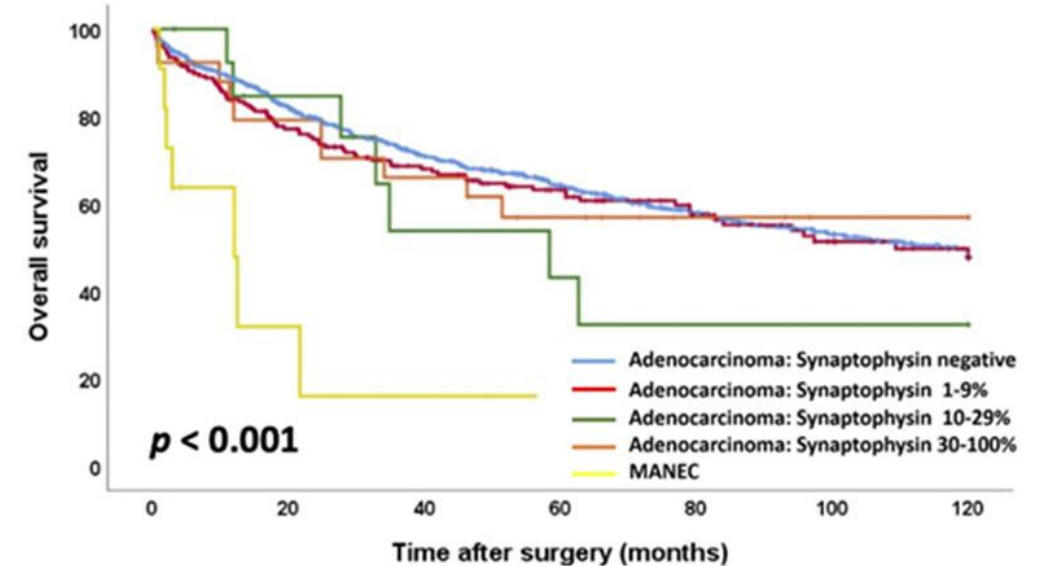
- **Morphology**

- 1 or more components?
 - NEC (1)
 - Adenocarcinoma (1)
 - Amphicrine carcinoma (1)
 - MiNEN (2)

Differentiating Adenocarcinoma from NEC

Neuroendocrine Differentiation in Conventional Colorectal Adenocarcinomas: Incidental Finding or Prognostic Biomarker?
Konukiewitz B et al; Cancers (Basel). 2021 Oct 12;13(20):5111

High expression of insulinoma-associated protein 1 (INSM1) distinguishes colorectal mixed and pure neuroendocrine carcinomas from conventional adenocarcinomas with diffuse expression of synaptophysin
Anne-Sophie Litmeyer et al; J Pathol Clin Res 2023 Nov; 9: 498–509



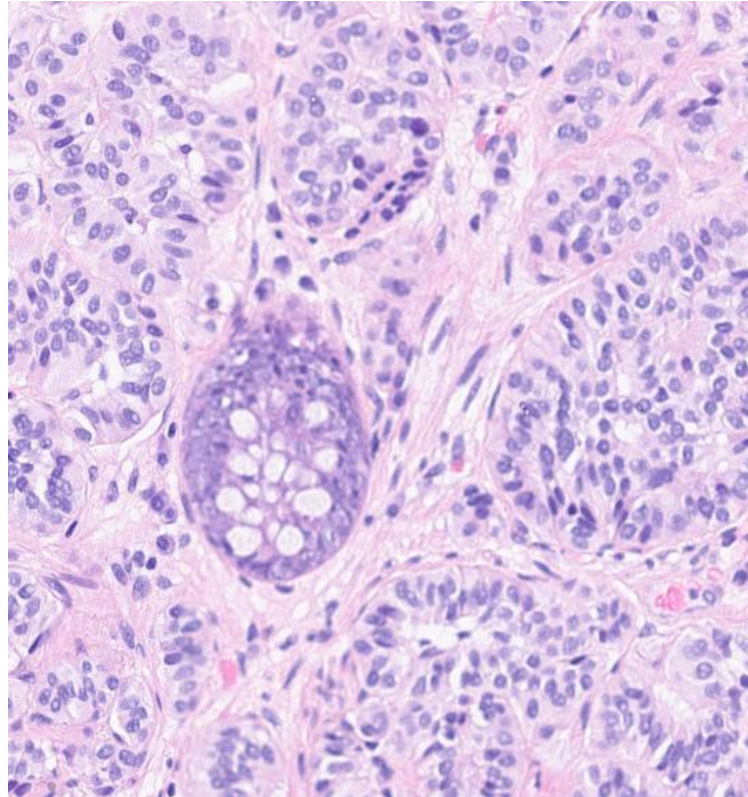
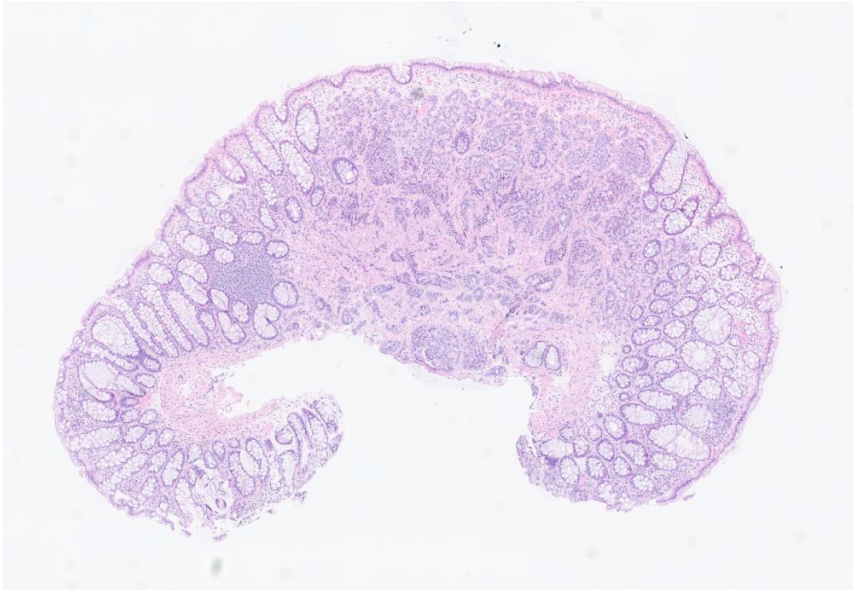
Differentiating Adenocarcinoma from NEC

Immunohistochemistry (IHC) is mandatory for the diagnosis of digestive NEC with two recommended neuroendo-crine markers, synaptophysin and CgA. NEC may lack or express low level of CgA, especially in SC-NEC. INSM1, a transcriptionfactor may help in this setting with an 85% sensitivity in NEC.

Sorbye H et al.; J Neuroendocrinol. 2023;35:e13249.

- ✓ “when morphological criteria for NENs are not fulfilled, immunoreactivity for general neuroendocrine markers alone is not enough to render a diagnosis of NEC. In such cases, one must consider the possibility of a poorly differentiated non-neuroendocrine carcinoma with neuroendocrine marker expression” .
 - ✓ G.Rindi et al; Endocrine Pathology (2022) 33:115–154

Why is this case a NET but Chromogranin negative?



- Morphology
- Other NE-markers; INSM-1
- Proliferation
- WHO classification:
 - In appendix and rectum more often L-cell NET
 - L-cell NET are Chromogranin B positive while “standard” Chromogranin stain reveals Chromogranin A

Standardised Pathology Reports



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NEUROENDOCRINE
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Standardised reports for endoscopy in neuroendocrine tumors

 [Standard Report Gastroenterology_Endoscopy of NEN_V 2.pdf](#)

Standardised reports for neuroendocrine tumor pathology

-  [Standard Report Pathology_App NEN_V4.pdf](#)
-  [Standard Report Pathology_ColoRectal NEN_V4.pdf](#)
-  [Standard Report Pathology_Duo NEN_V4.pdf](#)
-  [Standard Report Pathology_Gastric NEN_V4.pdf](#)
-  [Standard Report Pathology_NEN General_V4.pdf](#)
-  [Standard Report Pathology_Panc NEN_V4.pdf](#)
-  [Standard Report Pathology_Pulm NEN_V4.pdf](#)
-  [Standard Report Pathology_Small Intest NEN_V4.pdf](#)

- ✓ ENETS standardised (synoptic) reporting for neuroendocrine tumour pathology.
J Neuroendocrinol. 2022 Mar;34(3):e13100

Source of confusions in NEN pathology

- ✓ Evolving classification
- ✓ Differences in nomenclature in different organs
- ✓ Interpretation of immunohistochemical markers
- ✓ Lack of knowledge on differential diagnosis

Differential diagnosis of NET/NEC

- ✓ In all organs:
 - ✓ Paraganglioma: positive for NE markers but keratin negative (GATA3 positive)
 - ✓ But GATA3 is occasionally positive in NET
- ✓ Pancreas:
 - ✓ Acinicell carcinoma: varying positivity for NE markers, but relative high proliferation, SSTR2 negative (trypsin and BCL10 positive)
 - ✓ Solid pseudopapillary neoplasms: varying positivity for NE markers but keratin negative (b-catenin nuclear stain/mutation)
- ✓ Appendix
 - ✓ Goblet cell carcinoma; varying positivity for NE markers, but goblet-cells, irregular morphology, relatively high proliferation

Summary

- ✓ Organ dependent Evolution of classification and nomenclature
 - ✓ Grading with different cut-offs in different organs
 - ✓ Goblet cell carcinoma
 - ✓ NET vs Carcinoid
- ✓ Interpretation of immunohistochemical markers
 - ✓ Immunohistochemistry always in the context of morphology
 - ✓ INSM1 as new NE-marker
 - ✓ Usual chromogranin stain only reveals chromogranin A
- ✓ Differential diagnosis if NE-markers are positive
 - ✓ Paraganglioma
 - ✓ Acinic cell carcinoma
 - ✓ Solid pseudopapillary tumour
 - ✓ Goblet cell carcinoma



Most frequent confusions in NEN – PET Imaging and WHO status

Valentina Ambrosini

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IRCCS AOU di Bologna, Italy



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di Ricovero e Cura a Carattere Scientifico

POLICLINICO DI SANT'ORSOLA



DISCLOSURE INFORMATION

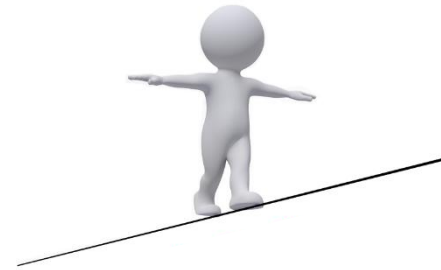
Speaker fees from industries/providers/societies: ESMIT/ESMO/EANM/AAA/Elma Academy (in the last 5years)

Member of: Oncology and theranostic EANM committee, the ESMO faculty staff for NET, ENETS theranostic task force lead

Travel grant: Thema supported an educational grant to my hospital later assigned to cover for the travel expenses of my attendance to a conference

«UNBOXING TUMOUR BIOLOGY»

TARGET SPECIFIC RADIOPHARMACEUTICAL



Guidelines

ENETS

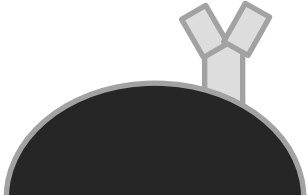
ESMO GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

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SST PET/CT

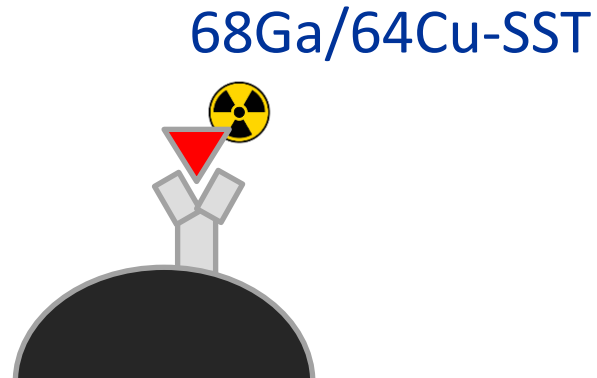
MOLECULAR **TARGET**

SOMATOSTATIN
RECEPTOR (SST)

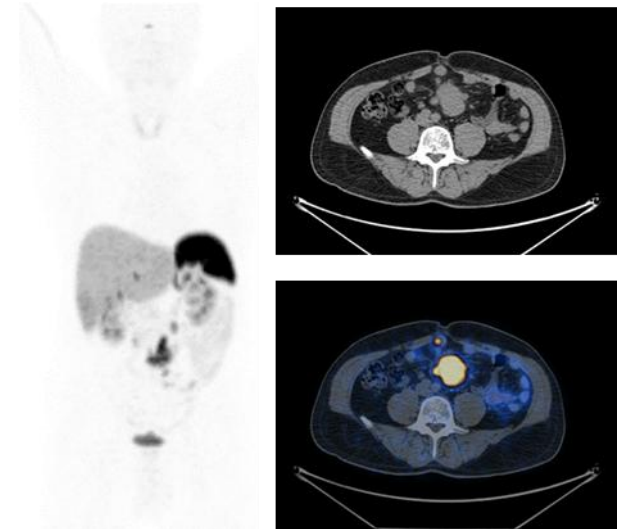


NEUROENDOCRINE TUMOURS

TARGET-SPECIFIC
DIAGNOSTIC
RADIOPHARMACEUTICAL



DIAGNOSTIC IMAGING



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SST PET/CT: Approved radiopharmaceuticals

FDA approved:

- [68Ga]Ga-DOTATATE (2016)
- [68Ga]Ga-DOTATOC (2019)
- [64Cu]Cu-DOTATATE (2020)

EMA approved:

- [68Ga]Ga-DOTATOC (2016)

European pharmacopoeia 11.3 (2024)

[68Ga]Ga-DOTANOC monography

All are clinically comparable

Geijer et al, EJNMMI 2013
Fendler et al, JNM 2017
Barrio et al, JNM 2017
Skoura et al, JNM 2016
Ambrosini et al, JNM 2010
Gabriel et al, JNM 2007
Putzer et al, JNM 2009
Ambrosini et al, EJNMMI 2009
Haug et al, EJNMMI 2009
Kayani et al, JNM 2009
Virgolini et al, EJNMMI 2010
Bokurtz, EJNMMI 2017
Bonazzi N, Cancers 2023

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SST PET/CT: When?

SNMMI Procedure Standard/EANM Practice Guideline for SSTR PET: Imaging Neuroendocrine Tumors

- initial staging at diagnosis,
- localisation of primary tumour,
- staging before surgery,
- selection of patients for PRRT,
- a post-PRRT study was included to serve as a new baseline 9–12 mo after the completion of treatment for future comparisons

Hope Ta, J Nucl Med. 2023

Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

- staging,
 - preoperative imaging and
 - restaging
- [IV, A]

Pavel et al, Ann Oncol. 2020

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AUC

Scenario no.	Description	Appropriateness	Score
1	Initial staging after histologic diagnosis of NETs	Appropriate	9
2	Localization of primary tumor in patients with known metastatic disease but unknown primary	Appropriate	9
3	Selection of patients for SSTR-targeted PRRT	Appropriate	9
4	Staging NETs before planned surgery	Appropriate	8
5	Evaluation of mass suggestive of NET not amenable to endoscopic or percutaneous biopsy (e.g., ileal lesion, hypervascular pancreatic mass, mesenteric mass)	Appropriate	8
6	Monitoring of NETs seen predominantly on SSTR PET	Appropriate	8
7	Evaluation of patients with biochemical evidence and symptoms of NET without evidence on CI and without prior histologic diagnosis of NET	Appropriate	7
8	Restaging at time of clinical or laboratory progression without progression on CI	Appropriate	7
9	New indeterminate lesion on CI, with unclear progression	Appropriate	7
10	Restaging of patients with NETs at initial follow-up after resection with curative intent	May be appropriate	6
11	Selection of patients with nonfunctional NETs for SSA treatment	May be appropriate	6
12	Monitoring in patients with NETs seen on both CI and SSTR PET with active disease and no clinical evidence of progression	May be appropriate	5

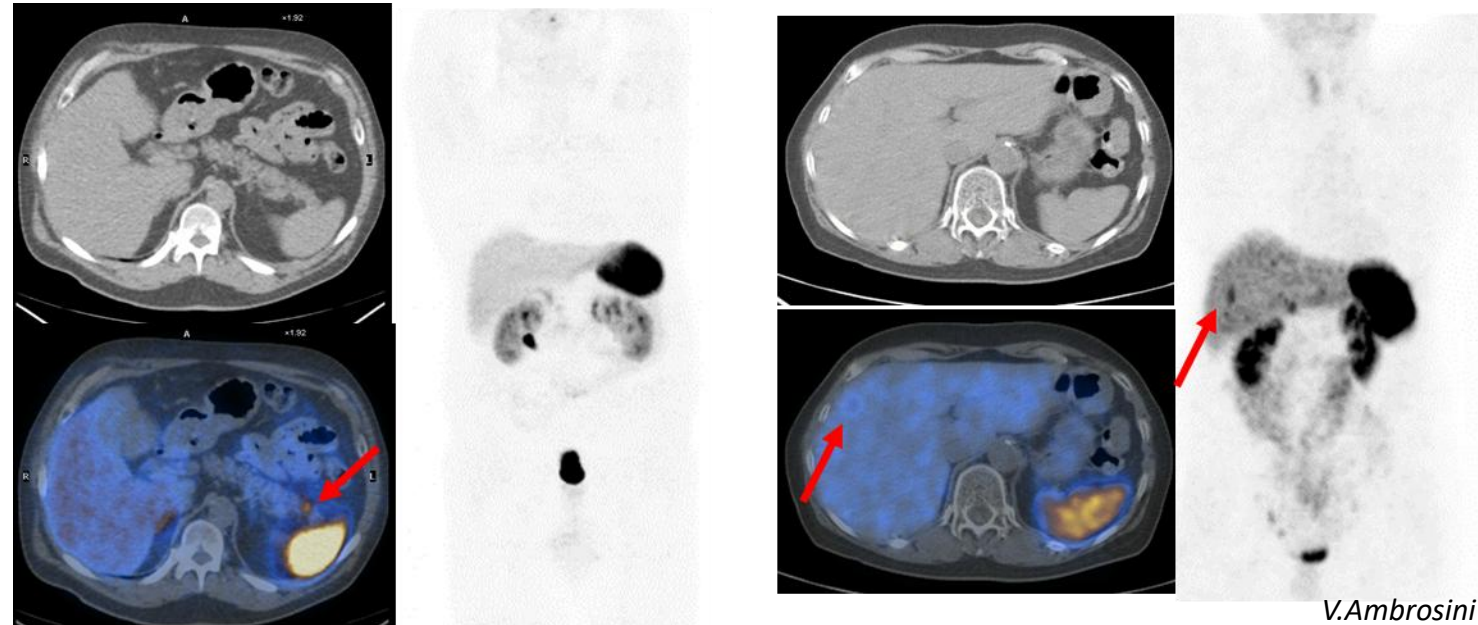
Hope Ta, J Nucl Med. 2018

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SST PET/CT: Advantages

- High accuracy (even for small lesions!)
 - High inter-observer agreement
 - Impact on clinical management
 - Uptake correlates with SST-expression (PRRT selection)
- ✓ **Impacts subsequent treatment decisions**

Geijer et al, EJNMMI 2013
Fendler et al, JNM 2017
Barrio et al, JNM 2017
Skoura et al, JNM 2016
Ambrosini et al, JNM 2010
Gabriel et al, JNM 2007
Putzer et al, JNM 2009
Ambrosini et al, EJNMMI 2009
Haug et al, EJNMMI 2009
Kayani et al, JNM 2009
Virgolini et al, EJNMMI 2010
Bokurtz, EJNMMI 2017
Bonazzi N, Cancers 2023



SST PET/CT: Pitfalls

1

Infection/inflammation

2

Non-NE SST-expressing tumours

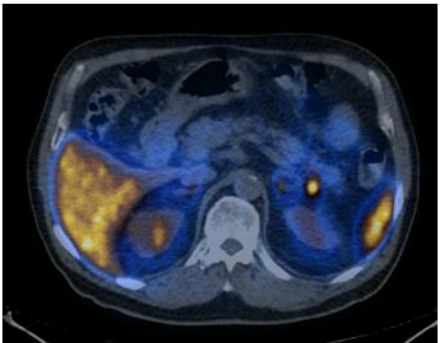
3

FN:

- dedifferentiation
- small size

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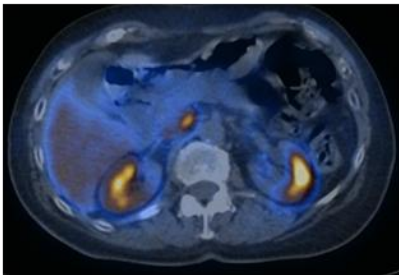
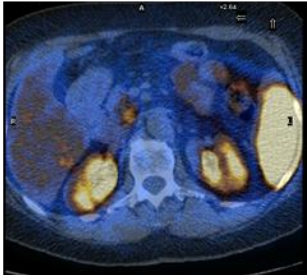
- ACCESSORY SPLEEN



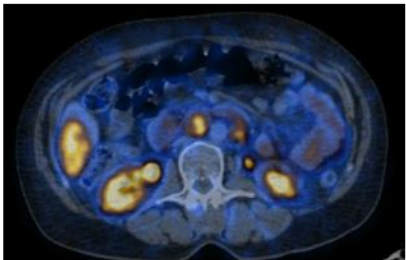
UP/PANCREAS HEAD

Diffuse

Focal



nonNEN tumours expressing SR
LYMPHOMA



Haemangioma

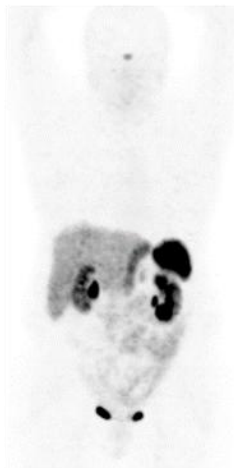


Skoura et al, Clin Nucl Med. 2015

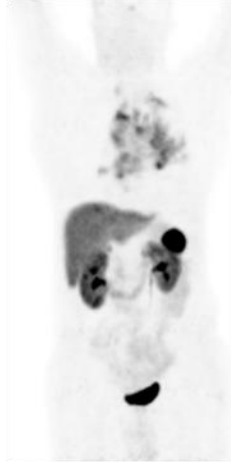
PANCREATITIS



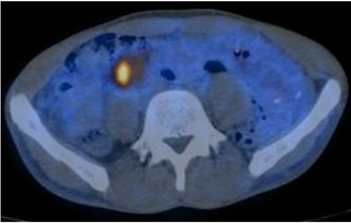
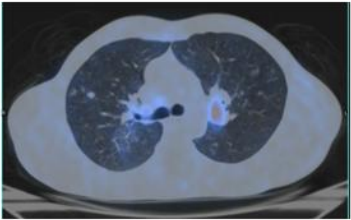
GASTRITIS



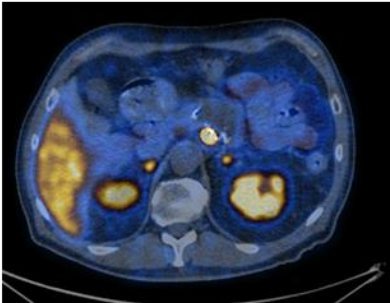
SARCOIDOSIS



TUBERCULOSIS

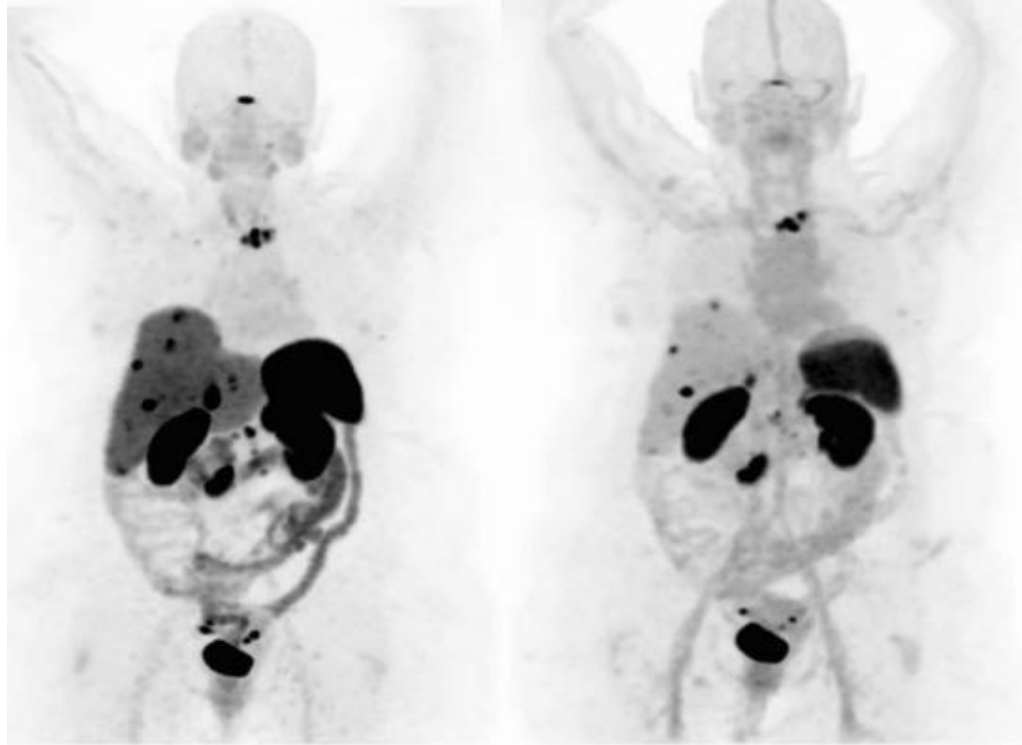


positive surgical margins (ABSCCESS)



