TNE pancréatiques et du grêle

Quand faire une TEP-DOTATOC ou FDG ou F-DOPA ?

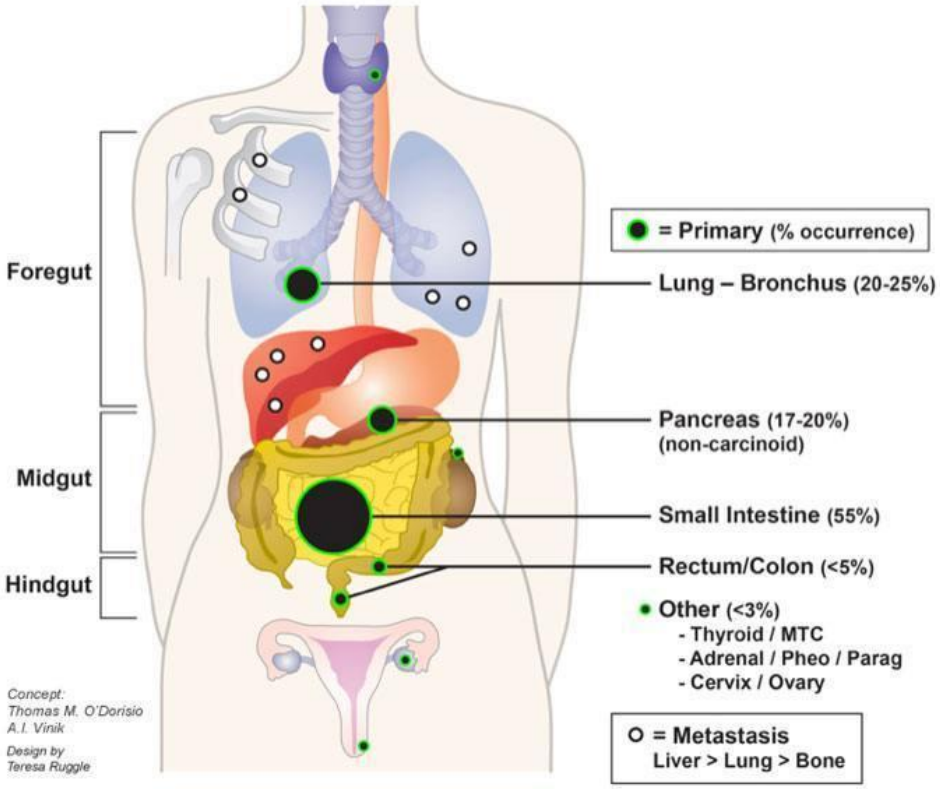
Elif Hindié
Médecine nucléaire – CHU de Bordeaux

J'associe ma collègue le Dr. Ghoufrane Tlili à cette présentation

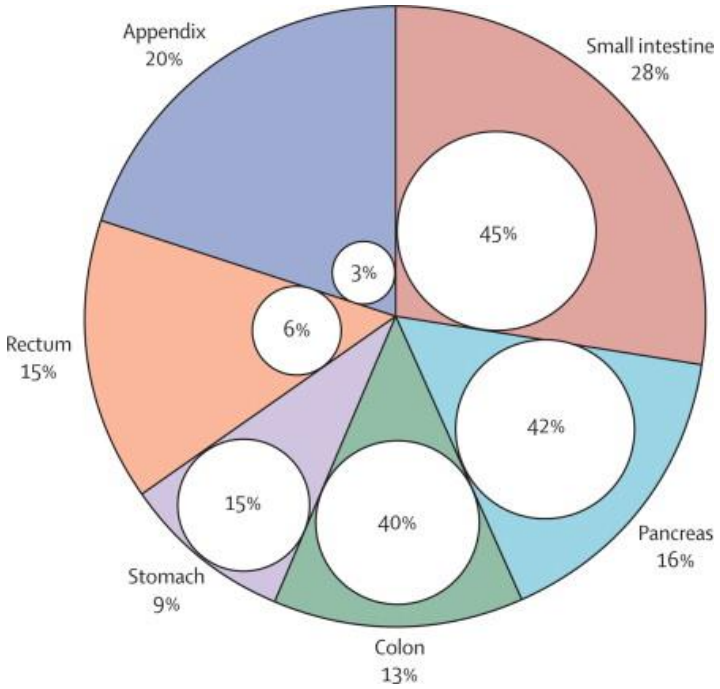
4 Mars 2022

1ère Journée Régionale RENATEN-Nouvelle Aquitaine

TNE : distribution des sites primitifs



TNE - GEP : Répartition par site
et Probabilité de métastases hépatiques



Frilling A, et al; Lancet Oncol. 2014 ;15:e8-21.