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SST PET/CT: SSA on-going treatment



Scan 1

21 days after
lanreotide injection

Scan 2

after 3 days
lanreotide injection

	Scan 1	Scan 2
<i>Scan parameters</i>		
Injected dose	205.2 MBq	205.9 MBq
Injection interval	61 minutes	47 minutes
Days after Lanreotide injection	21 days	3 days
<i>Measurements</i>		
Bloodpool (SUVmax)	2.1	3.6
Liver (SUVmax)	6.2	3.2
Spleen (SUVmax)	24.9	9.6
Liver metastasis (SUVmax)	48.2	27.7
TBR Metastasis - liver	7.8	8.7
TBR Metastasis -Bloodpool	23.0	7.7
Mesenterial Lymfnode metastasis (SUVmax)	26.3	15.7
TBR Metastasis - liver	4.2	4.9
TBR Metastasis -Bloodpool	12.5	4.4

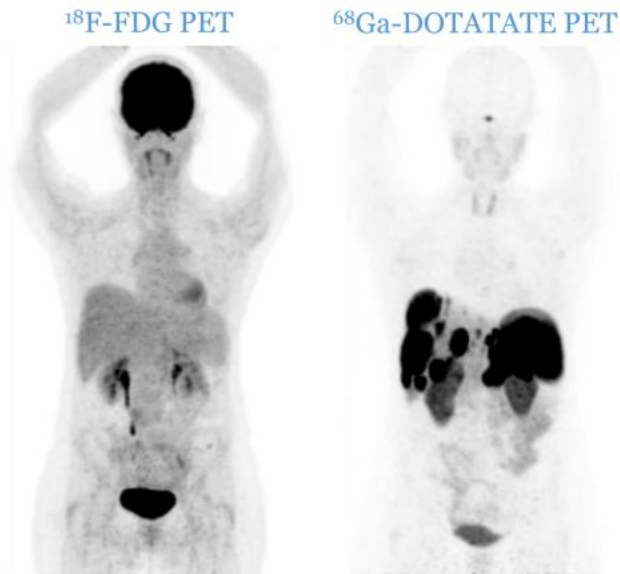
van de Weijer, EJNMMI 2024

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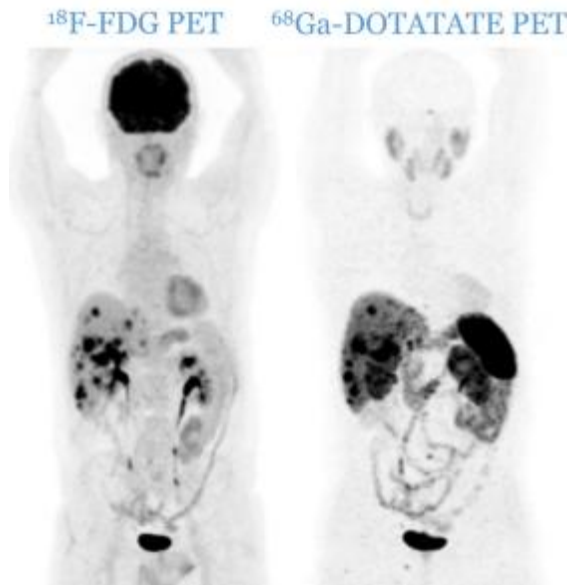
Beyond SST PET...

How to detect heterogeneity/dedifferentiation?

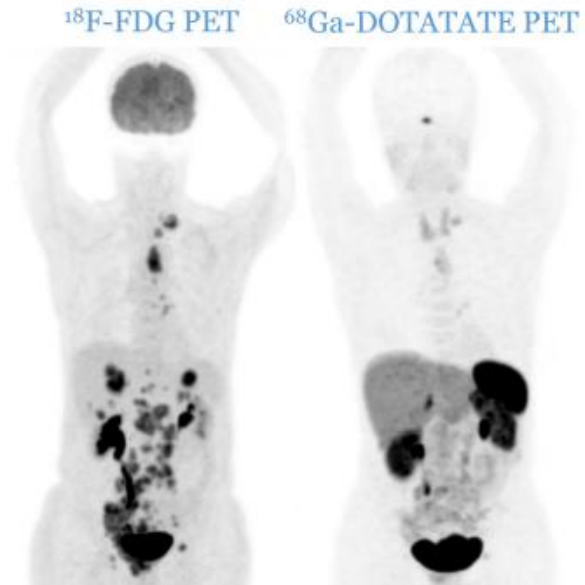
C1: FDG-neg; SA-pos



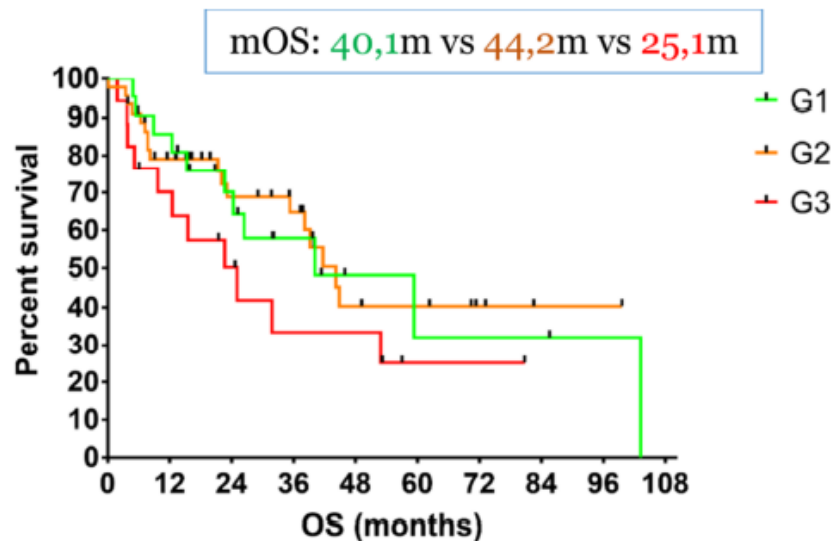
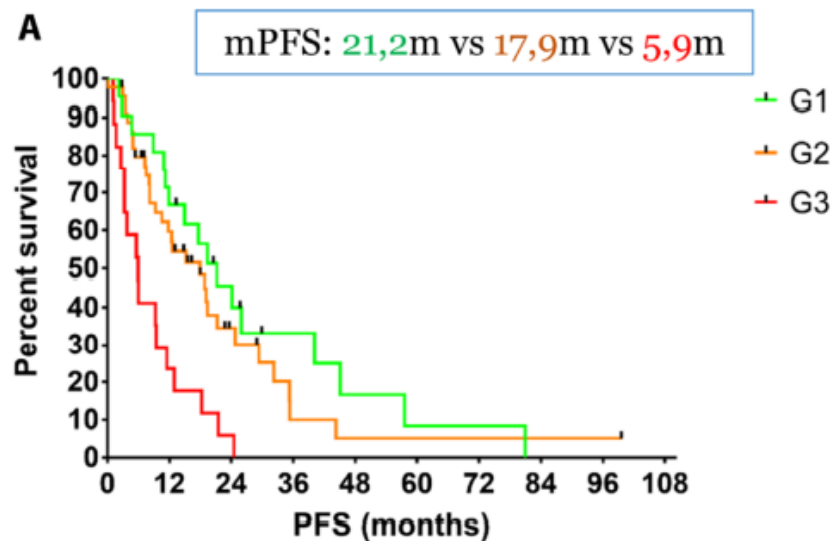
C2: >1 FDG-pos, all of them
SR-pos (**match**)



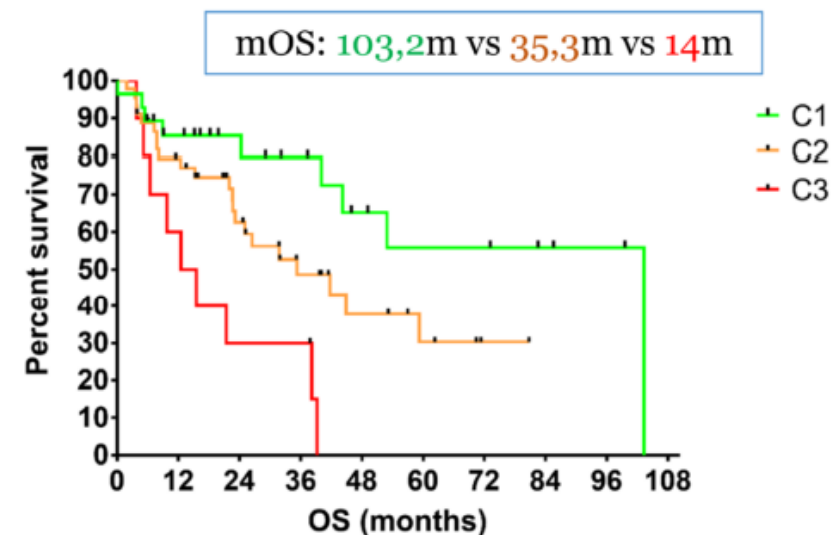
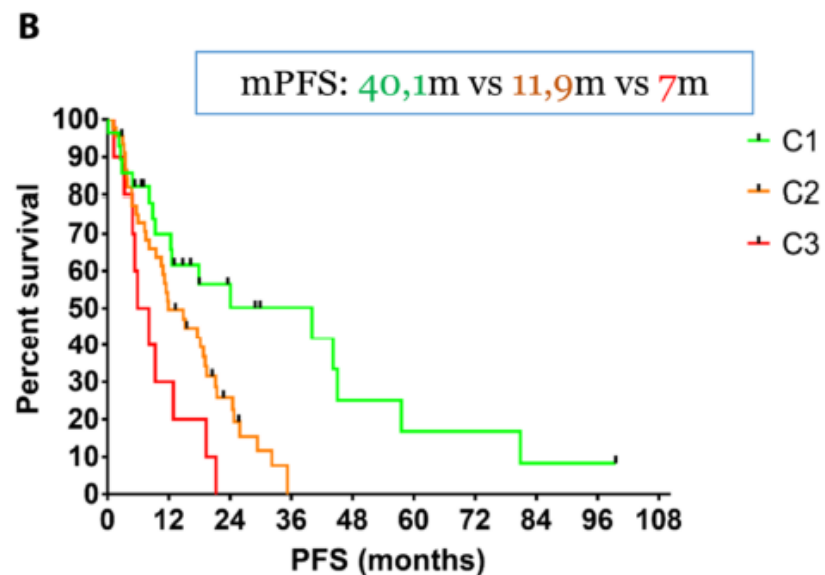
C3: >1 FDG-pos, at least 1 of them
SR-neg (**mis-match**)



WHO
GRADE

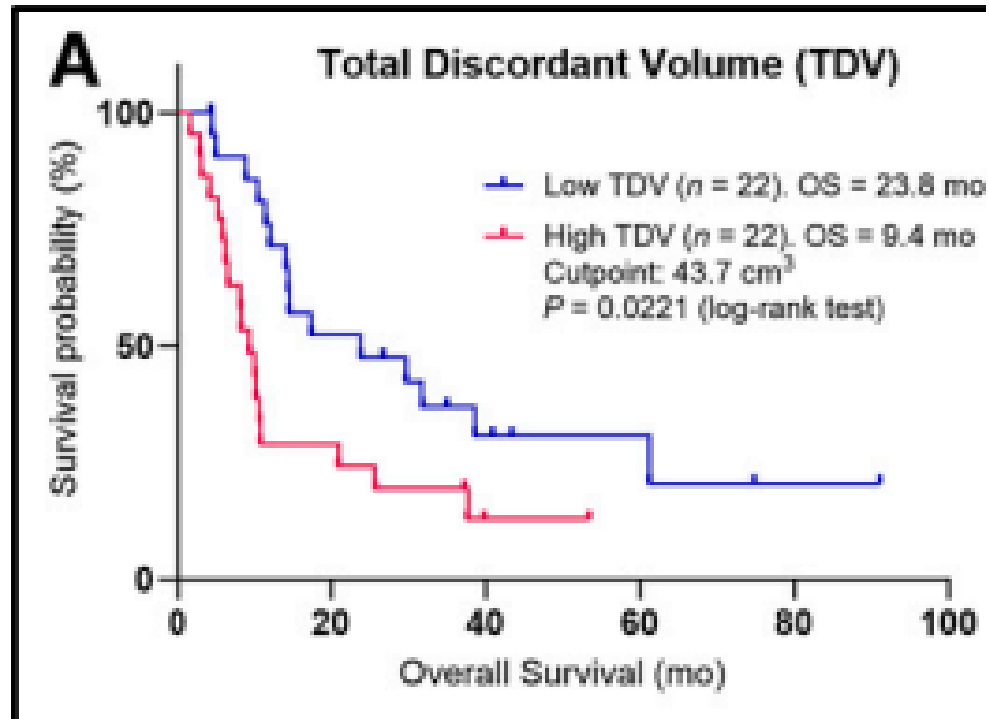


C1,2,3

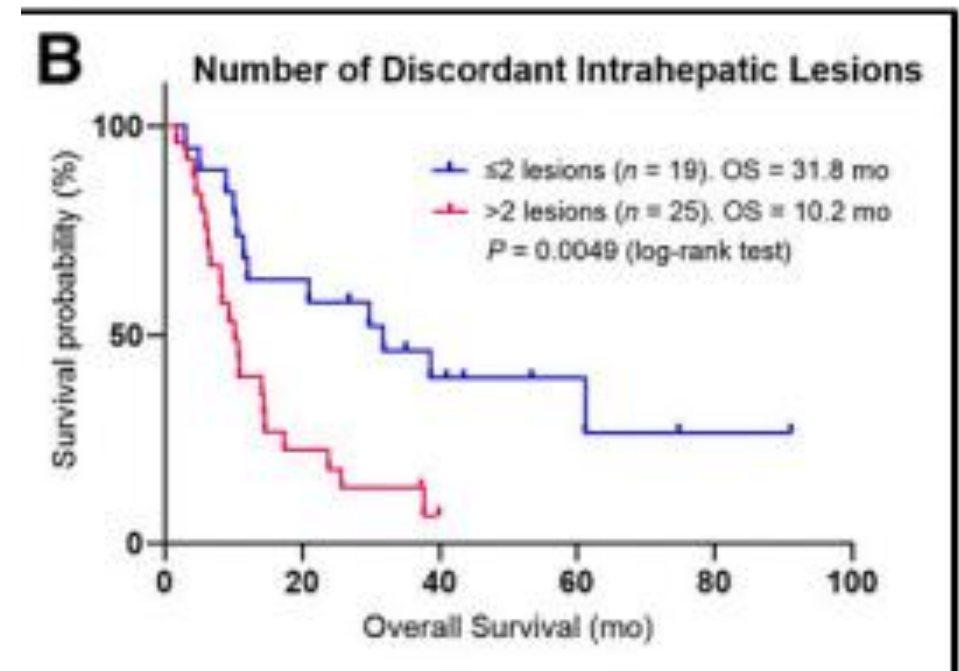


Functional
stratification
better
discriminates
pts with
different
outcomes

DISCORDANT TUMOUR VOLUME



Longer OS (mOS=23.6mo) in the low-discordant tumour volume subgroup (vs 9.4mo)



Longer OS (mOS=31.8mo) if $\leq$ or equal to 2 discordant intra-hepatic lesions (vs 10.2mo)

SST/FDG and tumour grade

Multicenter validation of the NETPETscore: 319 metastatic/unresectable GEP NEN pts

NETPET Grade	SSTRI scan status	FDG scan status
P0	-	-
P1	+	-
P2a	+	+
P2b	+	+
P3a	+	+
P3b	+	+
P4a	+	+
P4b	+	+
P4b	+	+
P5	+	+
P5	+	+
P5	-	+

Table 4. Distribution of NETPET score by histological grade.

NETPET score	Grade 1	Grade 2	Grade 3	Grade 3 Differentiation	Total
P1	37 (41%)	43 (26%)	1 (2%)	1 WD (100%)	81 (27%)
P2–4	54 (59%)	103 (63%)	28 (57%)	20 WD (71%) 6 PD (21%) 2 unk (7%)	185 (61%)
P5	0 (0%)	17 (10%)	20 (41%)	4 WD (20%) 14 PD (70%) 2 unk (10%)	37 (12%)
Total	91	163	49		303 ^a

^aTotal excluding those with unknown grade (n = 16). WD well-differentiated, PD poorly differentiated, unk unknown.

○ FDG positivity was detected in 73% overall

FDG: When?

Use and perceived utility of [¹⁸F]FDG PET/CT in neuroendocrine neoplasms: A consensus report from the European Neuroendocrine Tumor Society (ENETS) Advisory Board Meeting 2022

Full agreement (>75%) was reached for 3 statements (3/15, 20%; # 1,5,7)

1 (80%) 18F-FDG PET/CT should be performed **in NET irrespective of grade when mis-matched lesions** (dCT-visible and SST PET-negative or faintly positive) are present, **especially if PRRT is contemplated**

#5 (82%) 18F-FDG PET/CT should be done in **NET G3 if** curative surgery is considered

#7 (98%) 18F-FDG PET/CT should be performed in **NEC before** curative intended surgery

4 (74%) 18F-FDG PET/CT should be performed in all NET G3 (even in presence of matched lesions on dCT and SR PET/CT) as a baseline for response assessment (74%)

FDG: When?

although not reaching agreement, **>60% of the respondents supported**

- ☐ FDG PET/CT in NET G3 if loco-regional therapy is considered (#6; 65%)
- ☐ in NEC before initiating active therapy as a baseline for response assessment (#8; 61%).
- ☐ In the case of new FDG PET/CT-positive lesions on the background of a prior G1-2 NET, most attendees indicated that they would perform a biopsy to re-assess tumour grade prior to a change in therapeutic management (#14; 68%).
- ☐ Finally, 67% of the respondents were in favour of reconsidering PRRT in patients showing any residual SST-positive disease sites after achieving complete remission on FDG (“metabolic response”) of the SST-negative disease component (#15)

OTHER RADIOPHARMACEUTICALS?

CLINICALLY AVAILABLE: 18F-DOPA

EMERGING RADIOPHARMACEUTICALS

- Target SST: Different labelling (18F, 64Cu)
- Target SST: Antagonists
- New targets/labelling?

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• MEDULLARY THYROID CARCINOMA

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:2159–2169
<https://doi.org/10.1007/s00259-018-4045-9>

ORIGINAL ARTICLE



[¹⁸F]DOPA PET/ceCT in diagnosis and staging of primary medullary thyroid carcinoma prior to surgery

Conclusion This study revealed that DOPA PET/ceCT has high sensitivity in the detection of primary MTC and superior sensitivity in the detection of LN metastases compared to ultrasonography. DOPA PET/ceCT identification of N1b status predicts postoperative tumour persistence. Thus, implementation of a DOPA-guided LN dissection might improve surgical success.

Eur J Nucl Med Mol Imaging (2017) 44:2004–2013
[DOI 10.1007/s00259-017-3759-4](https://doi.org/10.1007/s00259-017-3759-4)



ORIGINAL ARTICLE

Diagnostic utility of PET/CT with ¹⁸F-DOPA and ¹⁸F-FDG in persistent or recurrent medullary thyroid carcinoma: the importance of calcitonin and carcinoembryonic antigen cutoff

Conclusions ¹⁸F-DOPA PET/CT appears to be superior to ¹⁸F-FDG PET/CT in detecting and locating lesions in patients with recurrent MTC. This technique tends to be especially useful in patients with negative results in other imaging modalities and Ct ≥ 150 pg/mL or CEA ≥ 5 ng/mL.

• NEUROBLASTOMA

dependent on vesicular storage. ¹⁸F-DOPA may currently be the best PET alternative to ¹²³I-mIBG for the evaluation of neural crest tumours, including neuroblastoma, due to its ability to track the metabolism of catecholamines [20, 109–112].

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:2009–2024
<https://doi.org/10.1007/s00259-018-4070-8>

GUIDELINES

Guidelines on nuclear medicine imaging in neuroblastoma

• PPLG... Single adrenal mass pheochromocytoma

...metastatic pheo/paraganglioma?

...midgut NEN

European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:2112–2137
<https://doi.org/10.1007/s00259-019-04398-1>

European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of pheochromocytoma and paraganglioma

updates

David Taïeb¹ · Rodney J. Hicks² · Elif Hindî³ · Benjamin A. Guillet⁴ · Anca Avram⁵ · Pietro Ghedini⁶ · Henri J. Timmers⁷ · Aaron T. Scott⁸ · Saeed Elojeimy⁹ · Domenico Rubello¹⁰ · Irène J. Virgolini¹¹ · Stefano Fanti⁶ · Sona Balogova^{12,13} · Neeta Pandit-Taskar¹⁴ · Karel Pacak¹⁵

V.Ambrosini

18F-SST

18F-AIF-NOTA-OC

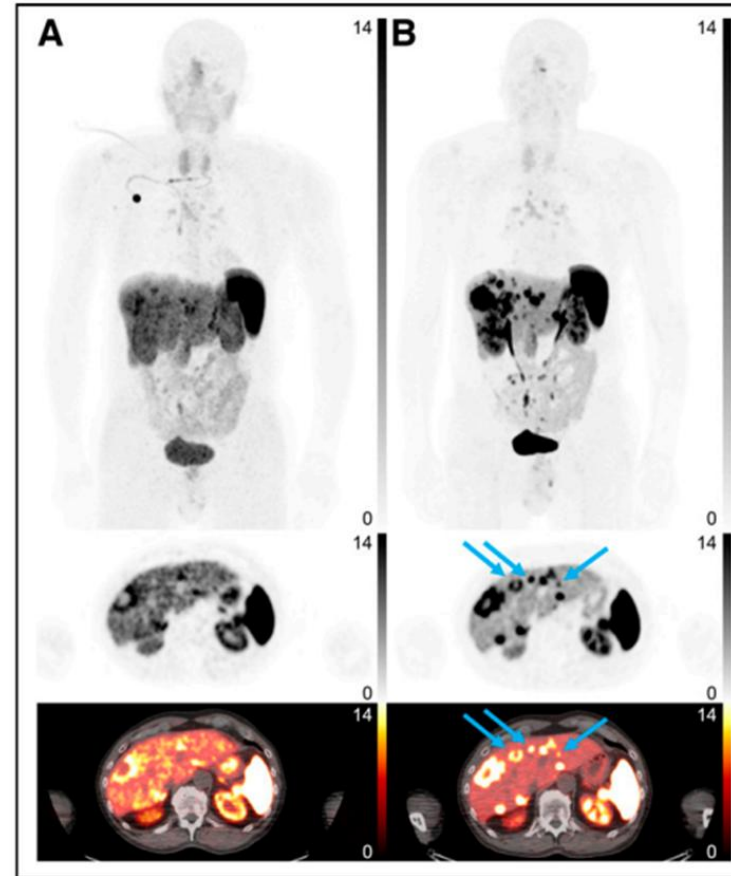


FIGURE 2. ^{68}Ga -DOTATATE (A) and ^{18}F -AIF-OC (B) images (from top to bottom: maximum-intensity projection PET, transversal PET, and fused PET/CT images) of 64-y-old male patient with pancreatic NET and liver, lymph node, and peritoneal metastases. Multiple lesions in all 3 sites were missed by ^{68}Ga -DOTATATE. Arrows indicate missed liver lesions. Lookup tables apply to PET images (SUV). Intensity scale bars indicate SUVs.

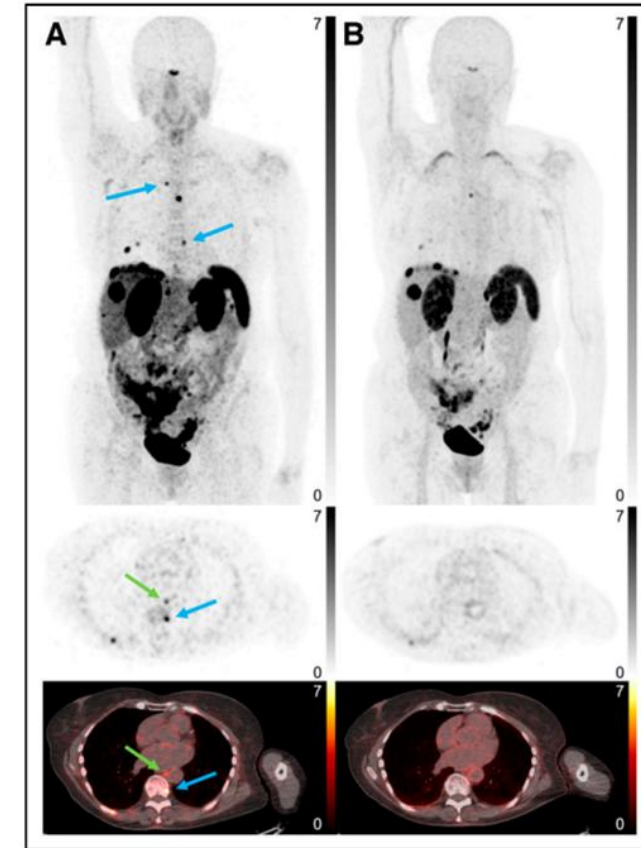


FIGURE 3. ^{68}Ga -DOTATATE (A) and ^{18}F -AIF-OC (B) images (from top to bottom: maximum-intensity projection PET, transversal PET, and fused PET/CT images) of 74-y-old female patient with intestinal NET and bone, liver, lymph node, and peritoneal metastases. Multiple lesions in all 3 sites were missed by ^{18}F -AIF-OC. Blue and green arrows indicate missed bone and lymph node lesions, respectively. Lookup tables apply to PET images (SUV). Intensity scale bars indicate SUVs.

Pawles, JNM 2023

V.Ambrosini

Pawels, EJNMMI 2020
Hou, EJNMMI research 2021
Hou, Mol Imaging biol 2021
Hou, Mol imaging 2022
Pawles, JNM 2023
Chen, EJNMMI 2023
Boeckxstaens, EJNMMI research 2023

ORIGINAL RESEARCH

Open Access

Low-activity [^{18}F]-somatostatin receptor (SSTR) imaging using [^{18}F]SiTATE on a long axial field-of-view PET/CT scanner

Dose of 1MBq/Kg $\rightarrow$ still offers good image quality and no significant variations in PET uptake parameters or MTV

Annals of Nuclear Medicine (2024) 38:483–492
<https://doi.org/10.1007/s12149-024-01922-8>

ORIGINAL ARTICLE

Parametric net influx rate imaging of ^{68}Ga -DOTATATE in patients with neuroendocrine tumors: assessment of lesion detectability

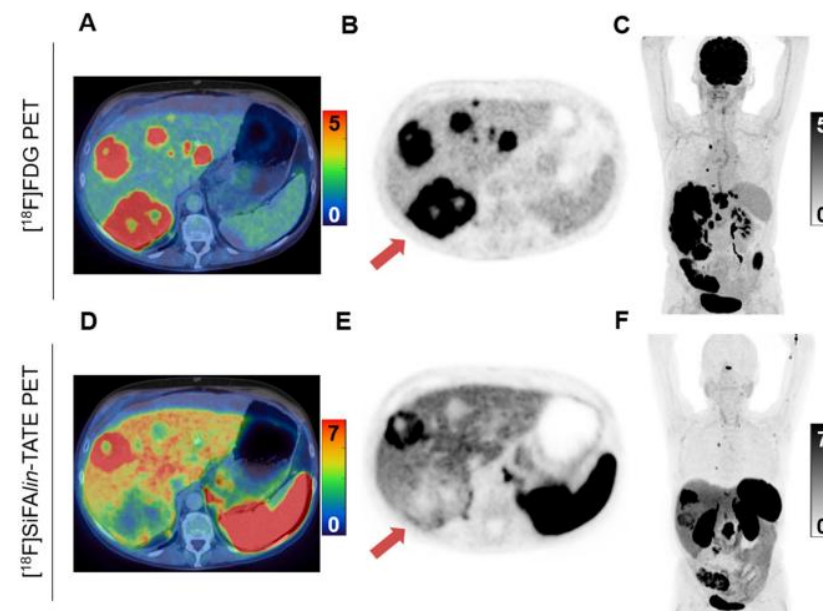
Approx dose of 1MBq/Kg

ORIGINAL ARTICLE



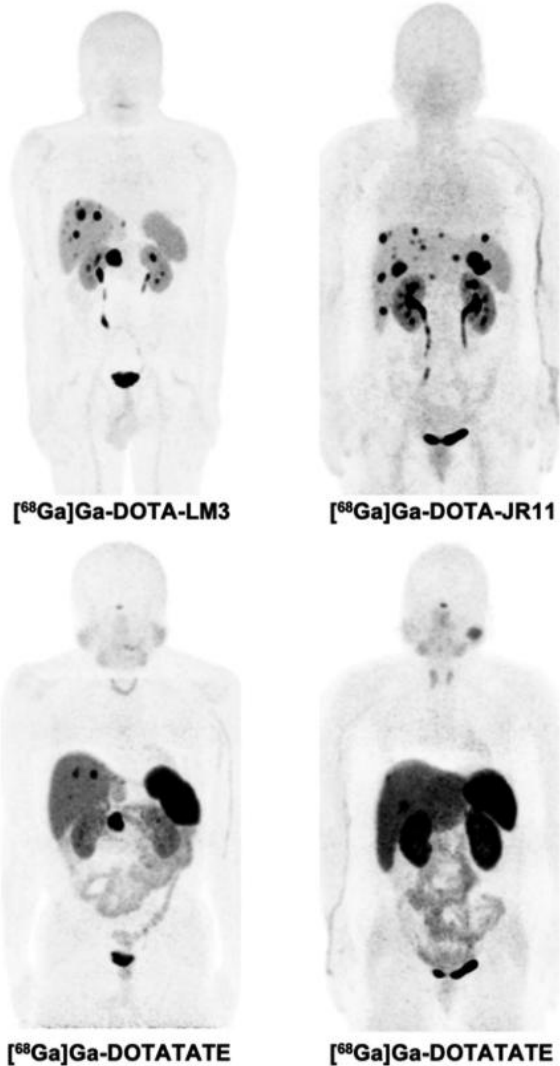
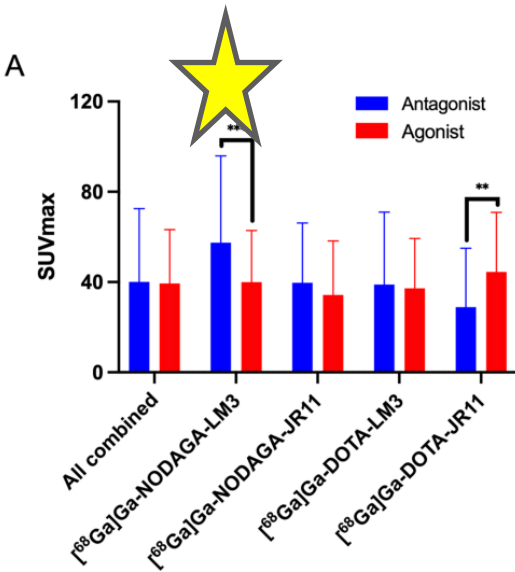
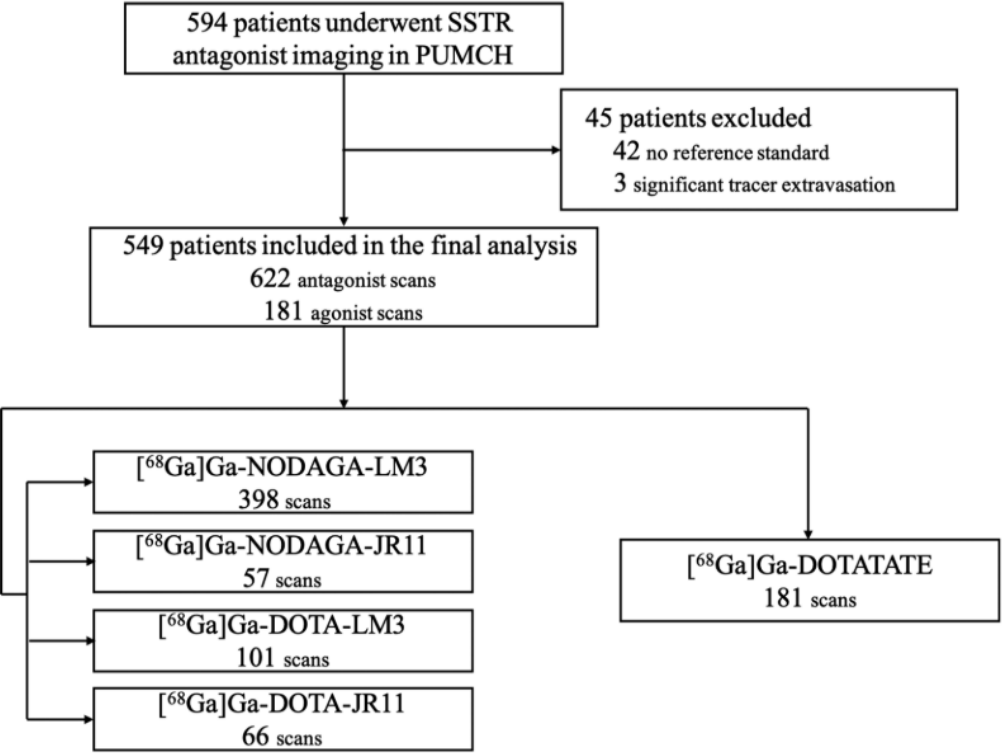
One-day dual-tracer examination in neuroendocrine neoplasms: a real advantage of low activity LAFOV PET imaging

- ☐ Low FDG activity (0.5 ± 0.01 MBq/kg; PET scan 60 min p.i.)
- ☐ After 4.2 ± 0.09 h
- ☐ Standard 18F-SifanlinTATE activity (3.0 MBq/kg; PET scan 90 min p.i.)



V.Ambrosini

SST-antagonists



SST-antagonists

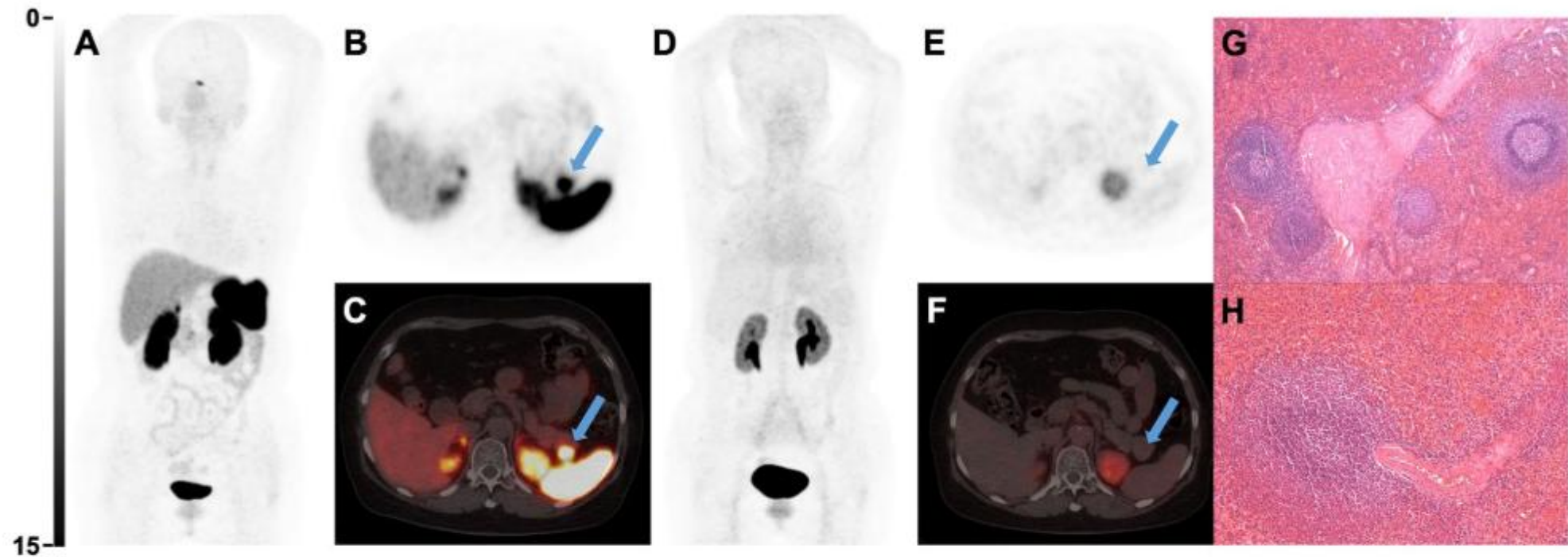
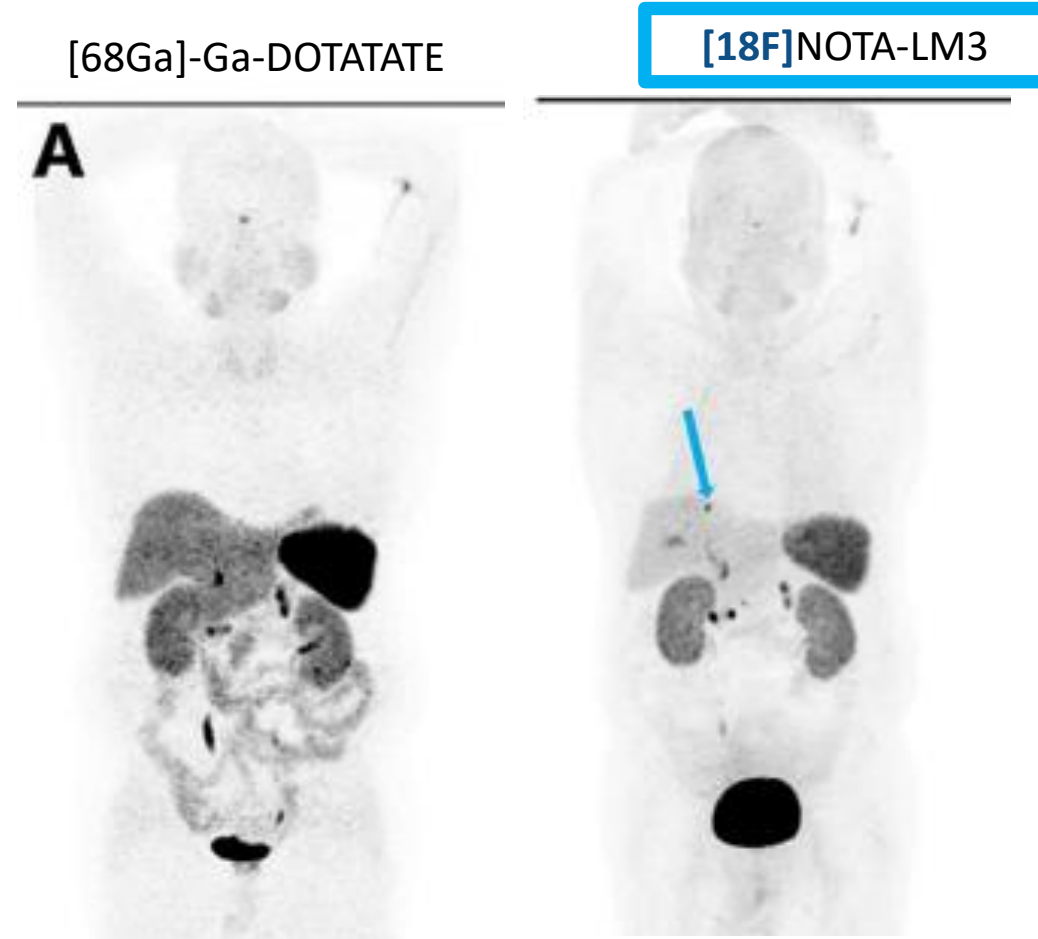
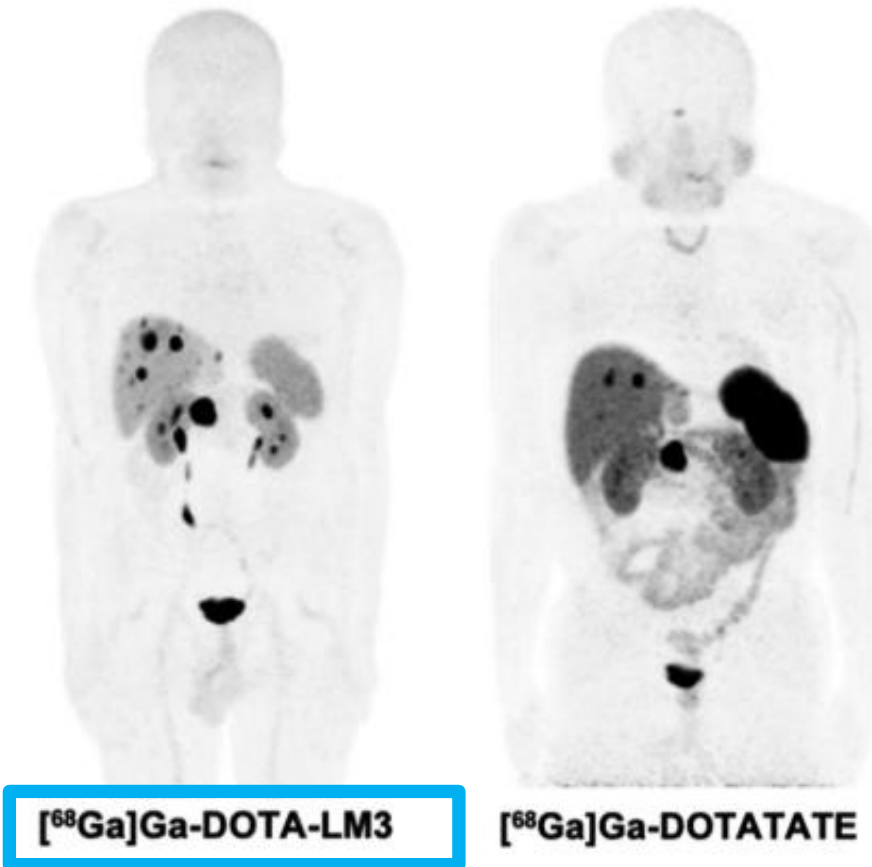


Fig. 4 Representative images of $[^{68}\text{Ga}]\text{Ga-DOTATATE}$ and $[^{68}\text{Ga}]\text{Ga-DOTA-JR11}$ in a patient with intrapancreatic accessory spleen. On $[^{68}\text{Ga}]\text{Ga-DOTATATE}$ (A-C), the spleen and accessory spleen located at the tail of pancreas (blue arrows) exhibited high uptake. On $[^{68}\text{Ga}]\text{Ga-DOTA-JR11}$ (D-F), both the spleen and intra-

pancreatic accessory spleen showed no uptake. The patient underwent surgery and histopathology (G. hematoxylin-eosin, original magnification x40; H. original magnification x100) confirmed intrapancreatic accessory spleen

SST-antagonists



Liu, EJNMMI 2024

Liu et al, EJNMMI 2024

V.Ambrosini

CONCLUSIONS

- PET/CT is the gold standard
- **SST** are the used on most SST-expressing NET for staging/restaging, PRRT eligibility; emerging role in combination with dCT for response assessment (but still lack of criteria..)
- **FDG**: Detects heterogeneity and is prognostic
- Emerging radiopharmaceuticals

V.Ambrosini



*Thank you
for your attention*



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ALMA MATER STUDIORUM
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Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di Ricovero e Cura a Carattere Scientifico

POLICLINICO DI **SANT'ORSOLA**

CONVENTIONAL IMAGING

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damiano.caruso@uniroma1.it



DISCLOSURE INFORMATION

- Nothing to disclose

GUIDELINES

ENETS[®] GUIDANCE & GUIDELINES PAPERS

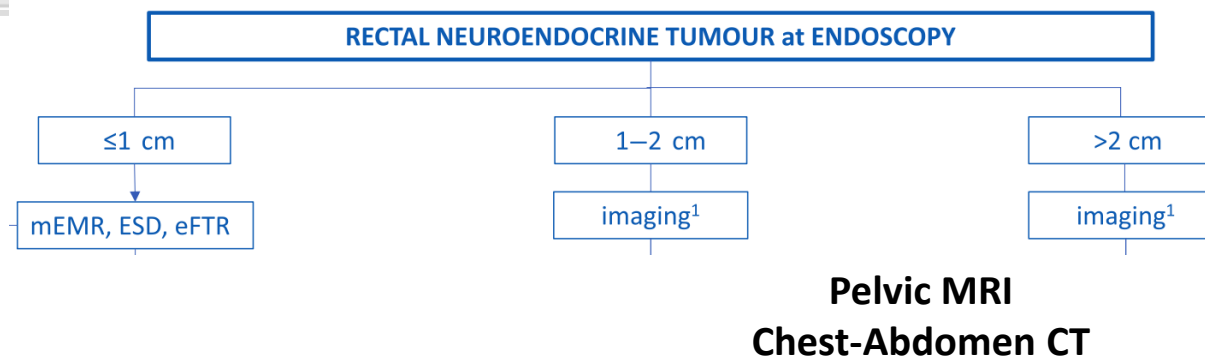
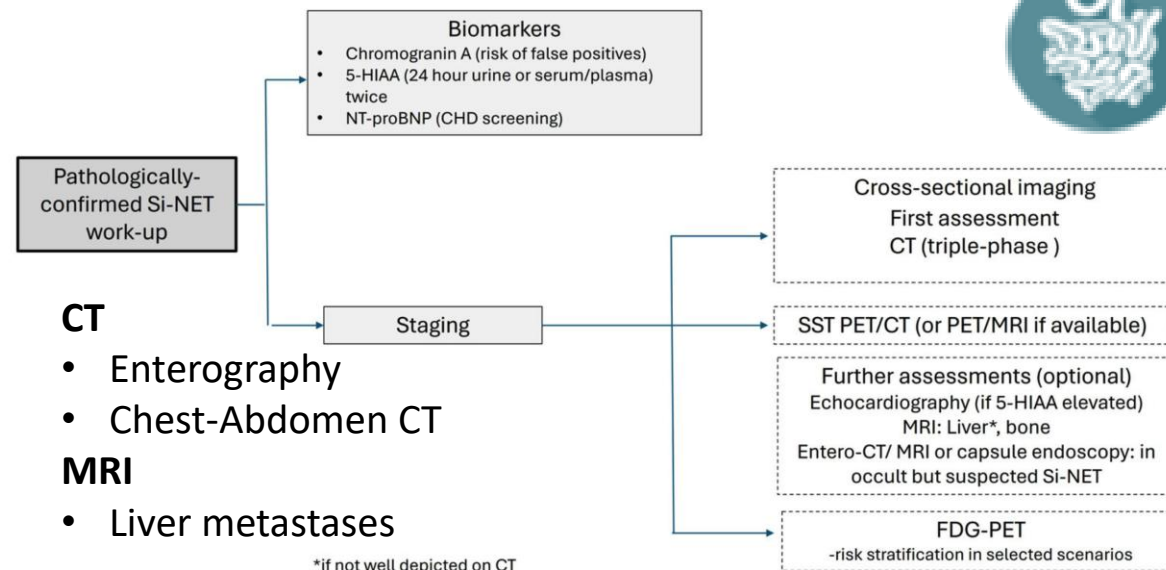


	Aim	Preferred modality
1	Determine total tumour burden in whole body as well as in the liver	SSTR PET/CT
		CT/MRI
2	Assess somatostatin receptor (SSTR) status	SSTR PET/CT
3	Evaluate cardiac function including valvular apparatus	Echocardiography
	CCT, CMRI	As required
4	Evaluate tumour growth rate	CT/MRI
5	Evaluate the possibility of locoregional therapy (TAE/TACE/SIRT as well as RFA, MWA, afterloading)	CECT/MRI
6	Determine the feasibility of liver directed surgeries	CECT/MRI



Colon NET:

- Staging – Contrast enhanced CT
- MRI (Liver)



Rinke A. et al., J of Neuroendocrinology 2023; Lamarca A. et al., J. of Neuroendocrinology 2024; Grozinsky-Glasberg S. et al., J. of Neuroendocrinology 2022

GUIDELINES

ENETS[®] GUIDANCE & GUIDELINES PAPERS

Identification of Pan-NET

- Contrast-enhanced CT
- Dynamic contrast-enhanced MRI (DWI) & MRCP



Follow-up

- MRI (DWI) for liver mts
- Chest-Abdomen CT for extra-hepatic mts

G-NET:

- Staging – CT Always: Type III
- Restaging - CT & MRI (Liver)



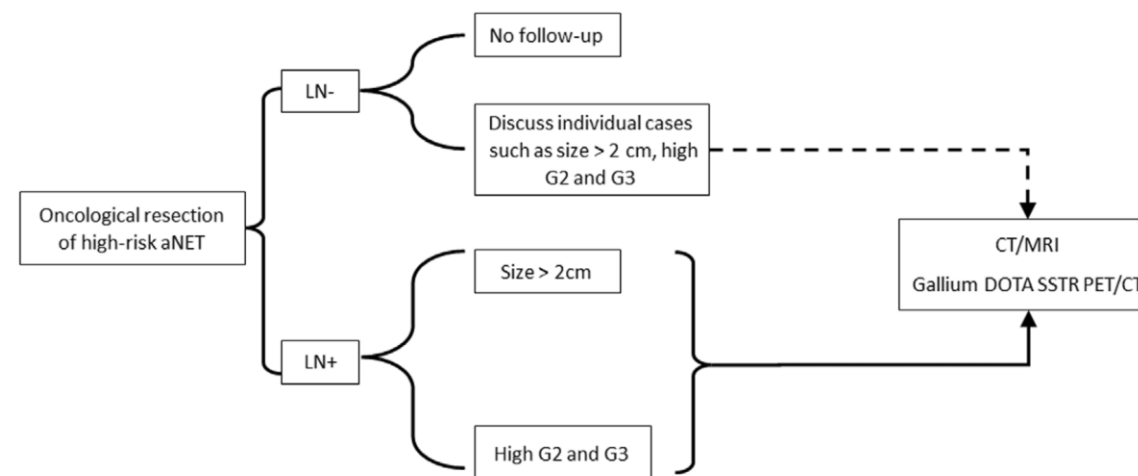
Duodenal NET:

- Staging – CT Enterography & MRI (Liver)
- Restaging - CT & MRI (Liver)

Staging



Restaging



Kos-Kudla B et al., J. of Neuroendocrinology 2023; Kaltas G. et al., J. of Neuroendocrinology 2023; Panzuto F. et al., J. of Neuroendocrinology 2023;

BACKGROUND

Imaging Features

Qualitative Evaluation

- Shape
- Location
- Adjacent structure behaviour
- L & M metastasis presence
- Enhancement behaviour
- DWI/ADC qualitative restriction

Quantitative Evaluation

- Dimensions
- HU values
- ADC (IVIM) values
- Perfusion maps
- Iodine maps
- Radiomics

COMPUTED TOMOGRAPHY – CT

- CT is the first-line imaging modalities of choice in the evaluation of patients with suspected PNETs allowing the investigation of the pancreas.
- The late arterial (30 s) or pancreatic phase (40 s) is mandatory allowing an increased detection of small functioning PNET in particular insulinoma
- CT is preferred over MRI for assessment of vascular invasion and resectability

Smaller tumours:

- Hypervascular
- Tend to be homogenous and well-circumscribed

Larger tumours:

- May appear heterogeneous and contain areas of cystic or necrotic change

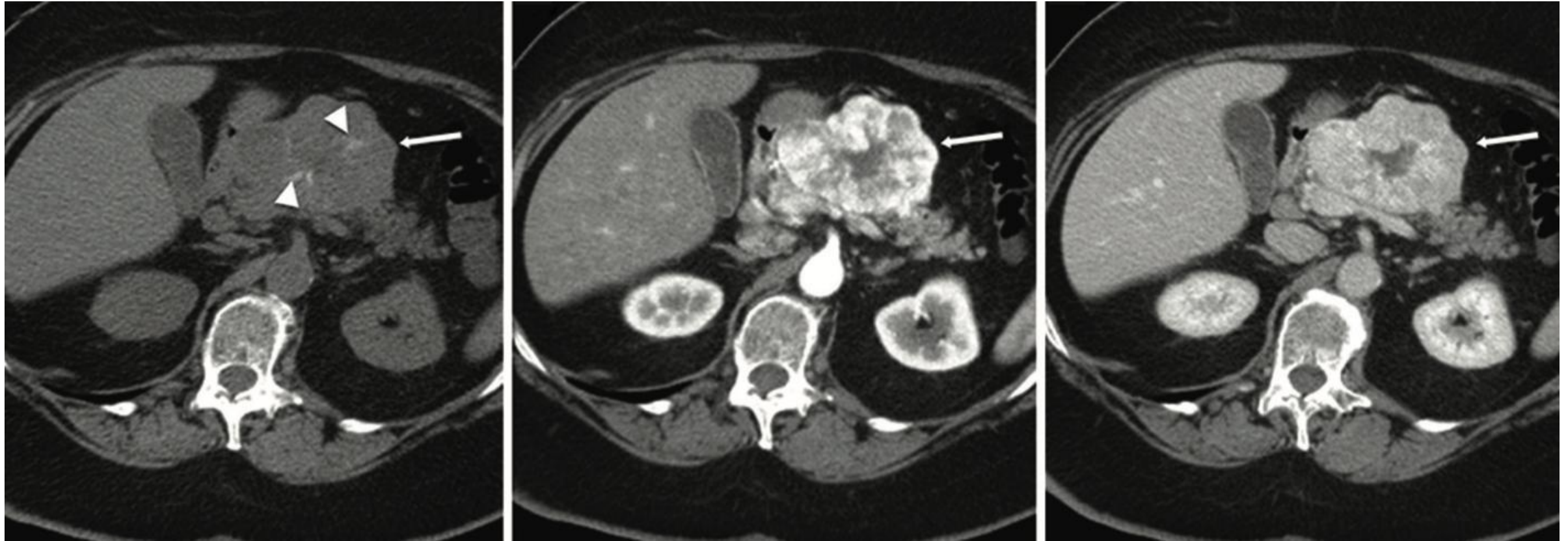
COMPUTED TOMOGRAPHY – CT



Hypervascular pNET with hypovascular metastases

Bicci E. Gland Surg 2020

COMPUTED TOMOGRAPHY – CT



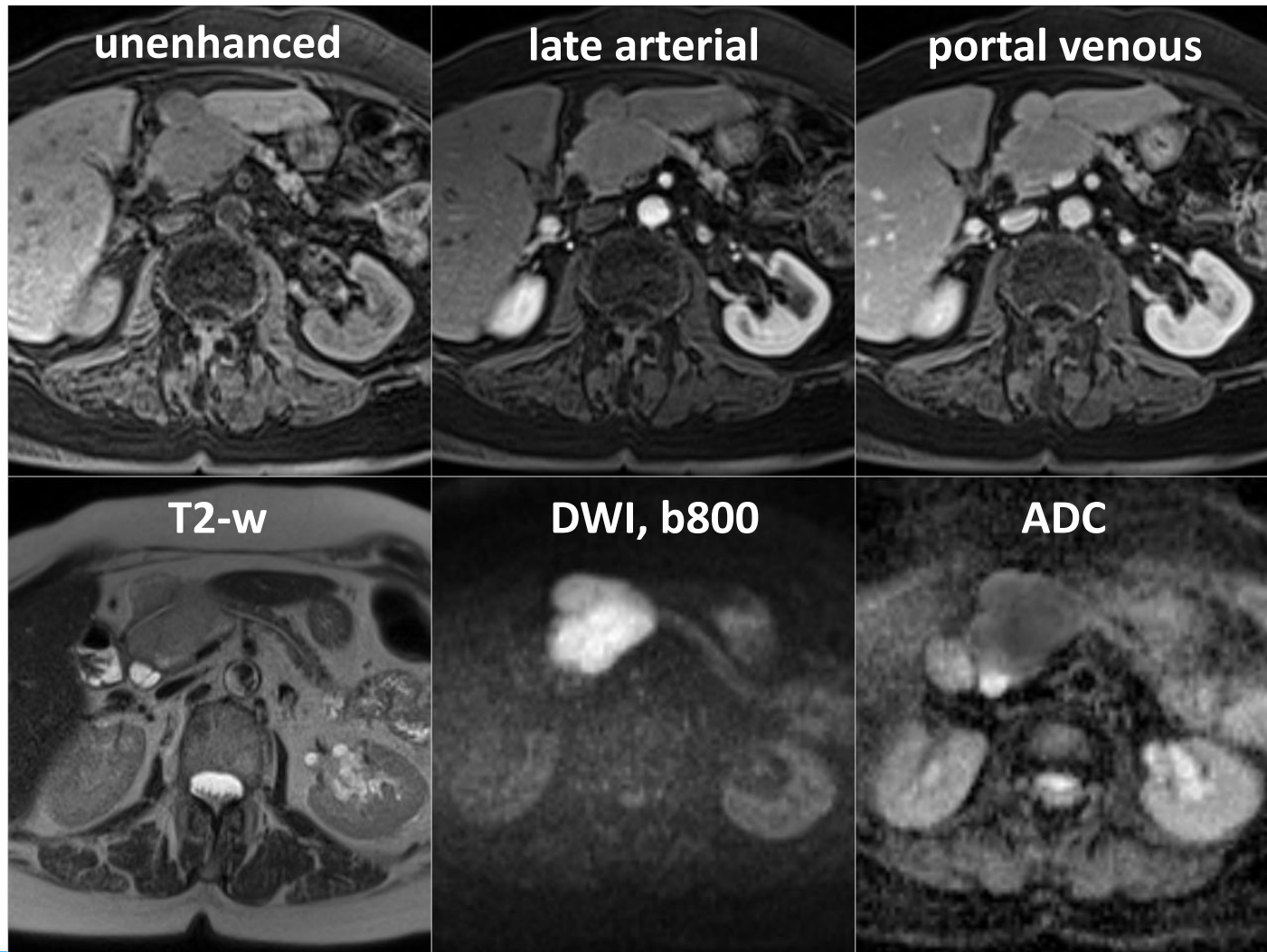
Hypervascular pNET with calcifications and area of central necrosis

Courtesy of Kartalis

MAGNETIC RESONANCE – MRI

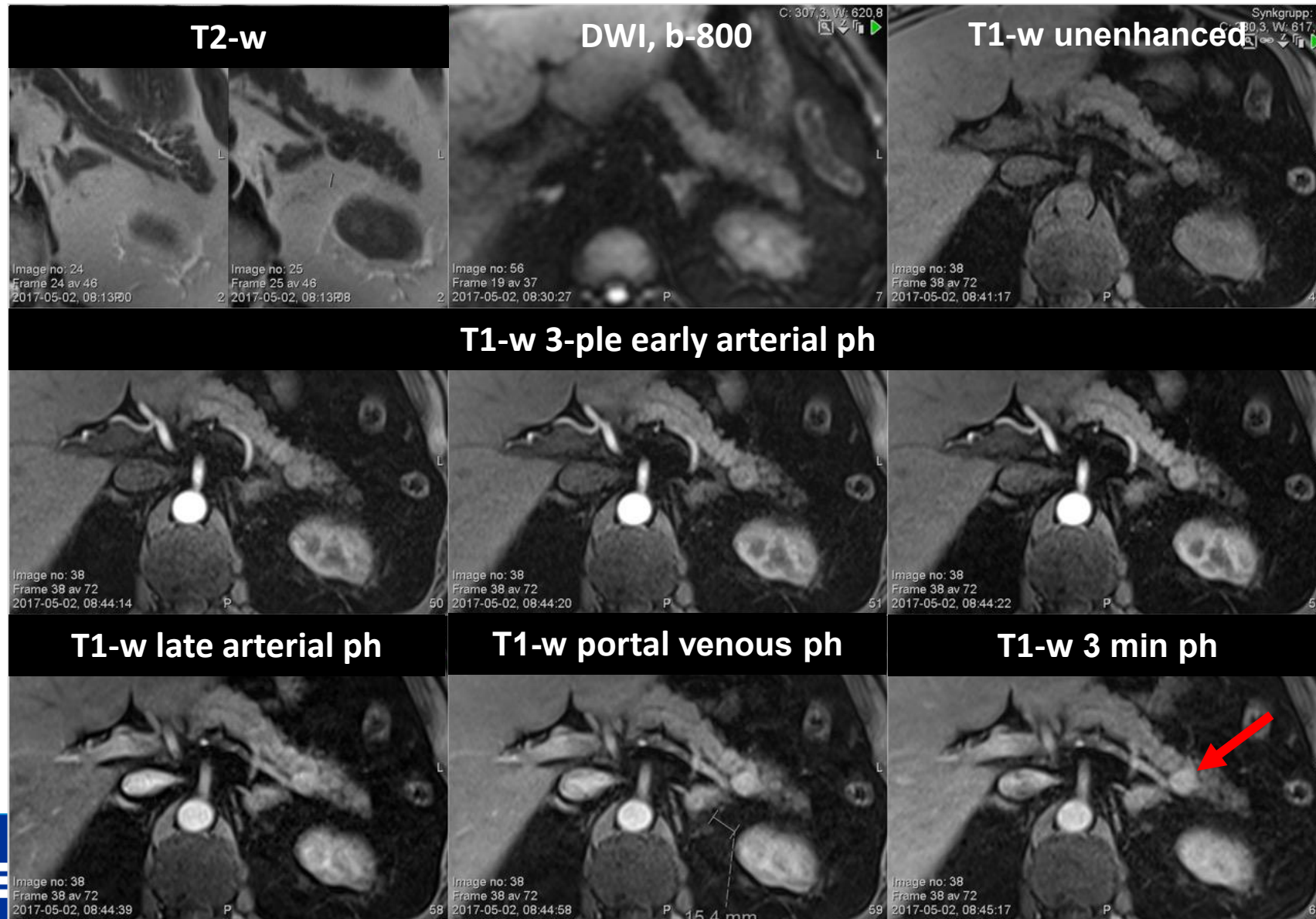
- Sensitivity is similar to CT, but multiparametric
- **T1:** Hypointense relative to pancreas
- **T2:** Typically hyperintense relative to the pancreas, but there is a range of signal intensities, better visualised with fat-suppression techniques
- **3D T1 C+ (Gd):** Hyperintense/hypervascular relative to pancreas
- **DWI/ADC:** Restricted diffusion is usually present and tends to correlate to the degree of tumour differentiation
- MRI is helpful in small lesion detection, surgical planning and assessment of the relationship of the tumour to the main pancreatic duct

MAGNETIC RESONANCE – MRI



Highly-
differentiated (G1)
PNET

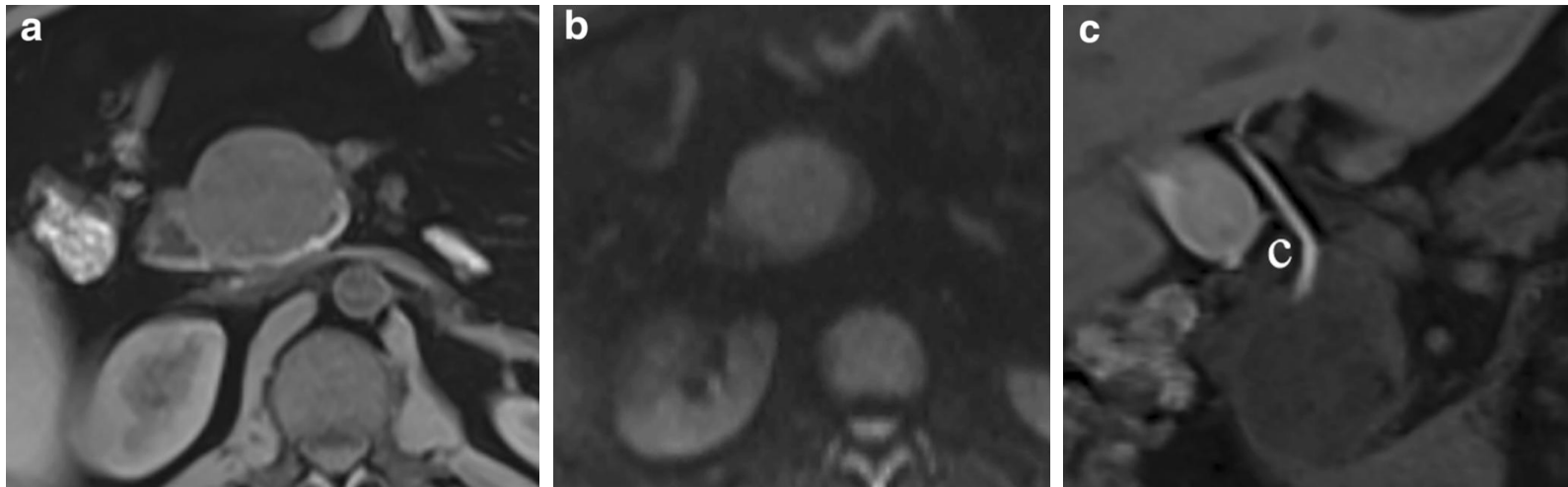
MAGNETIC RESONANCE – MRI



pNET G2

Imaging features – Typical

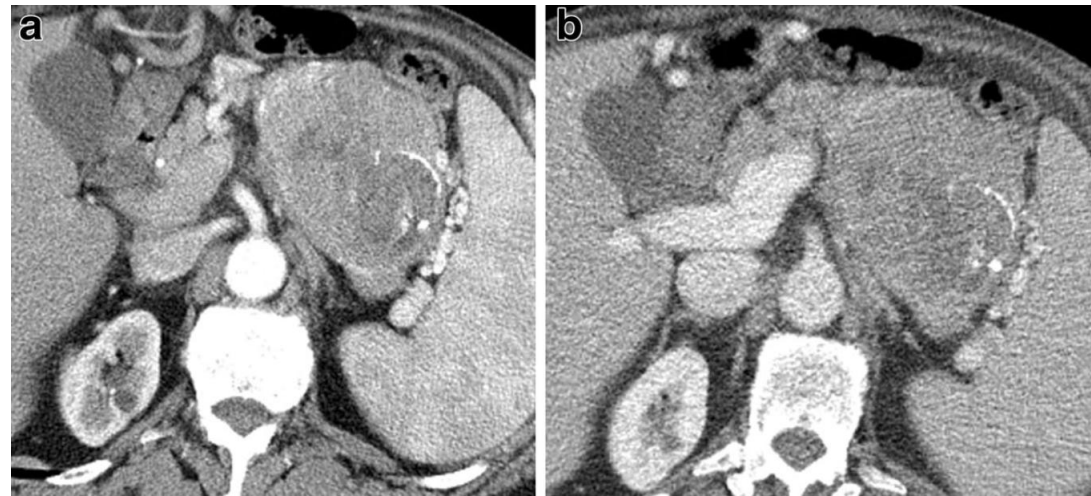
- P-NENs present as a solitary, solid, hypervascular, delineated mass with a rounded margins and a sharp delimitation from the surrounding parenchyma
- Often show expansive growth pattern with compression of adjacent structure, such as the main pancreatic and/or biliary ducts
- Depending on the aggressiveness, P-NENs can grossly show features of malignancy with evident invasive growth pattern infiltrating adjacent ducts, structures, and organs.



Ciaravino V. et al Insights Imaging 2018

Imaging features – Atypical

- Hypoenhancing pattern, mimicking ductal adenocarcinoma
- Rarely encapsulated
- Intraductal growth; in the case of a lesion that is exclusively intraductal, this is very difficult to observe at imaging
- In 5–10% of cases, P-NENs could present a cystic degeneration
- Calcifications may occur in P-NENs, unlike intra-tumour calcifications, which are not often seen in ductal adenocarcinoma



Non-functioning NEN

Ciaravino V. et al Insights Imaging 2018

Imaging features – Typical vs. Atypical

CT

MR

Typical P-NENs

Isodense or slightly hypodense, well-defined, hyperdense in arterial phase, hyperdense or isodense in portal phase

Well-defined, hypointense on T1W and hyperintense on T2W (better conspicuity in FAT-SAT)
Clear restriction signal at DWI
Hypervascular in arterial phase and isointense or slightly hyperintense in portal phase

Atypical P-NENs

Hypoenhancing pattern

Hypodense in arterial phase, possible enhancement in portal and late phases

Isointense or slightly hyperintense on T2-weighted sequences
No strong restriction at DWI
Hypointense in arterial phase, possible enhancement in portal and late phase

Calcified pattern

Hyperdense areas with high HU values

Signal void artefact

Intraductal growth

Filling defect at MRCP
Possible enhancement after contrast media

Intravessel growth

Intravessel vascularized thrombus

Absence of flow void artefact
Intravessel vascularized thrombus

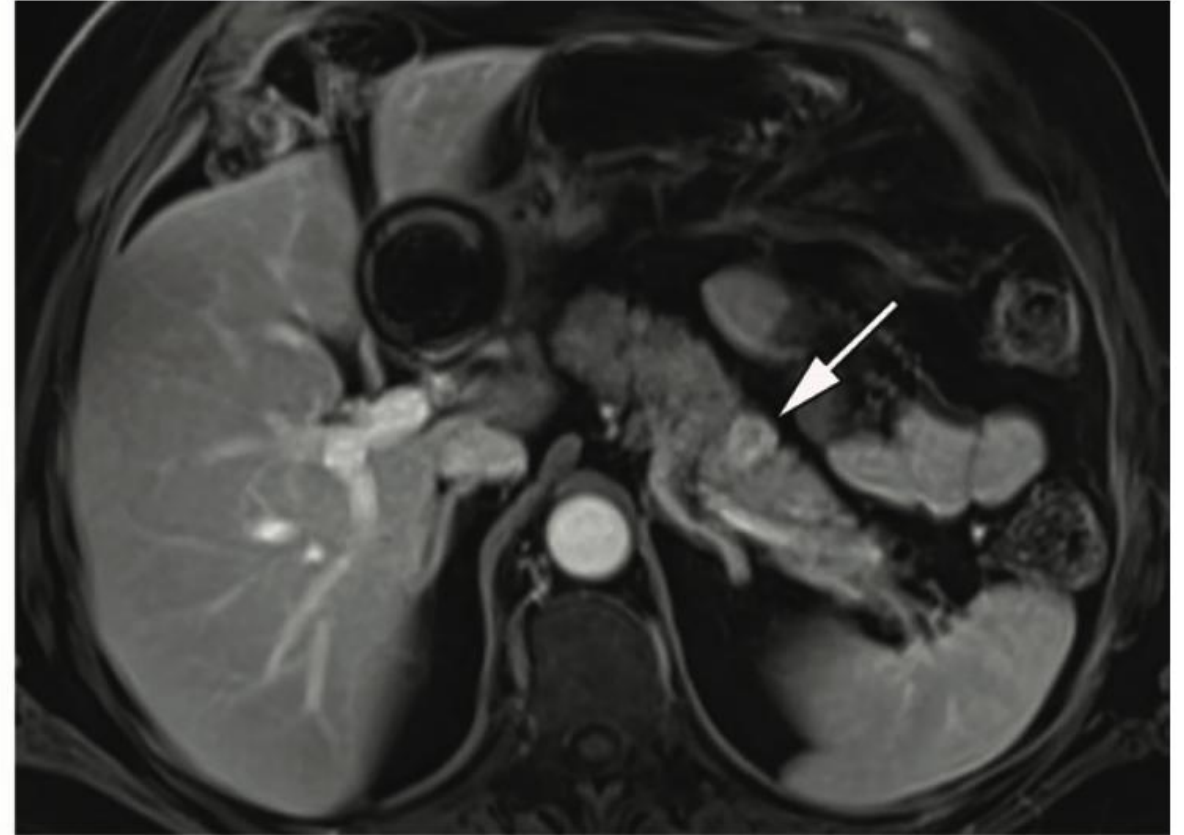
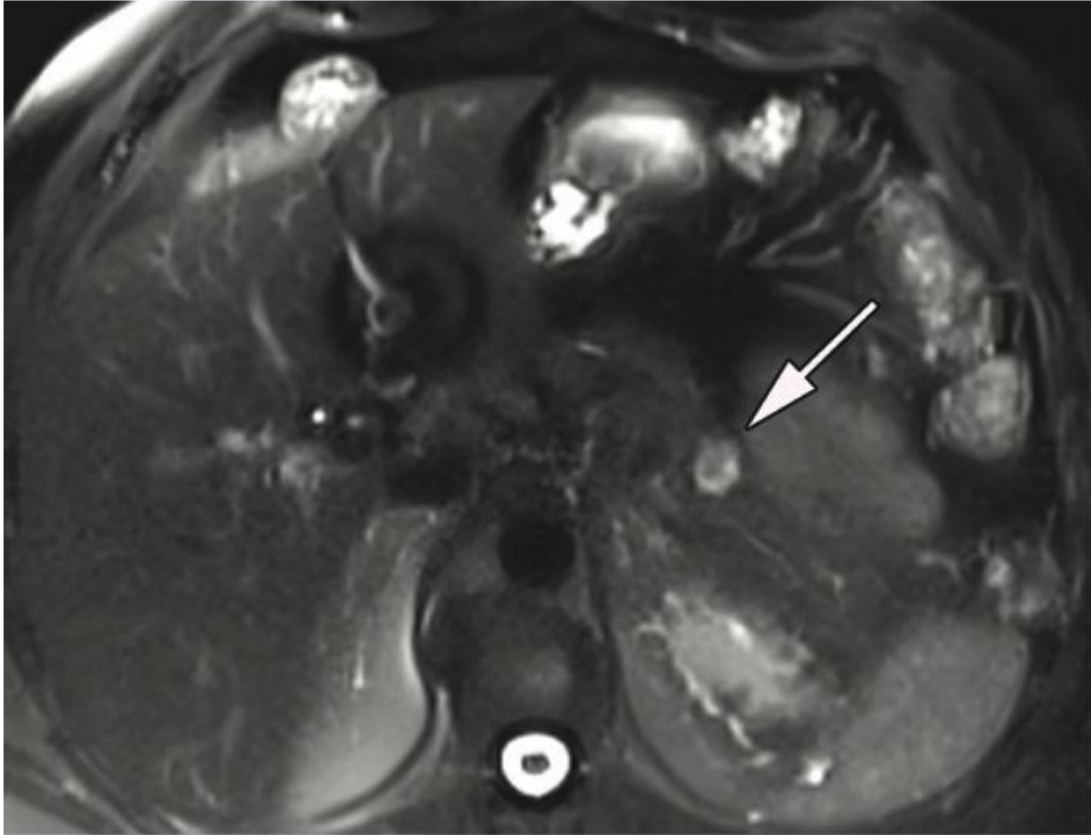
Cystic pattern