TNE – GEP : Diversité des sites, diversité du potentiel métastatique, diversité pronostique.

J'évoquerai surtout les TNE bien différenciées

1ST STEP: ENDOSCOPIC DIAGNOSIS, CONVENTIONAL IMAGING (CI)

EANM Focus3 -2020

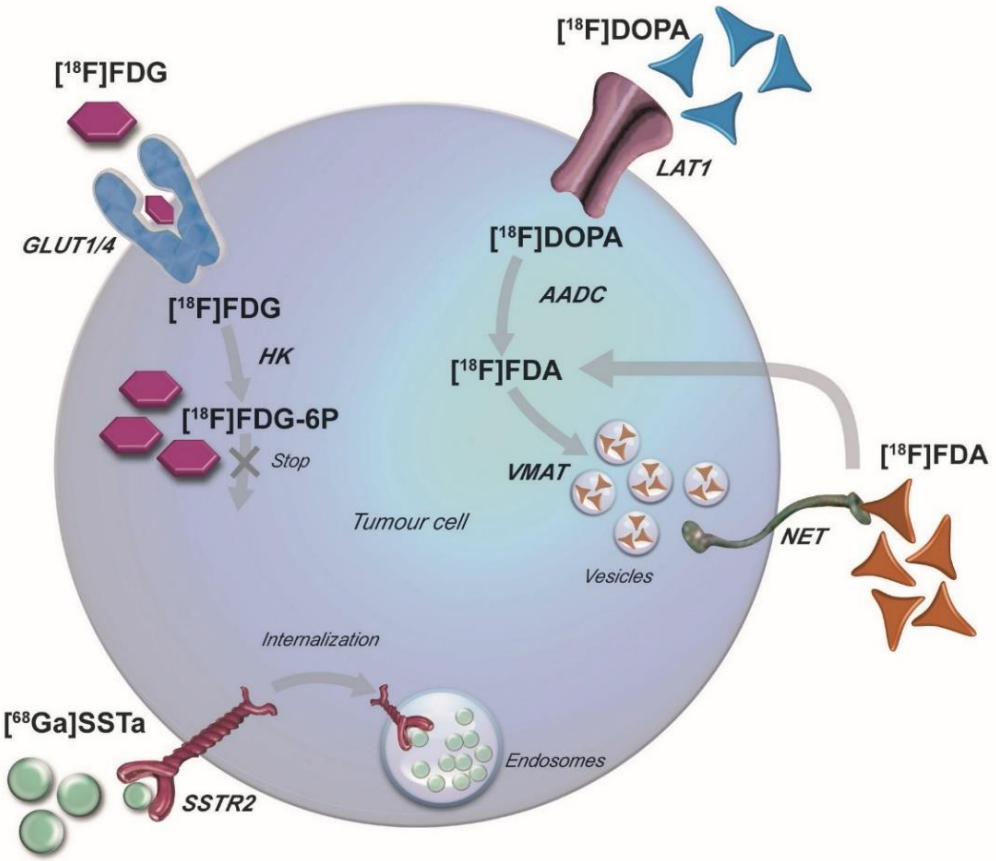
	Primary	Loco-regional	Distant
Pancreas	CT, MRI, endoscopy (EUS)	CT/MRI	CT, MRI for liver, bone (selected cases) and brain (selected cases)
Small intestine	CT (CT enteroclysis) DB enteroscopy (unknown primary)	CT	
Duodenum	EUS, duodenoscopy	CT	
Colon	Colonoscopy, CT	CT	
Rectum	Rectoscopy, EUS, CT		
Bronchial	Bronchoscopy, CT	CT	
MTC	Neck US	Neck US, CT	

CT: Triple phase CE-CT

Principaux traceurs TEP : Mécanismes de captage et de rétention

Taïeb D, Neumann H, Rubello D, Al-Nahhas A, Guillet B, Hindié E.

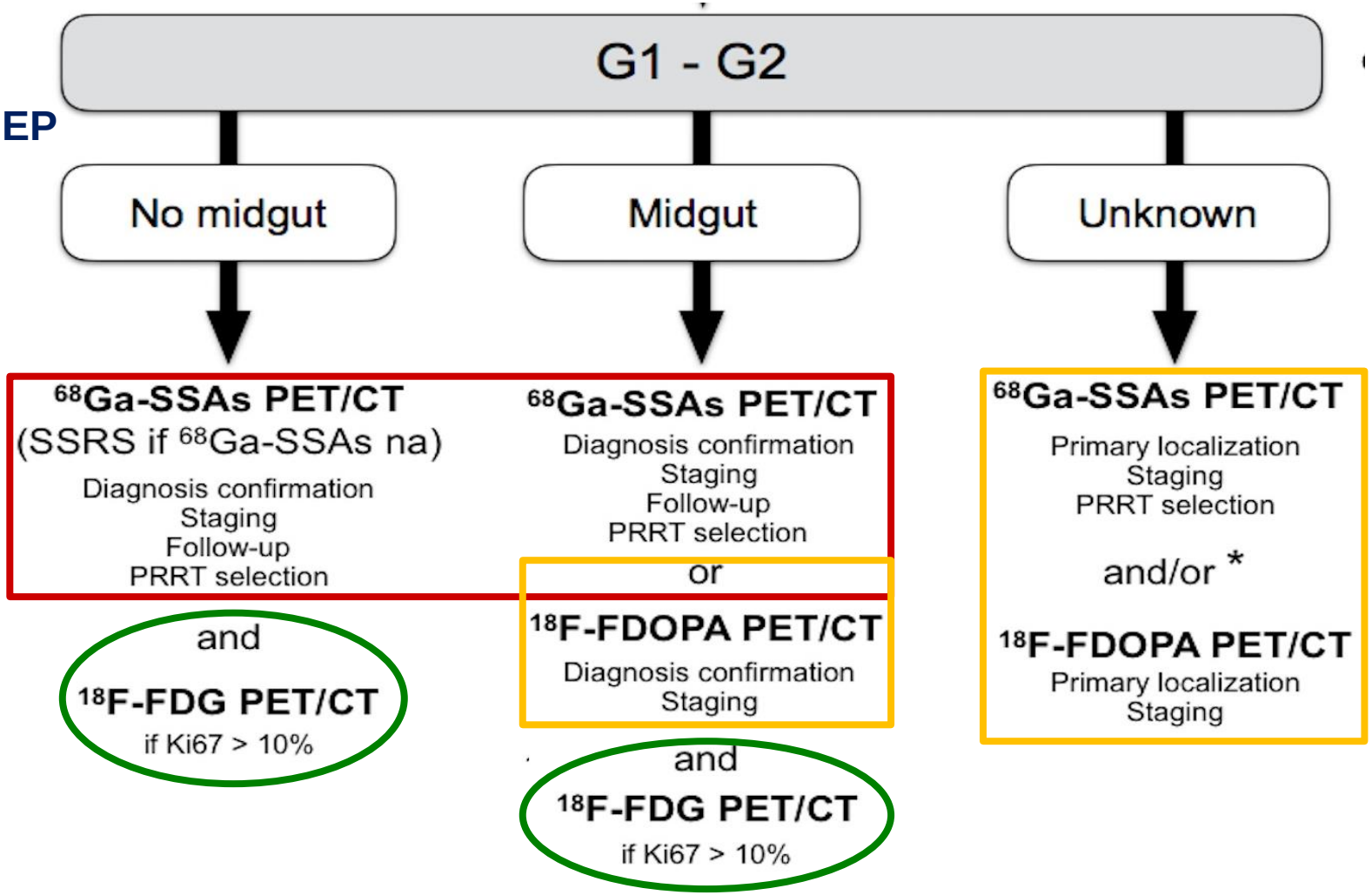
J Nucl Med. 2012;53:264-74.



J'évoquerai également quelques traceurs du futur

Beaucoup de guidelines sur le sujet, parfois avec des divergences (ENETS, EANM, NANETS, SNMMI, ATA, ESMO). **Pas de consensus ferme : je donnerai un point de vue personnel.**

TNE - GEP



Molecular Imaging of Gastroenteropancreatic Neuroendocrine Tumors: Current Status and Future Directions.