Hypodense cystic portion
Hypervascular enhancement of wall and septa

Hypointense in T1W, hyperintense in T2W
Hypervascular enhancement of wall and septa

Imaging features

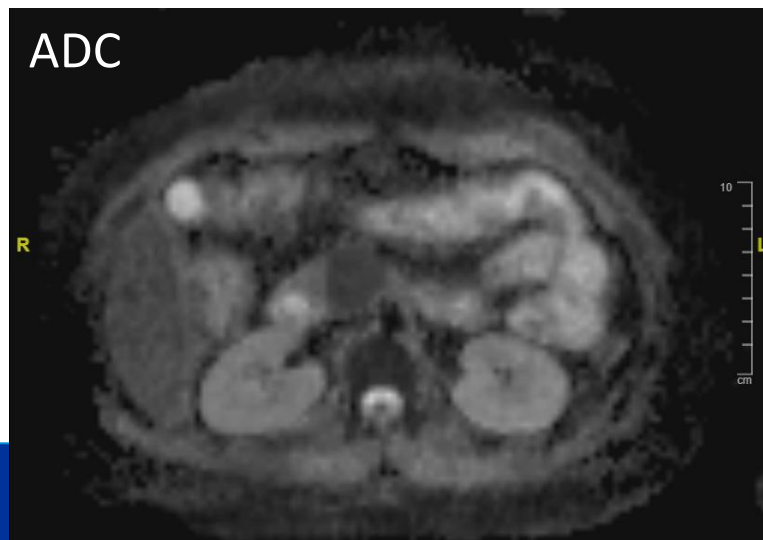
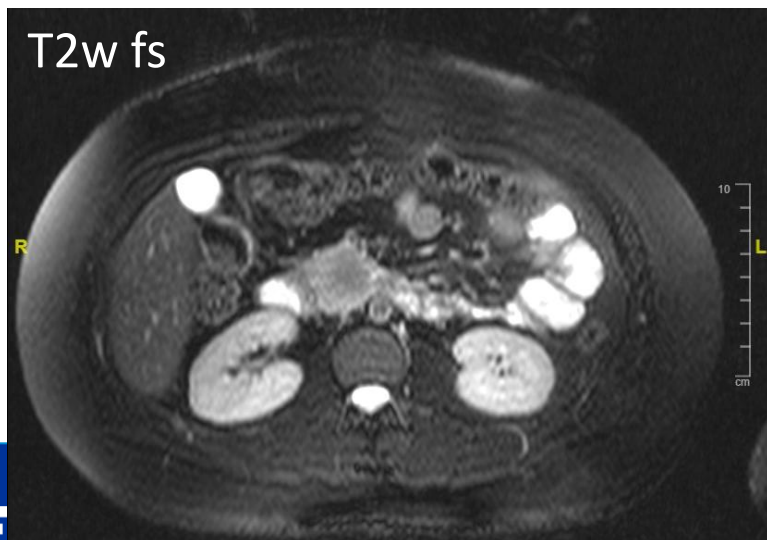
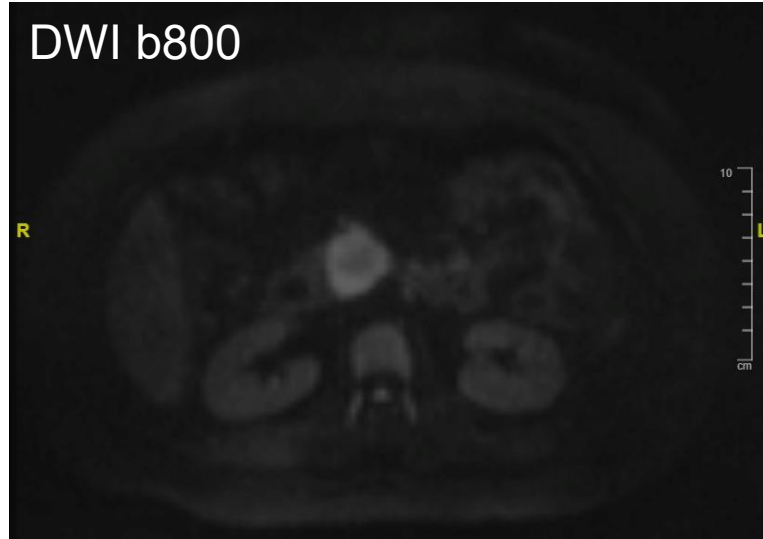
pNET G1



Khanna L Radiographics 2020

Imaging features

pNET G2



Challenging Case

M 56 abdominal pain

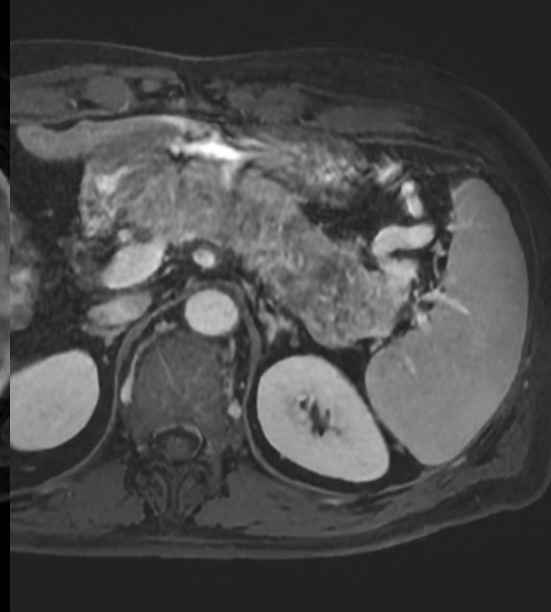
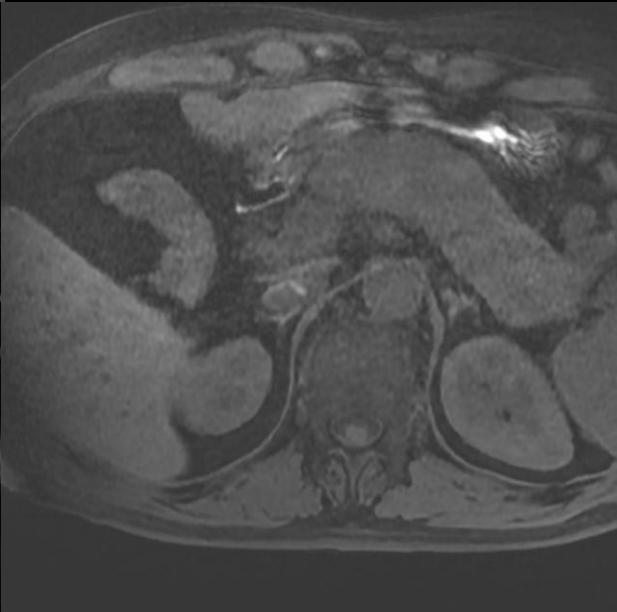
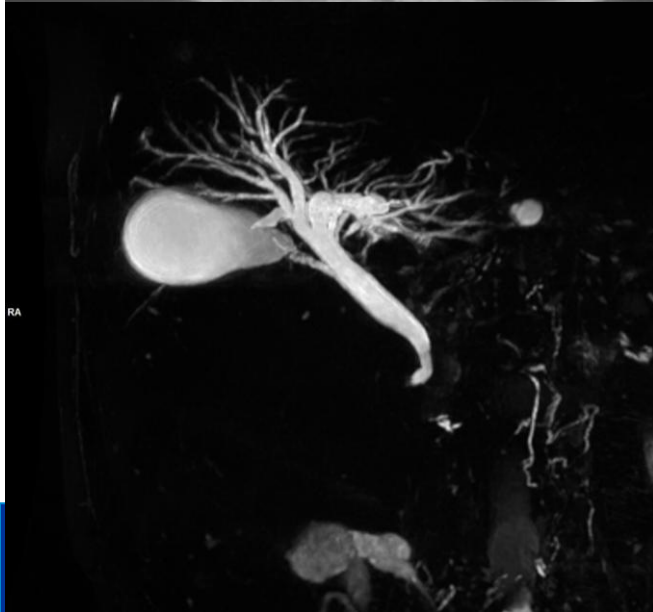
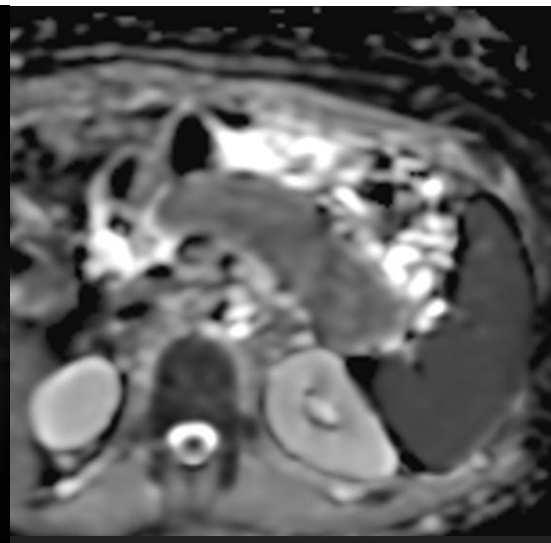
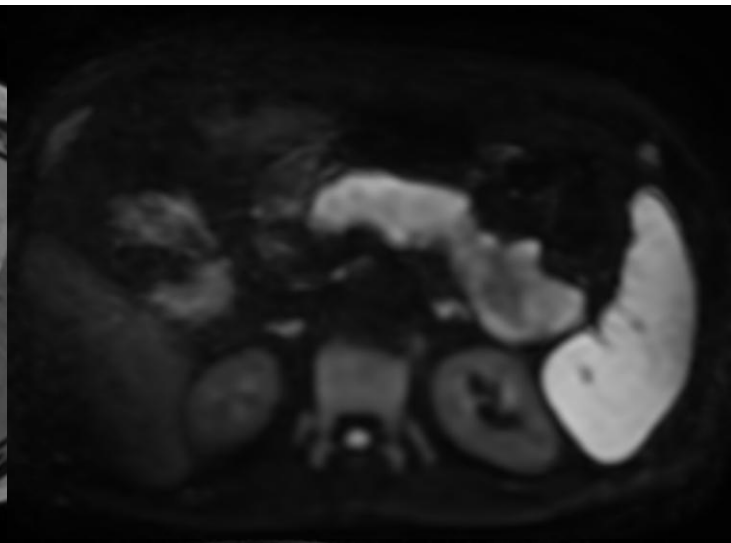
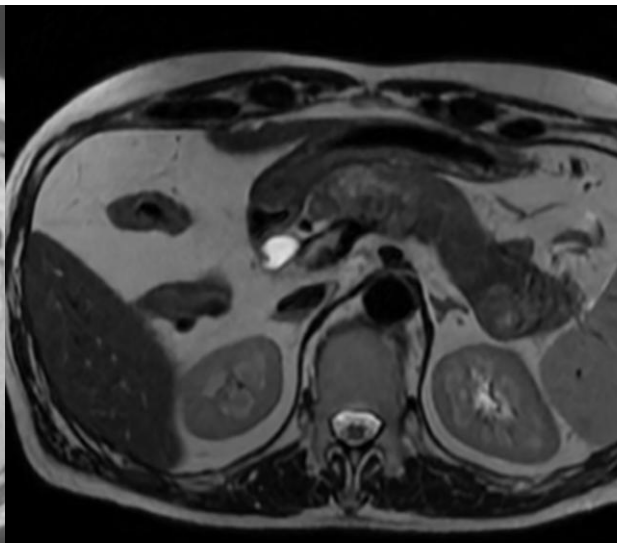
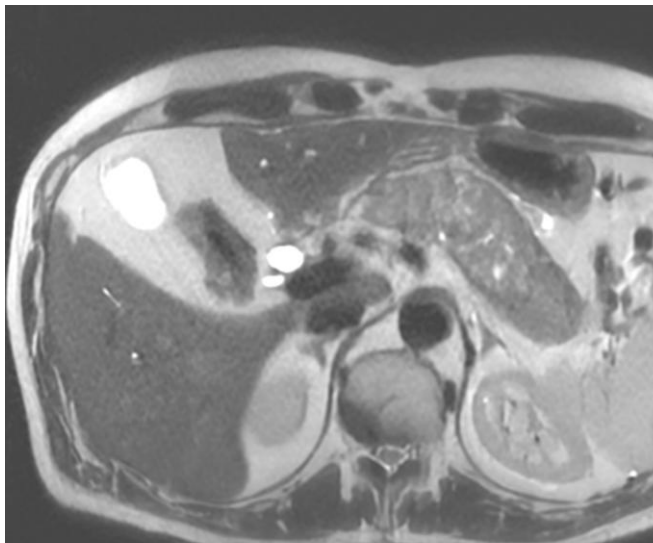
US: pancreas enlarged, CT is required



Pancreatic Lymphoma?

Lab Negative

Challenging Case



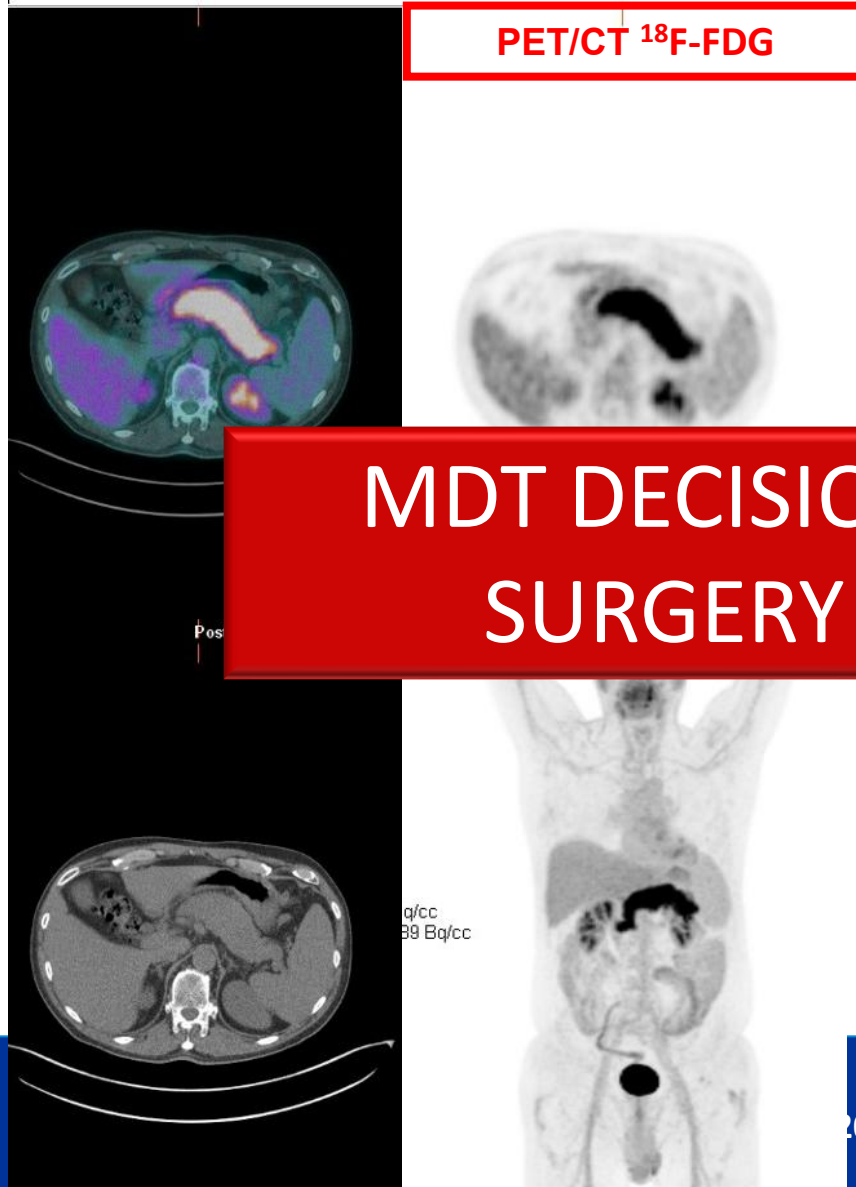
Challenging Case

Eco-Endoscopy

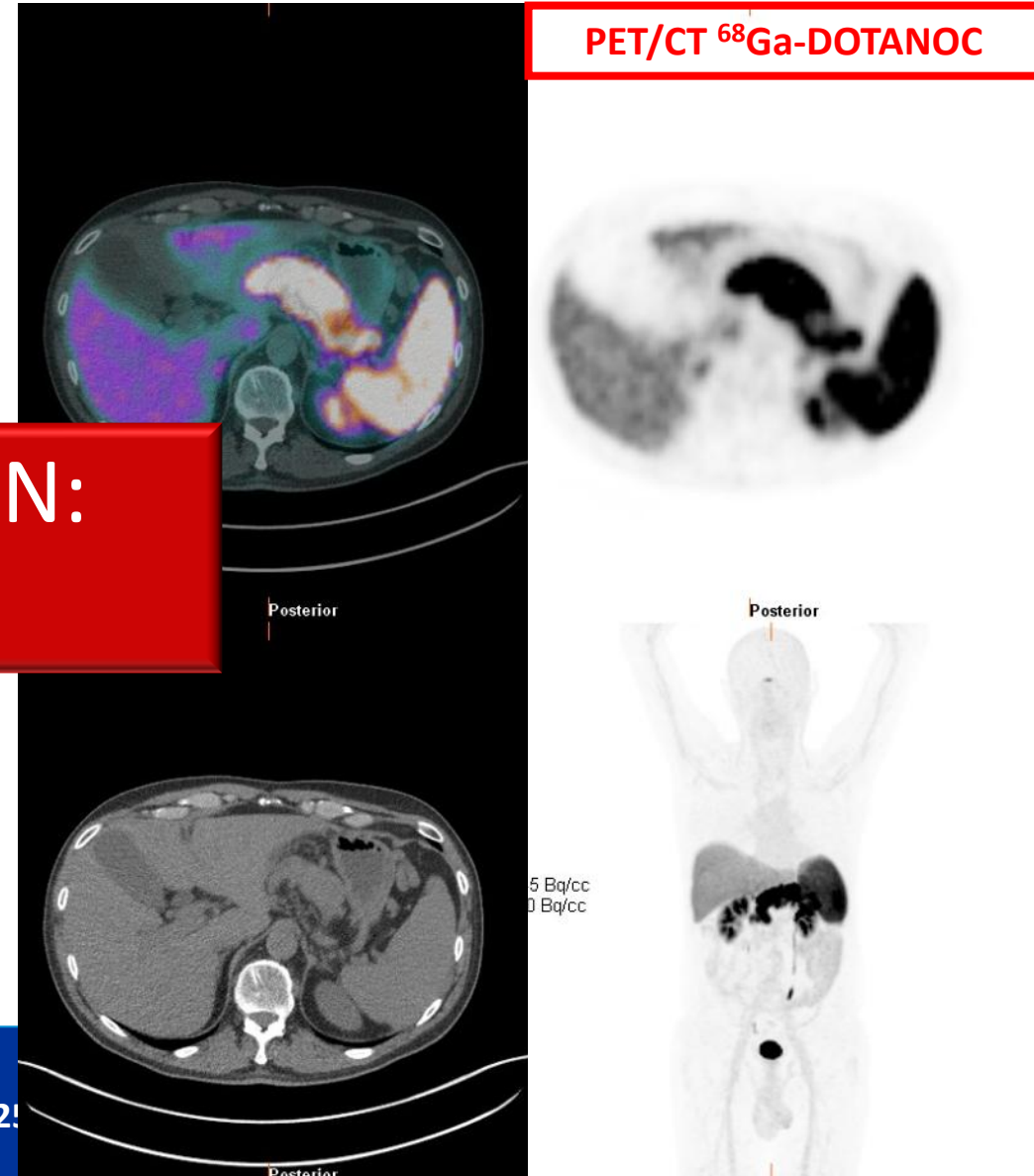
Intraductal lesion
Possible IPMN Main
Duct
Possible NEC

Surgery
NET G2, intraductal
growth
Ki67 16%

PET/CT ^{18}F -FDG



PET/CT ^{68}Ga -DOTANOC



RECIST vs. CHOI CRITERIA or TGR?

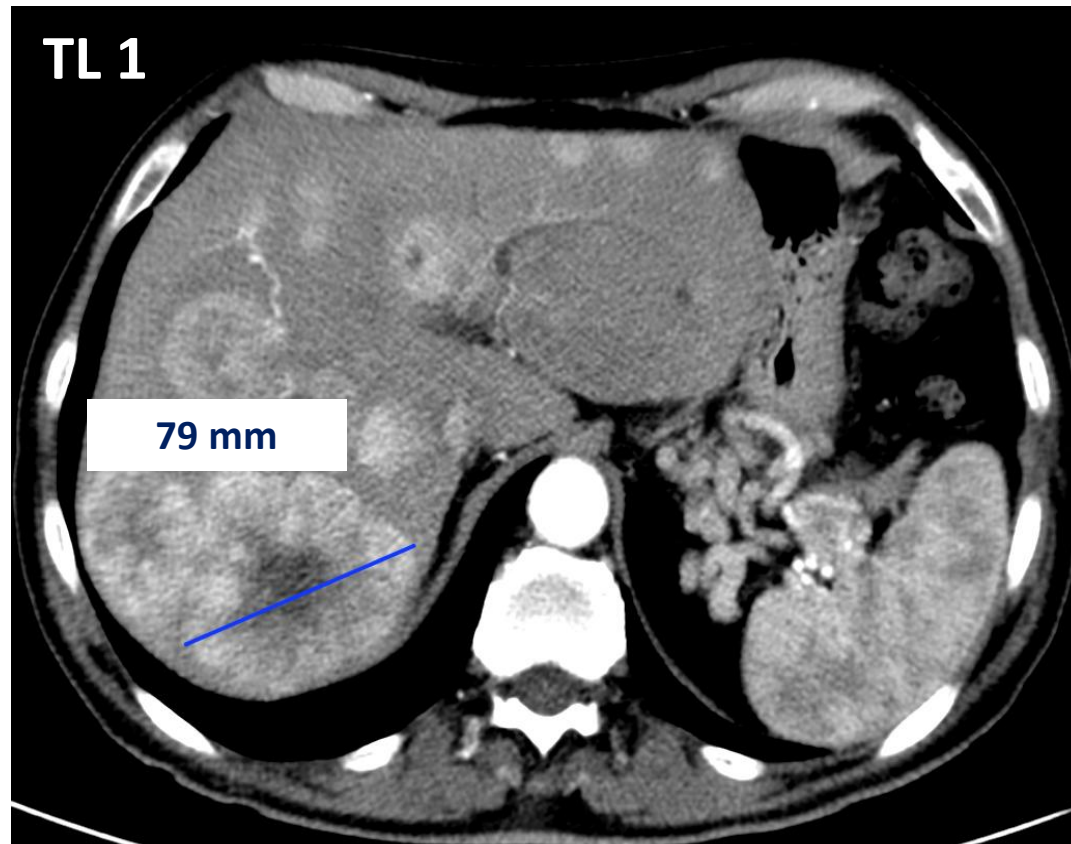
Response	RECIST	CHOI
Complete Response (CR)	Disappearance of all target lesions. Any pathological LN must have reduction in SAD <10 mm	Disappearance of all target lesions. No new lesions
Partial Response (PR)	≥ 30% decrease in the SOD of target lesions	A decrease in size (SOD) of ≥10% or a decrease in tumour density (HU) ≥15% on CT.
Progressive disease (PD)	≥ 20% increase in SOD of target lesions or New lesions = progressive disease	An increase in tumour size of ≥10% and does not meet criteria of PR by tumour density (HU) on CT. New lesions.
Stable Disease (SD)	Does not meet the criteria for CR, PR or PD.	Does not meet the criteria for CR, PR or PD.