Deroose CM, Hindié E, Kebebew E, Goichot B, Pacak K, Taïeb D, Imperiale A.

J Nucl Med. 2016; 57:1949-1956

PATIENTS WITH AN UNKNOWN PRIMARY AND METASTATIC DISEASE (LIVER) ON CT

(EANM-Focus3 – 2020)

PET using specific tracer is recommended to detect an occult primary tumour: all consensus

Midgut is the most common location in this setting

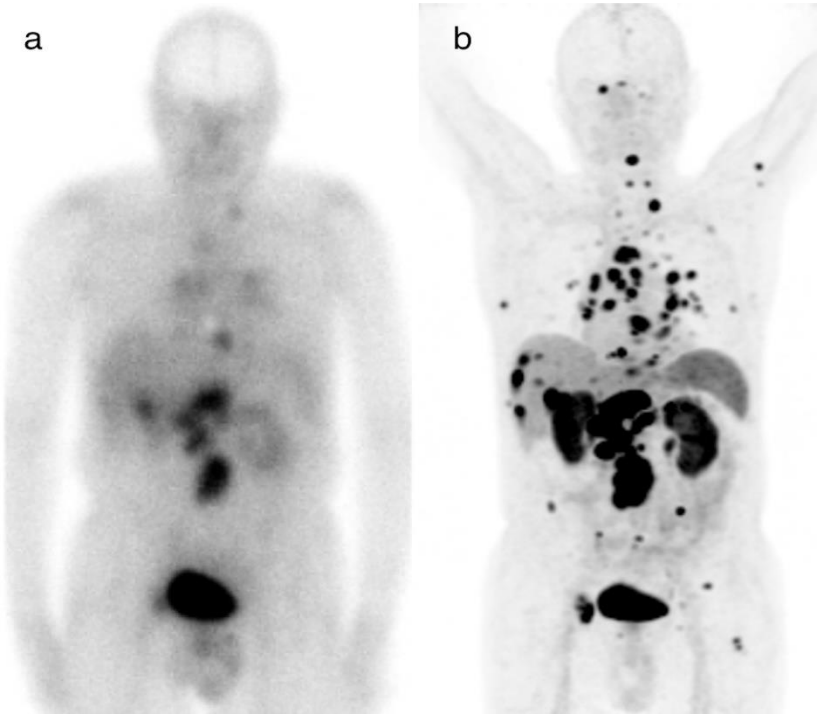
The site of origin of NET can be oriented by secretion profile, CI findings, IHC (CDX2: small bowel, PAX6/PAX8 or Islet 1: pancreas, TTF-1: lung or MTC) or genetic (somatic *RET* mutation: MTC) studies performed on metastatic tissue

Detection of the primary can lead to resection in selected cases or influence choice of systemic therapies and protocol selection

Consensus on molecular imaging and theranostics in neuroendocrine neoplasms.
Ambrosini V, et al. Eur J Cancer. 2021;146:56-73.

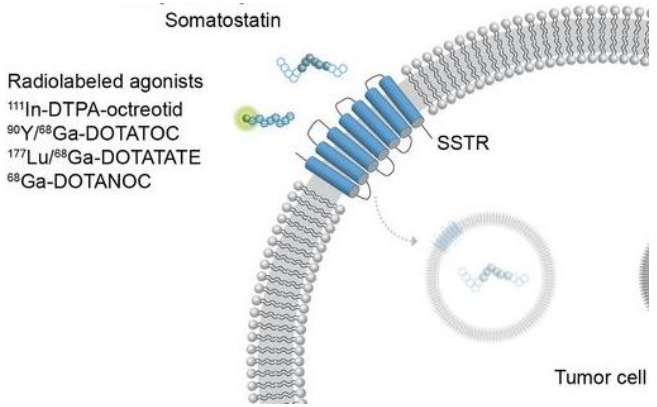
Imagerie des TNE par ciblage des Récepteurs de la Somatostatine

TNE métastatique



^{111}In-Octreoscan
Scintigraphie

^{68}Ga-DOTATATE
TEP-TDM



Analogue de la somatostatine + Chélate + Radionucléide

Une rationalisation du nombre de traceurs passe tout d'abord par une substitution complète des examens ^{111}In-Octreoscan par le ^{68}Ga-DOTATOC *(ou ^{68}Ga-DOTATATE)*