Clinical Case

PNET G1 ki67 2%

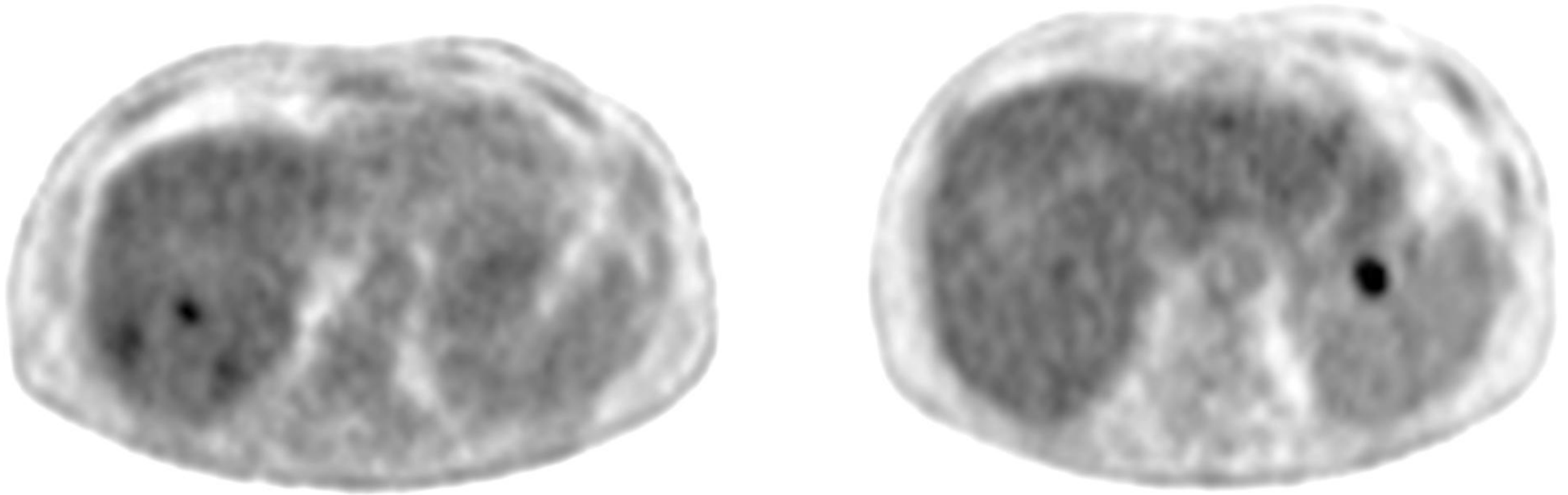
PRRT

CT BASELINE: 23/02/2022



Clinical Case

FDG PET/CT BASELINE: 07/09/2022



Only few lesions were FDG avid

Clinical Case

CT FOLLOW-UP: 11/01/2023

No new lesions

BL

TL 1

79 mm

TL 2

63 mm

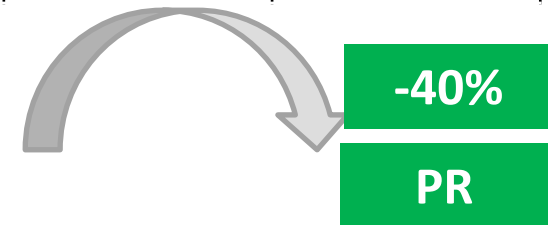
FU

TL 1

54 mm

30 mm

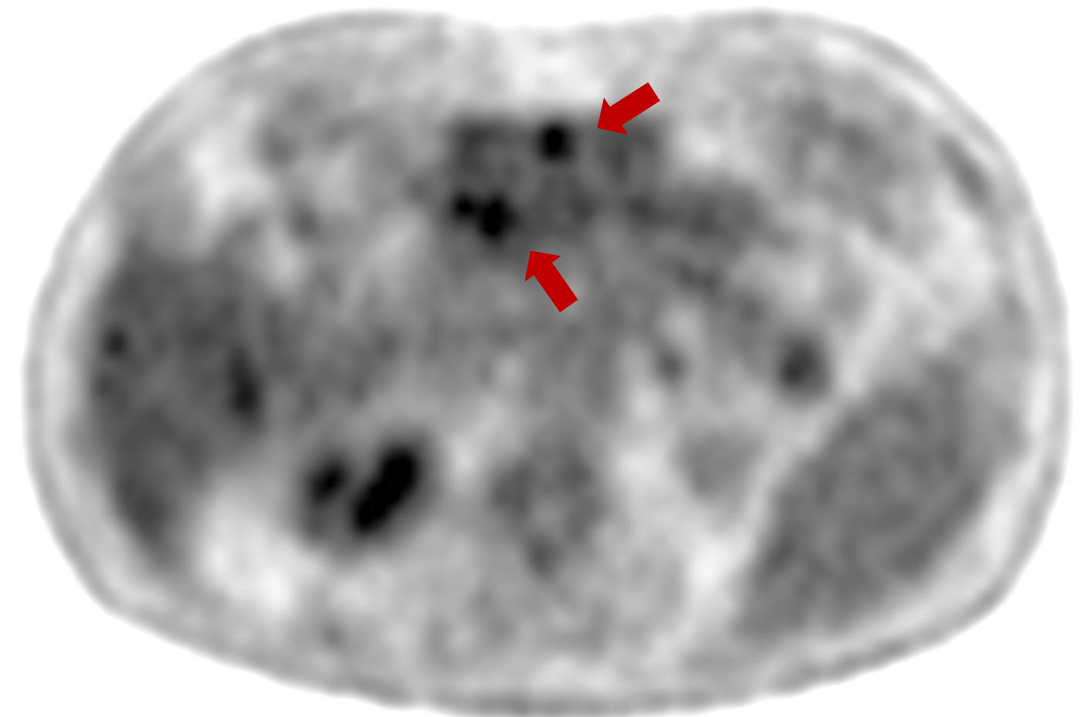
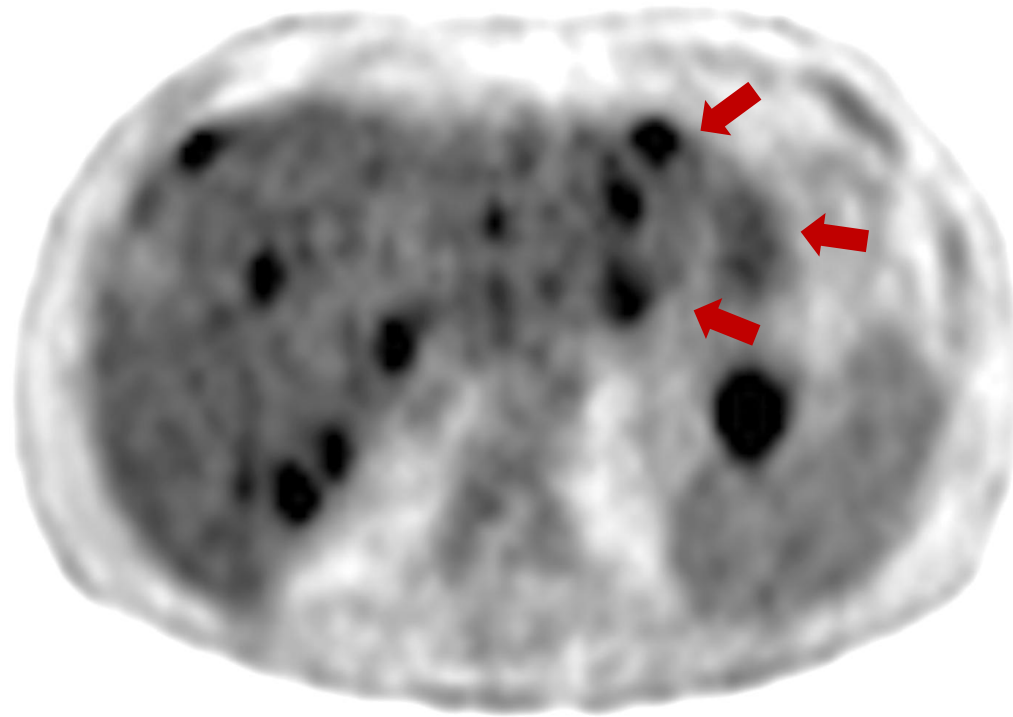
	BASELINE	FOLLOW-UP
TARGET 1	79 mm	54 mm
TARGET 2	63 mm	30 mm
SOD	142 mm	84 mm



Clinical Case

FDG PET/CT FOLLOW-UP

New lesions?

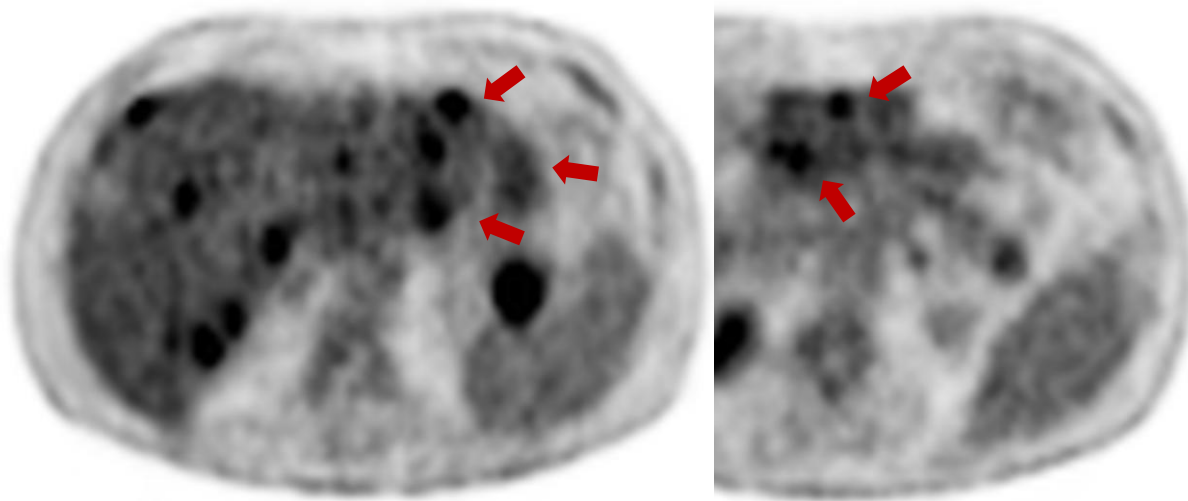


Multiple lesions were FDG avid

Clinical Case

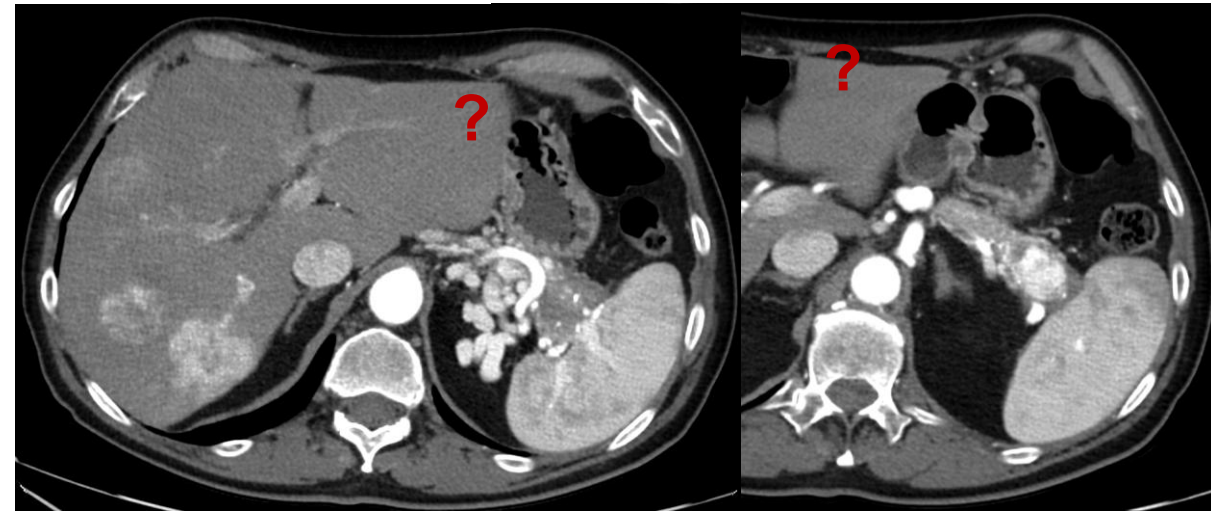
OPEN QUESTION?

FDG PET/CT FOLLOW-UP



**Nuclear Medicine:
Progressive Disease**

CT FOLLOW-UP



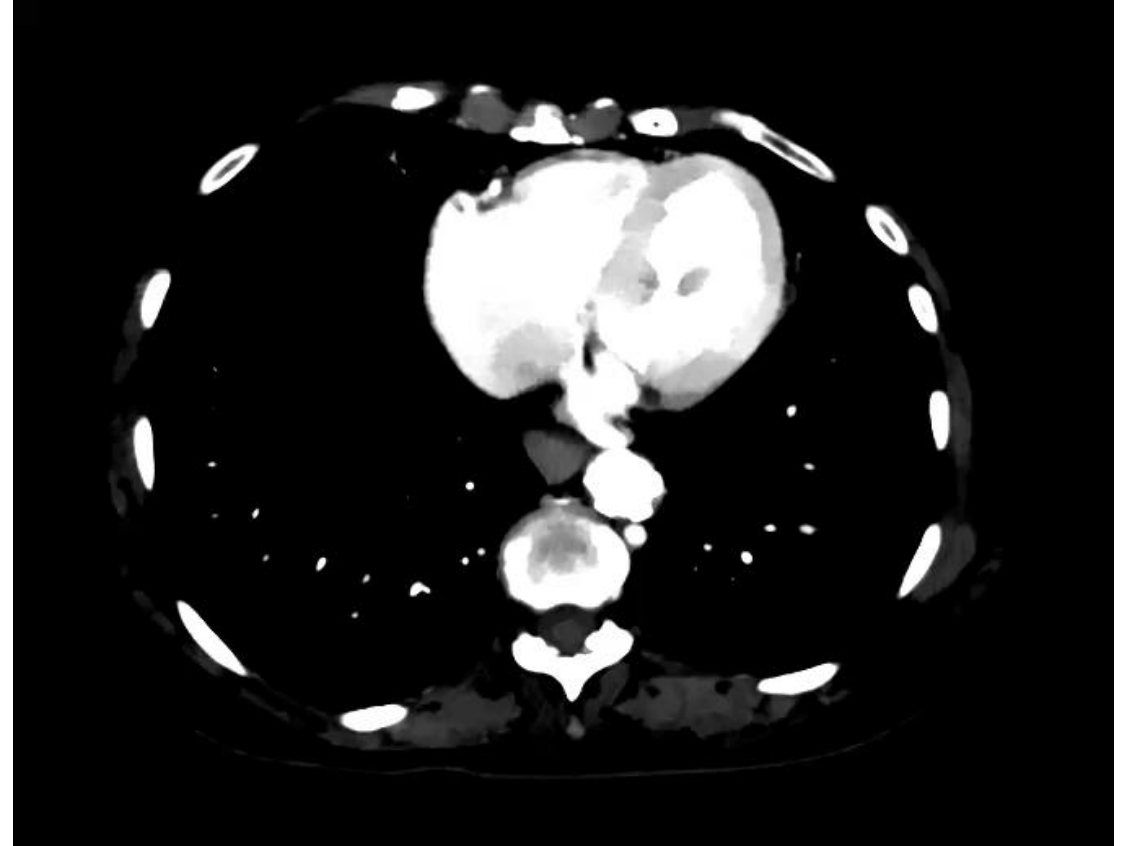
**Radiological:
Partial Response**

New Perspectives

Conventional Imaging

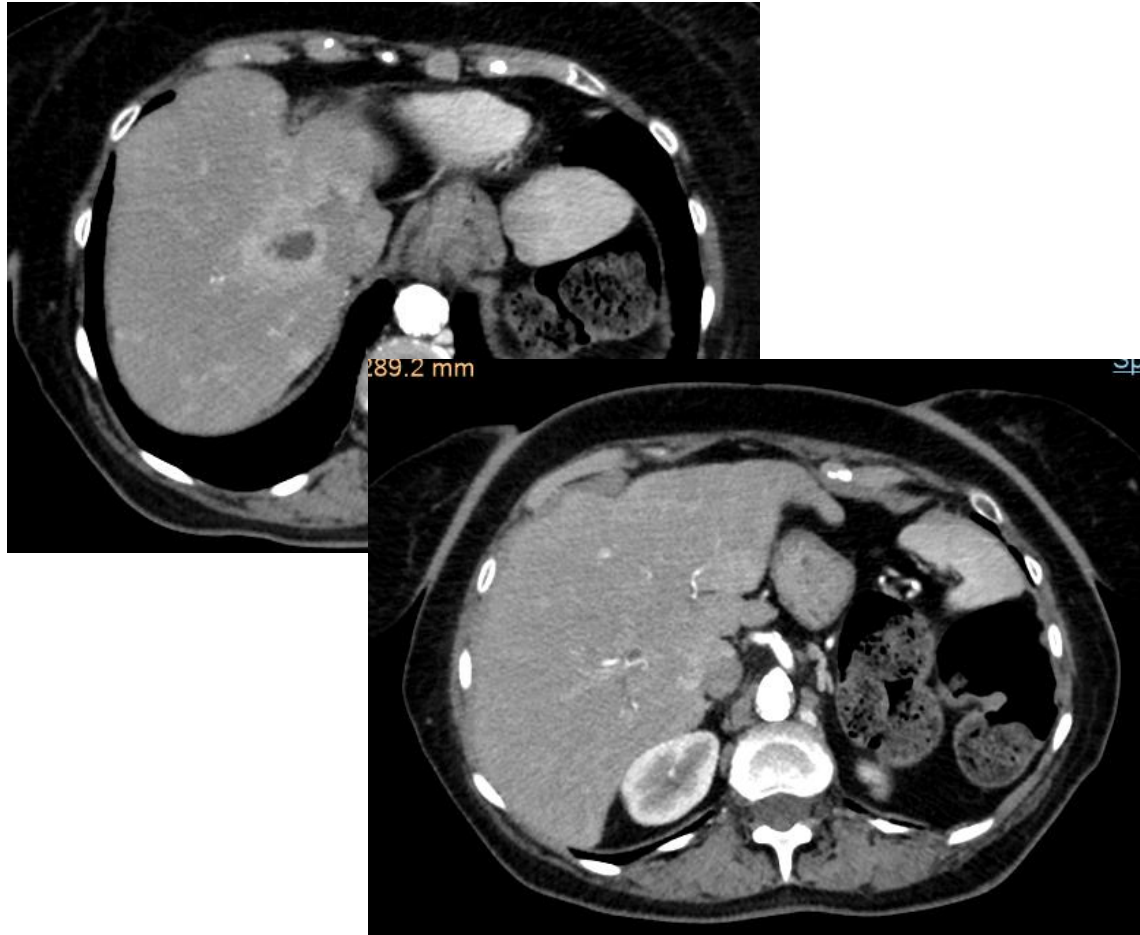


Spectral Imaging

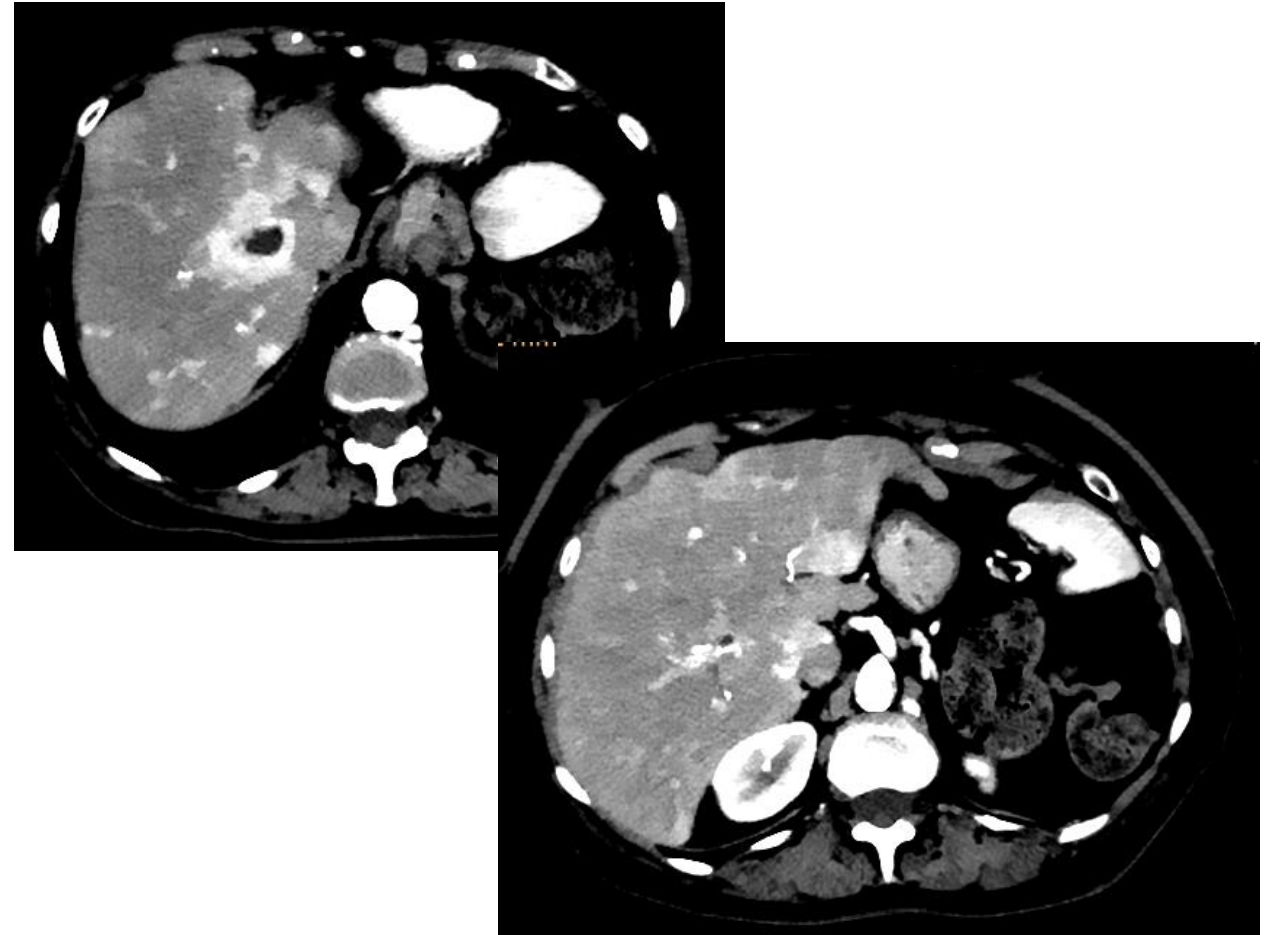


New Perspectives

Conventional Imaging



Spectral Imaging

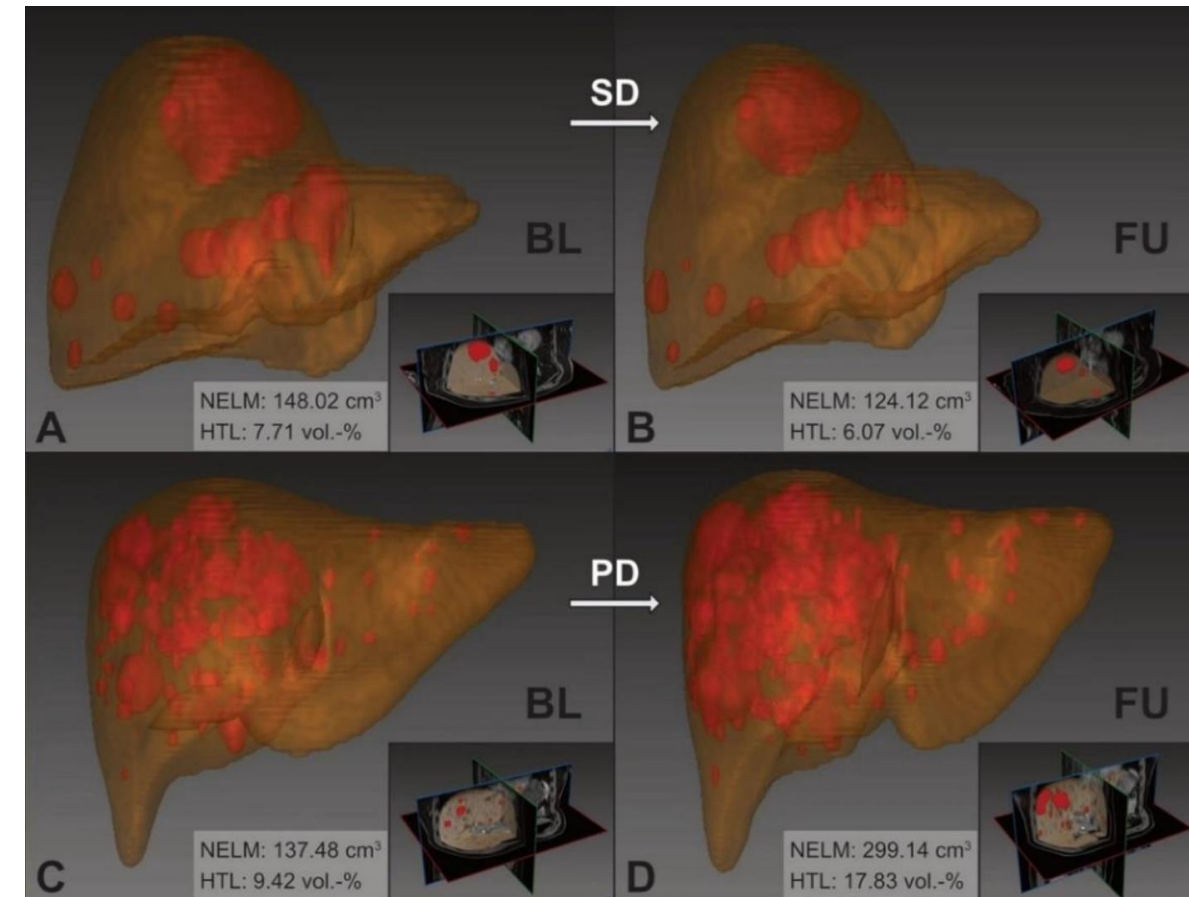


New Perspectives

AI-based Hepatic Tumour Load

A deep learning model using manual 3D segmentation of liver metastases and hepatic parenchyma was trained in 149 patients with NEN.

The model analysed the NELM volume and HTL of the 33 patients in the baseline (BL) scan and the follow-up (FU)



Fehrenbach U et al. Cancers 2021

THANK YOU

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Sapienza University of Rome
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Most frequent confusions in NEN management: Primary location

Julien Hadoux, MD, PhD

Endocrine oncology, Gustave Roussy, Villejuif, France
& ENDOCAN network

DISCLOSURE INFORMATION

- Honoraria for speaker engagements, advisory roles or funding of continuous medical education:

Lilly, AAA, IPSEN, Roche, Pharma Mar, Eisai, Bayer, HRA pharma, ITM

- Research grants:

Novartis, Lilly, Sanofi

- Private healthcare provider: none
- Commercial medical education provider: none
- Stocks or ownership interest: none

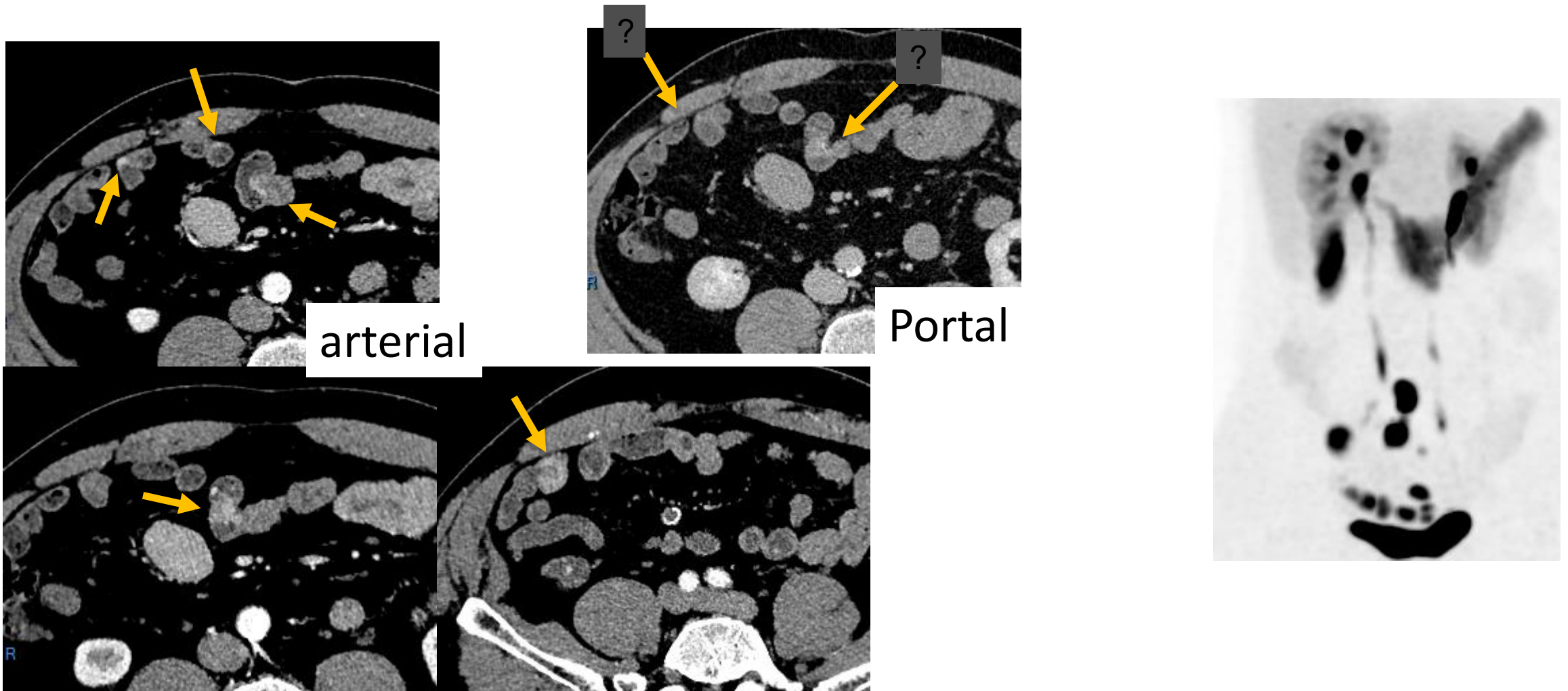
Most frequent confusions in NEN management: Primary location AGENDA

- ✓ Confusions in Ileal NET management
- ✓ Confusions in pancreatic NET management
- ✓ Primary confusions or unknown primary?

Two third of the primaries are in the lung, small intestine or pancreas

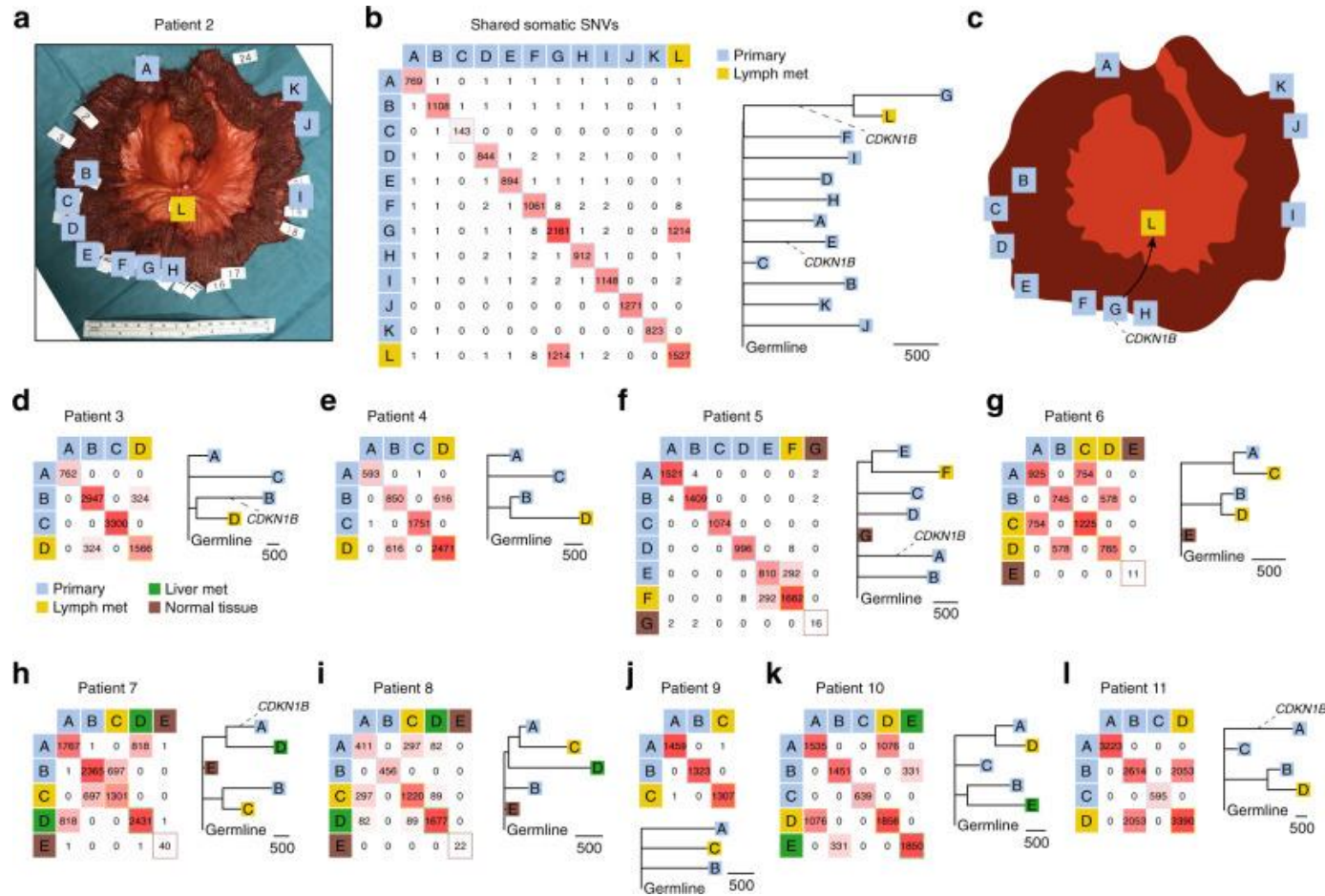
Primary	SEER database	ENETS registry	French GTE database
Bronchus	30,6%	8,6%	12%
Ileum	22%	27%	21%
pancreas	11%	27%	34%

Multiple Ileal NET primaries: In 40 to 60% of the patients!



Pr Yves Menu, Gustave Roussy

Ileal NET primaries: Independent oncogenic pathways



Elias et al, Nat Com 2021

GTE-Endocan-RENATEN Network, the CentralChirSINET multicenter Study

N= 157 patients
2019-2021

N= 90 patients in 4 high volume centers

- Laparotomy 86%
- Right hemicolectomy 64.4%
- **Bi-digital palpation of the entire Small intestine: 95.6%**
- Mesenteric mass resection 70%
- Cholecystectomy: 95.6%
- ≥ 8 LN resected 96.3%

→ **Multiple primaries: 43.3%**

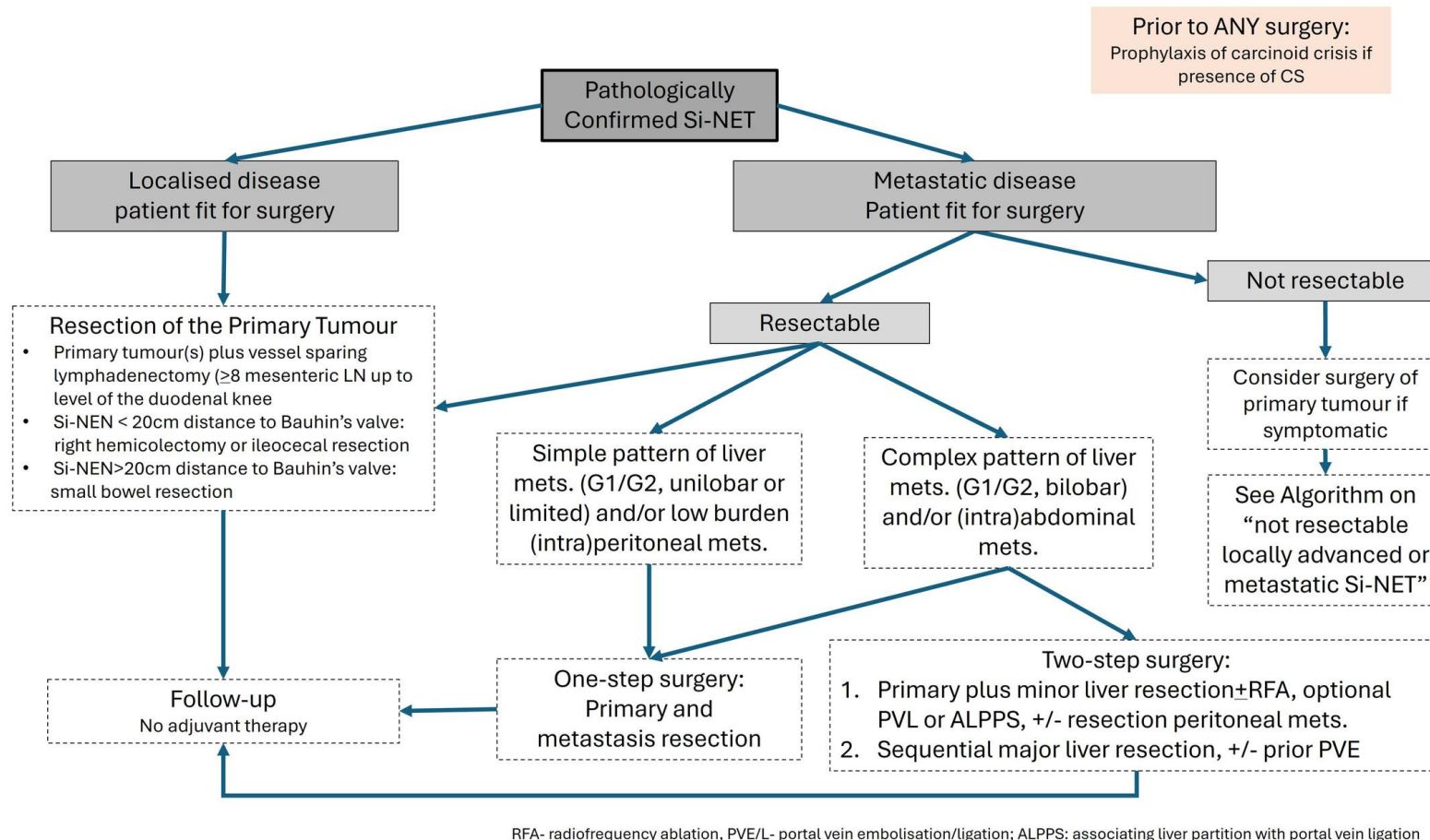
N= 67 patients in 29 low volume centers

- Laparotomy 59.7%
- Right hemicolectomy 38.8%
- **Bi-digital palpation of the entire Small intestine: 34.3%**
- Mesenteric mass resection 35.8%
- Cholecystectomy: 14.9%
- ≥ 8 LN resected 65.1%

→ **Multiple primaries: 25.4%**

Kalifi et al, Annals Surgical Oncology 2023

ENETS guidance paper SI NET



Lamarca et al, JNE 22024

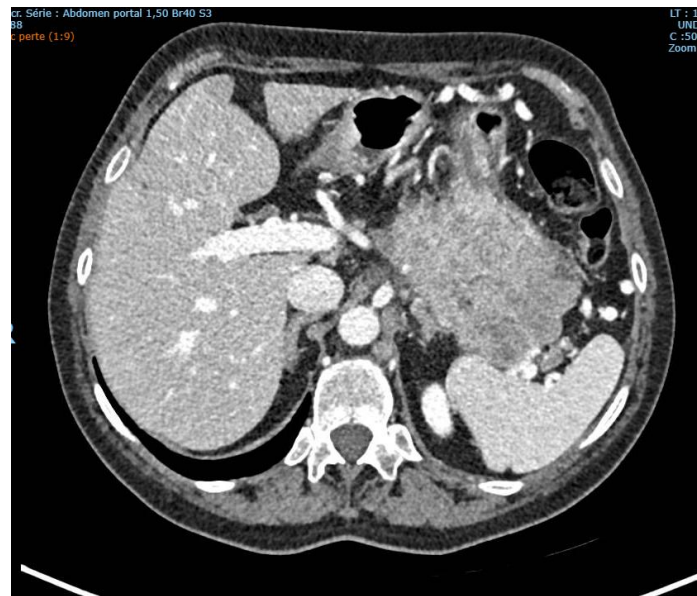
Ileal Primaries: Take home message

Perform PET and Palpate

To avoid confusions when it is too late!

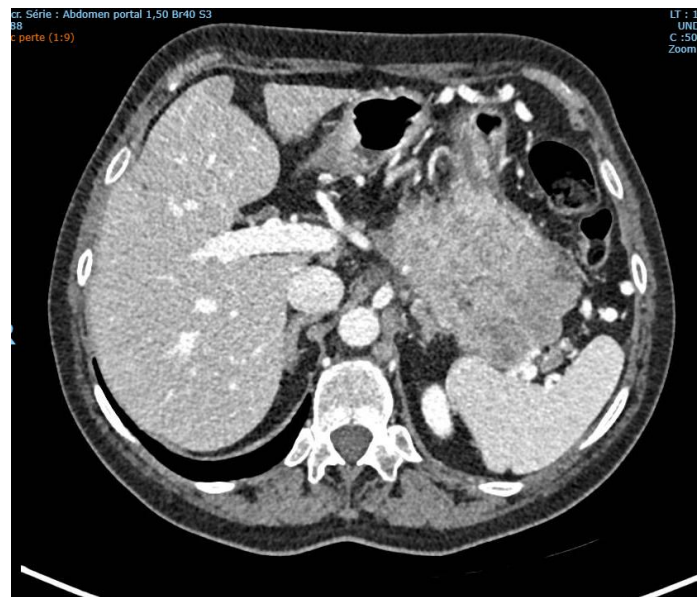
Primary from the pancreas or the stomach?

- 75 year old woman
- Grade 2 NET, Ki67 15%, CK +, DAXX + ATRX +, CDX2 + MGMT + (H-score 250)



Primary from the pancreas or the stomach?

- 75 year old woman
- Grade 2 NET, Ki67 15%, CK +, DAXX + ATRX +, CDX2 + MGMT + (H-score 250)



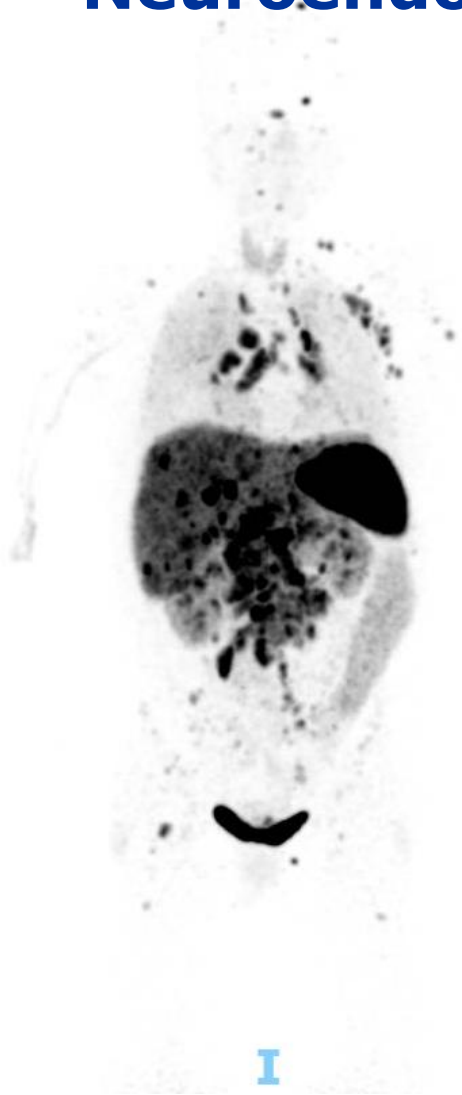
« This NET infiltrates the gastric mucosa in a particular manner with tumor foci in the chorion and intra-epithelial that might suggest extension from the periphery of the stomach » Pr Couvelard review, tenpath network

Neuroendocrine tumour of unknown primary

50 year old woman

NET G2, Ki67 10%, unknown primary, CK+, CDX2 low, TTF1 -, PDX1 -

Metastatic sites: lymph nodes, liver, bone



**As long as the whole extensive diagnostic
work-up has not been done,
You are facing an OCCULT primary, not an
unknown primary.**

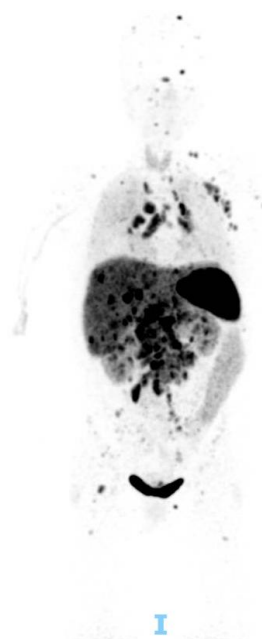
How to identify Primary?

Immunohistochemistry work-up

IHC should be carried out to exclude paragangliomas (cytokeratin) and to identify the primary [as a minimum: thyroid transcription factor-1 (TTF-1) and caudal-type homeobox 2 (CDX-2)]. Calcitonin, serotonin and other IHC markers may be used [IV, B].

Hormonal work-up

Secretory syndromes should be diagnosed based on hormone-related symptoms. **As a minimum, metanephrines, 5-HIAA and calcitonin** should be measured in those with UKP-NETs [V, A].



Imaging work-up

Cross-sectional imaging metastatic patterns suggestive of a primary site? [IV, A]. Endoscopy and endoscopic ultrasound (US) for pancreatic primaries [V, A]. SRI-PET for G1-2 UKP-NETs [IV, A]. FDG-PET-CT for G3NENs [V, B]. [^{18}F]F-DOPA-PET-CT for ileum primary or PPGL [V, B].

Unknown primary NET

CgA + → non specific
Synaptophysin+, CD56+ → non specific

Cytokeratins (AE1/AE3) ?

yes

Medullary thyroid cancer

→ Calcitonin, CEA

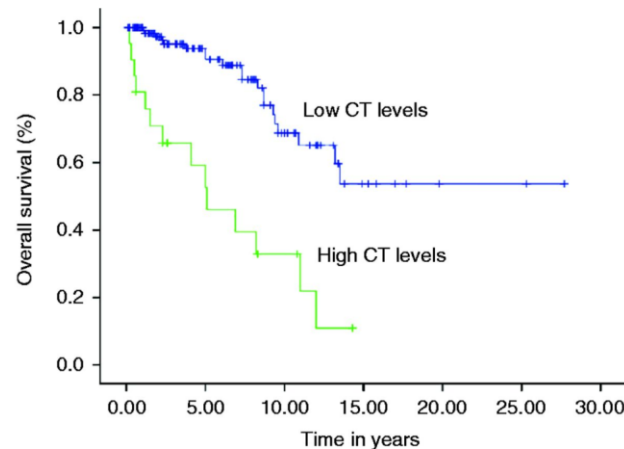
No

Pheochromocytoma and
paraganglioma

→ PS100, metanephrens

NOT all calcitonin secreting NET are MTC...

- Retrospective series from Lyon
- 21/176 NET patients: calcitonin > 100 ng/l
- Pancreas & lung
- G2-G3 90% of the cases

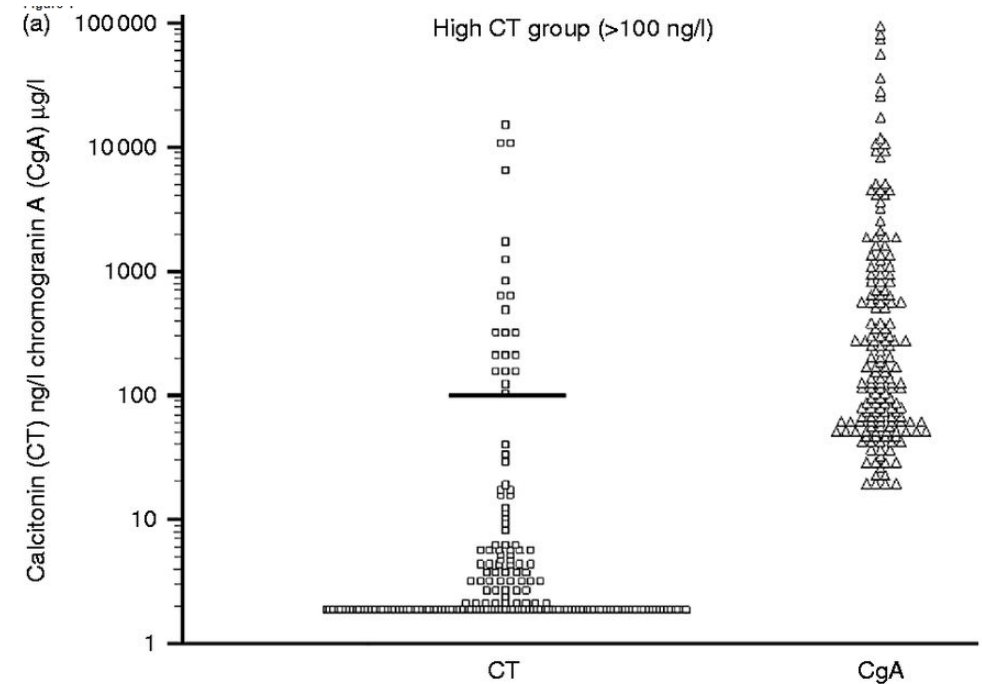


Number of patients by groups:

Low CT levels:	155	66	24	9
High CT levels:	21	8	4	1

Median OS:

- 13.2 years whole population:
- 5.1 (1.8–8.4) years for pts high CT
- Not reached for patients with low CT ($P < 0.0001$)



Unknown primary NET

CgA + → non specific
Synaptophysin+, CD56+ → non specific

Cytokeratins (AE1/AE3) ?

yes

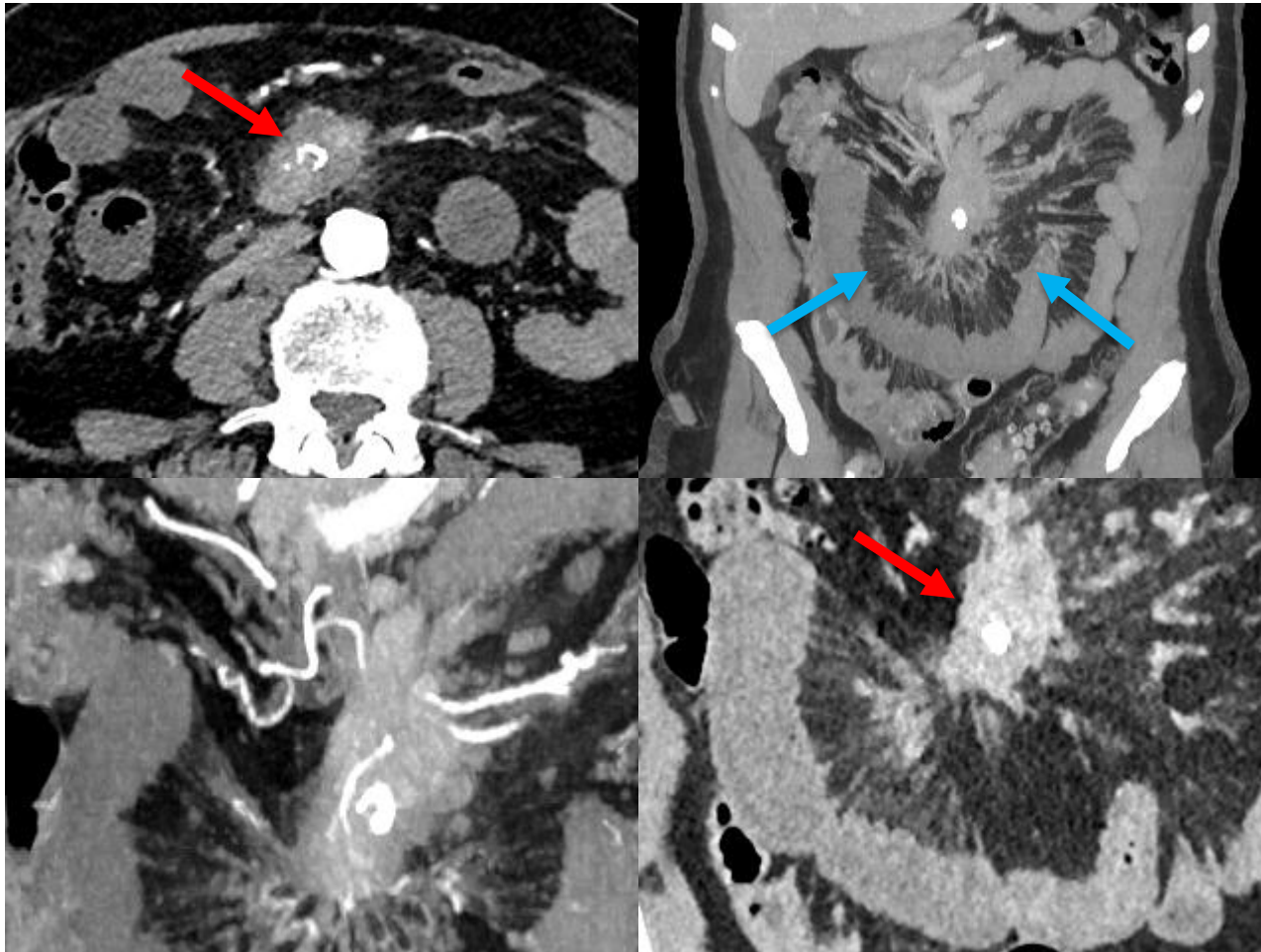
Medullary thyroid cancer
→ Calcitonin, CEA
→ RET status

No

**Pheochromocytoma and
paraganglioma**
→ PS100, metanephryns
→ Multiple lymph node,
retroperitoneum + multiple lytic
bone lesions

Both can be DOTATOC & DOPA +

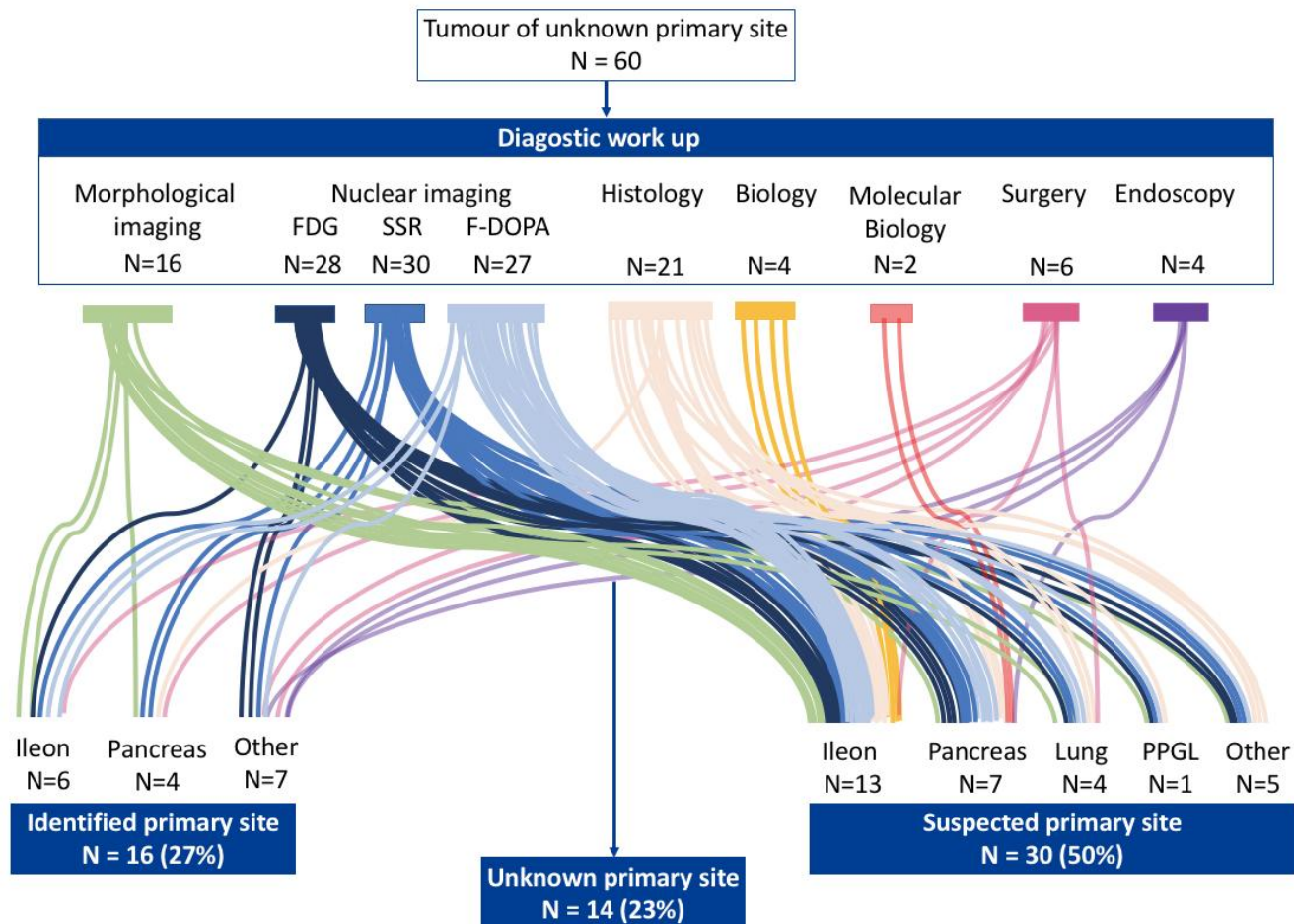
Evocative imaging patterns



- Mesenteric mass: ileum
- Para-aortic lymph node: PCC–PGL, genitourinary
- Mediastinal lymph node and thyroid mass: lung NET, MTC
- Isolated superficial NEC lymph node: Merkel-cell carcinoma, UKP-NEC

**As long as the whole extensive diagnostic
work-up has not been done,
You are facing an OCCULT primary, not an
unknown primary.**

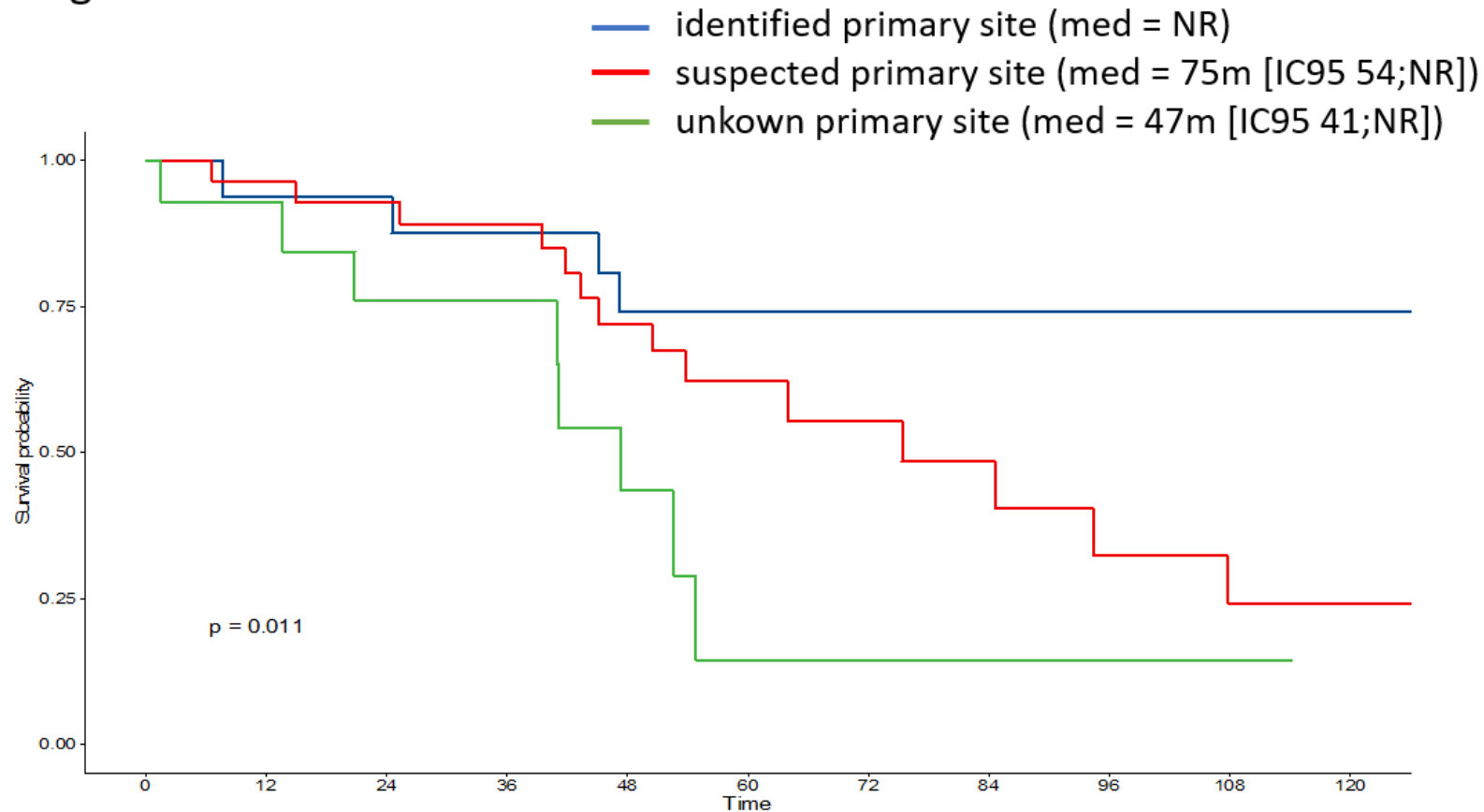
From occult to really unknown primary



Roy et al, ENETS 2023

From occult to really unknown primary

Figure 2. Overall survival



Neuroendocrine tumour of unknown primary

50 year old woman

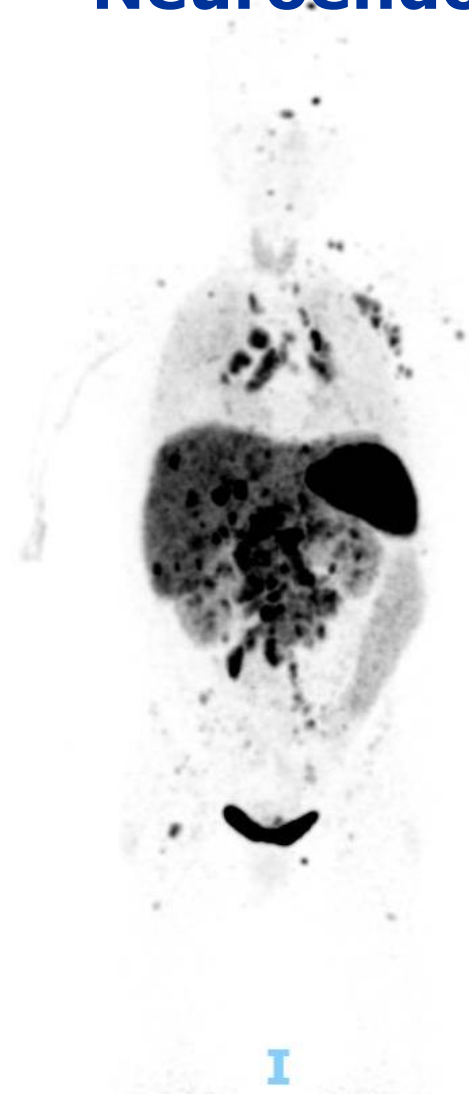
NET G2, Ki67 10%, unknown primary, CK+, CDX2 low, TTF1 -, PDX1 -

Metastatic sites: lymph nodes, liver, bone

Liquid biopsy: ATM 0.31 %, NF1 0.27 %, PIK3CA 0.18 %, PTEN 13.8 %, TMB 3 Mut/Mb, MSS.

DOTATOC PET +

MGMT + (H-score 200)



Neuroendocrine tumour of unknown primary

SSA: no response

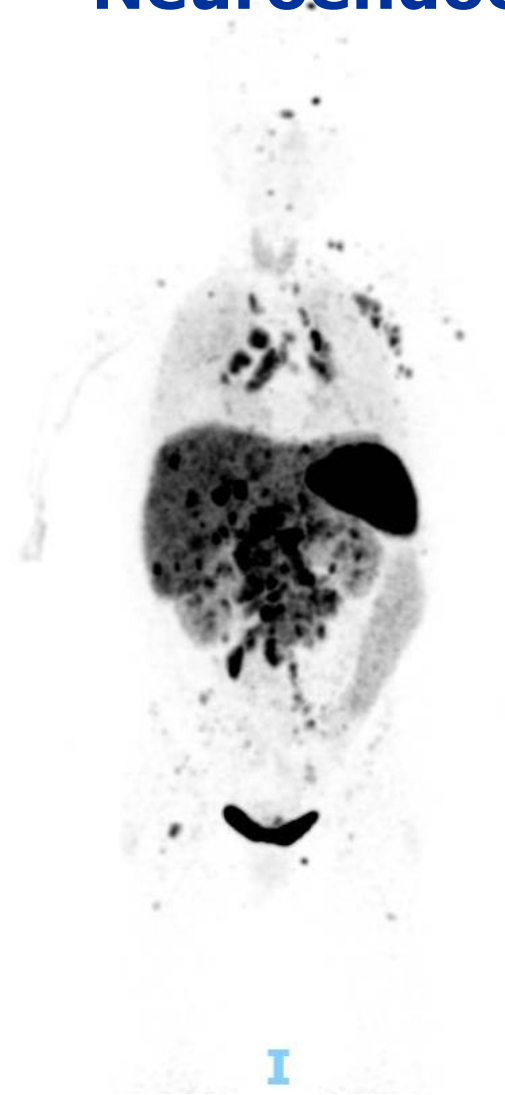
CapTem: SD

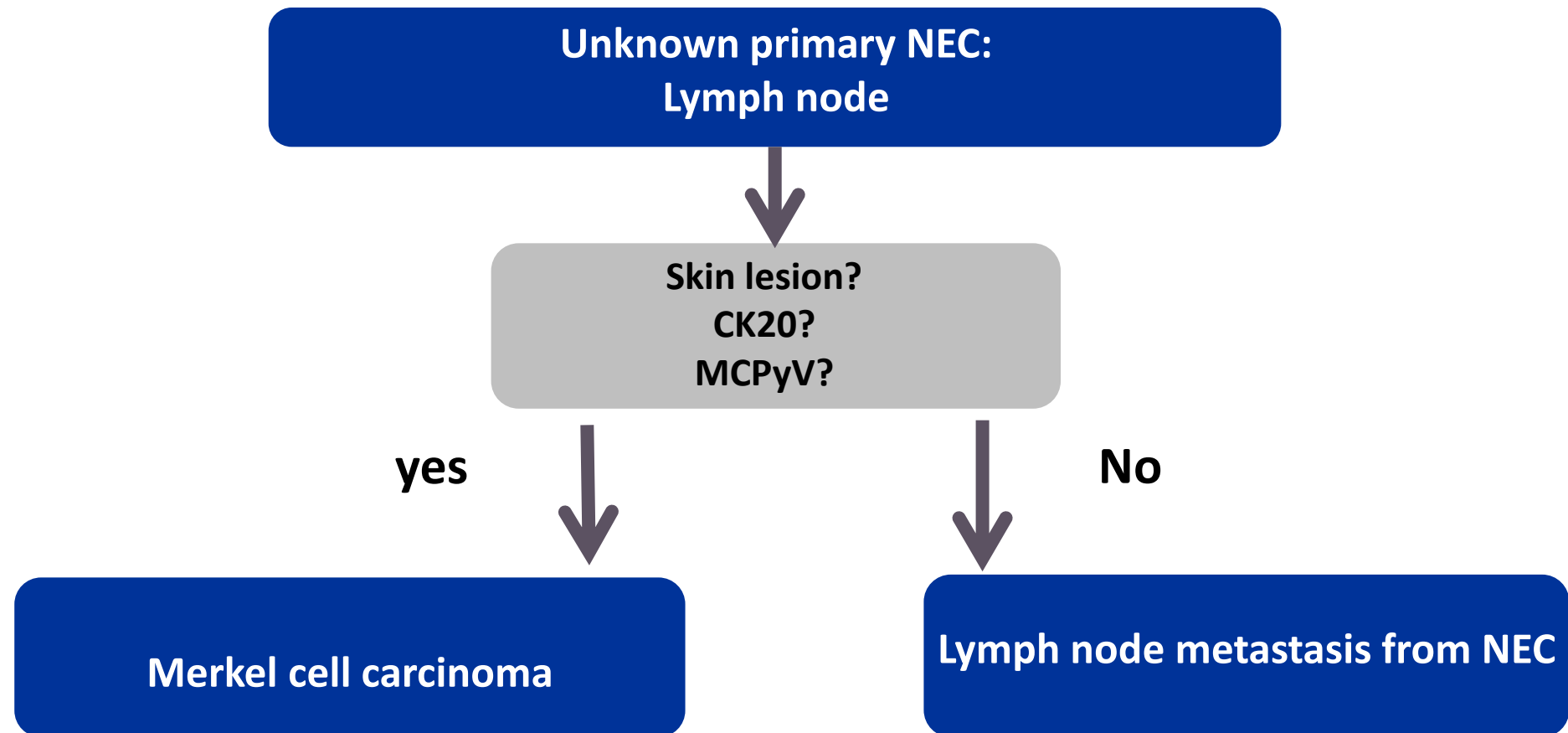
Everolimus: SD

Surufatinib: PR -50%

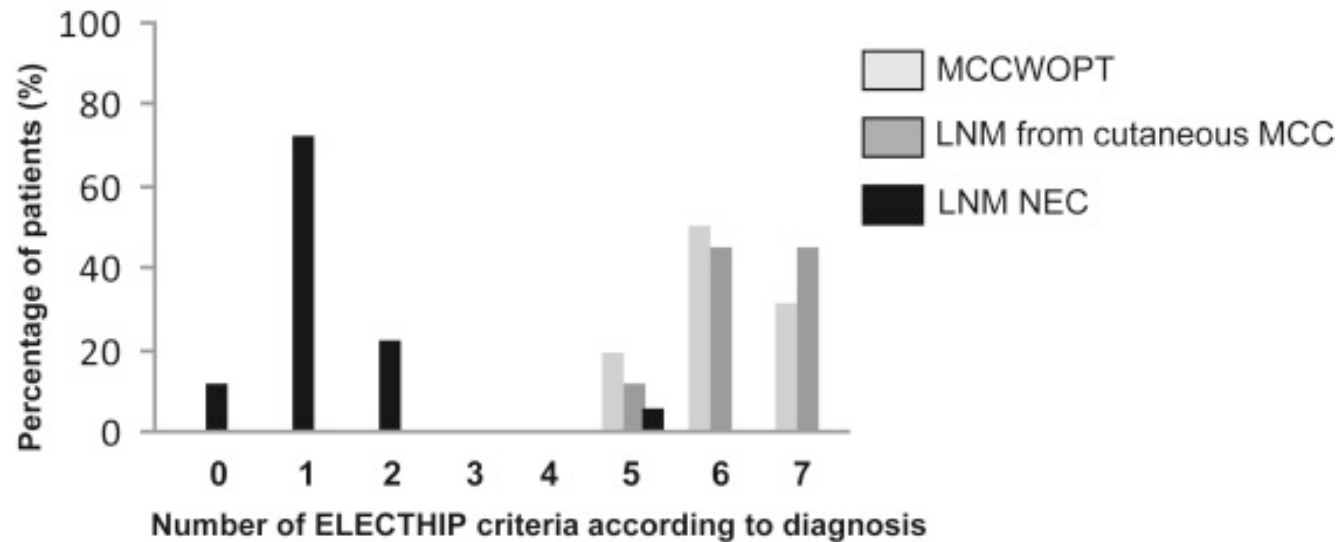
FOLFOX: SD

What is the primary based on responses?





“Lymph node” Neuroendocrine carcinoma of unknown primary



Elderly: ≥ 70 years,
Location: inguinal or parotid,
Extent restricted to the lymph node area,
CK20 positivity,
TTF-1 negativity,
Histologic type: small cell carcinoma,
Polyomavirus detection

Kervarrec et al, Journal Am Ac Dermatol, 2018

Most frequent confusions in NEN management:

Primary location

- PET imaging SSTR +/- DOPA +/- FDG is key in all situation
- Small intestine NETs are often multiple
- Large invasive lesions might be hard to accurately locate
- The main differential diagnosis are: Pheo/PGL & MTC for NET and Merkel cell carcinoma for NEC (skin lesions).
- Immunohistochemistry is not always effective.
- In case of unknown primary: you might be facing an ileal or pancreas or bronchial NET
- Do not miss carcinoid syndrome
- Primary is occult until the complete work-up has been performed

Why primary is important? → to choose which ENETS guidance paper to follow!

Recent ENETS guidance papers

ENETS is in the process of establishing question-based guidance papers, written by experts in the field. The purpose of these guidance papers is to collect the latest development and present comprehensive guidance to all our colleagues, helping them to establish a best-practice solution for their patients in their daily work.

Eight guidance papers, offering comprehensive insights into the management of various neuroendocrine tumours (NETs), have already been published in the Journal of Neuroendocrinology (open access).

We are happy to share with you the eight publications of the series:

- [Management of well-differentiated small intestine neuroendocrine tumours](#) – Published on 8 July 2024
- [Nonfunctioning pancreatic neuroendocrine tumours](#) – Published on 5 October 2023
- [Appendiceal neuroendocrine tumours](#) – Published on 16 August 2023
- [Functioning pancreatic NET syndromes](#) – Published on 20 June 2023
- [Colorectal neuroendocrine tumours](#) – Published on 2 June 2023
- [Gastroduodenal NET G1-G3](#) – Published on 20 May 2023
- [Digestive neuroendocrine carcinoma](#) – Published on 1 March 2023
- [ENETS guidance paper for carcinoid syndrome and carcinoid heart disease](#) published on 25 April 2022

Stay informed with these key updates, reflecting the latest advances in the field of NETs.

<https://www.enets.org/guidelines.html>

NEN management should be done in expert centers: Example of the ENDOCAN network in France



All NET cases are discussed in dedicated Multidisciplinary tumour board

- **Regional MTB of ENDOCAN-RENATEN**
- **National MTB:** RENATEN, once a month
- In association with the French NET group GTE: Groupe d'étude des tumeurs endocrines (GTE)

Site: <https://www.reseau-gte.org/>



NEN management is always a team work!



Julien.hadoux@gustaveroussy.fr



Discussion



Closing comments

Take-home messages

- ✓ Classification has changed many times lately, important to consider
- ✓ All NENs are not CgA positive and a positive NE marker does not always indicate a NEN
- ✓ PET/CT is gold standard in the work-up of NENs
- ✓ SST- and FDG-PET give us different information and may complement each other
- ✓ Choose wisely between CT and MRI for diagnosis and staging
- ✓ Primary is occult until complete work-up is performed

A BIG "Thank You" to

- ✓ Our speakers and moderators
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- ✓ The ENETS Education Group
- ✓ YOU, our valued participants

The ENETS Education Group

- **Simona GLASBERG (Lead)** | Endocrinology | Israel
- **Mairéad McNAMARA (Lead)** | Oncology | United Kingdom
- Eric BAUDIN | Endocrinology | France
- Emanuel CHRIST | Endocrinology | Switzerland
- Timm DENECKE | Radiology | Germany
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- Margot TESSELAAR | Oncology | The Netherlands

ENETS Educational Grants



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NextGEN ENETS Scientific Workshop 2025

- 1 to 3 Oct 2025 in Seville, Spain
- Designed for **early-career physicians and scientists** in the field of neuroendocrine neoplasms.

Application deadline:
20 June 2025

ENETS CoE Preceptorship 2025

- Designed for **young clinicians and researchers** to advance their expertise in NET patient management at an ENETS Center of Excellence.

Application deadline:
1 August 2025

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