Molecular Imaging of Gastroenteropancreatic Neuroendocrine Tumors: Current Status and Future Directions.
Deroose CM, Hindié E, Kebebew E, Goichot B, Pacak K, Taïeb D, Imperiale A.
J Nucl Med. 2016; 57:1949-1956

It is likely that SSR-PET will prove to be a more accurate than SRS for selection for PRRT, although **criteria** for positive disease have yet to be developed on PET: JOINT CONSENSUS EANM 2020

The value of ^{68}Ga-SSA is dependent on embryological origin of the NET (can fails in insulinoma, hindgut NET, thymic NET and MTC) (EANM Bozkurt 2017)

The Nuclear physicians should be aware of false positive findings and caveats.

FALSE POSITIVE FINDINGS ON ^{68}Ga-SSA PET

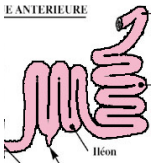
(EANM-Focus3 – 2020)

Uncinate process (PP cells density)
Duodenal heterotopic pancreatic tissue
Accessory spleen (pancreatic tail), splenosis
Pancreatic serous cystadenoma
Bone haemangioma (vertebral), enchondroma, fibrous dysplasia
Active chronic inflammation (e.g., sarcoidosis, tuberculosis, Hashimoto's thyroiditis)
Others SSR-expressing tumors (e.g., meningioma, breast cancer, renal cancer, lymphoma, thyroid neoplasms)

Interprétation délicate également dans les maladies héréditaires avec plusieurs tumeurs de natures différentes comme dans les NEM1, VHL,…

Midgut : ^{18}F-Dopa vs ^{68}Ga-SR-TEP

MIDGUT



- ✓ Jéjunum
- ✓ **Iléon**
- ✓ Appendice
- ✓ Colon droit

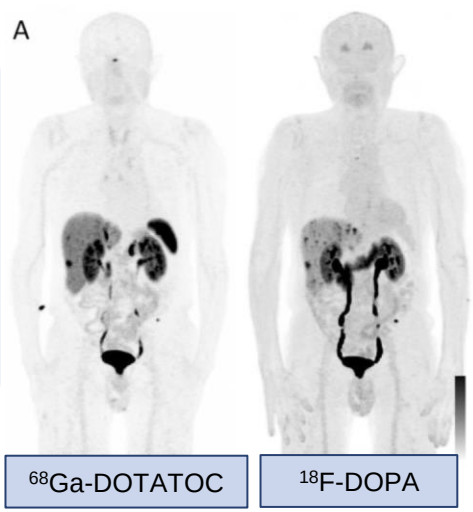
➢ Quelques résultats récents d'équipes Françaises

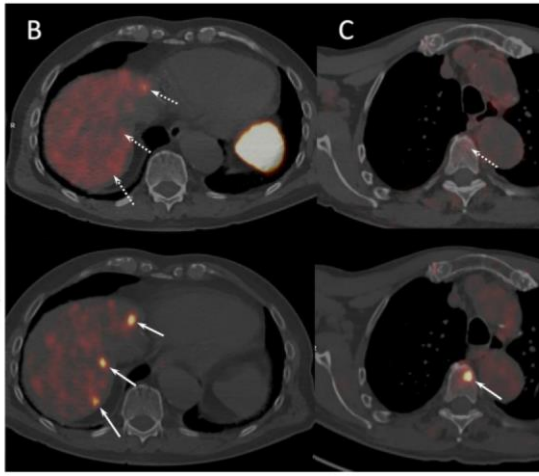
Intraindividual comparison of ^{18}F-FDOPA and ^{68}Ga-DOTATOC PET/CT detection rate for metastatic assessment in patients with ileal neuroendocrine tumours.

Ouvrard E, Chevalier E, Addeo P, Sahakian N, Detour J, Goichot B, Bachellier P, Karcher G, Taïeb D, Imperiale A.

Clin Endocrinol (Oxf). 2021; 94: 66-73.

- Strasbourg/Nancy/Marseille
- 41 TNE iléales (analyse retrospective)
- Pas de différence par patient (sensibilité 97% pour les 2 traceurs)
- Pas de différence par région (F-DOPA 94%, DOTATOC 88%, P=.35)
- F-DOPA > DOTATOC par lésion (96% vs 80%; P < .001)





^{18}F-Dopa > ^{68}Ga-DOTATOC en analyse par Lésions

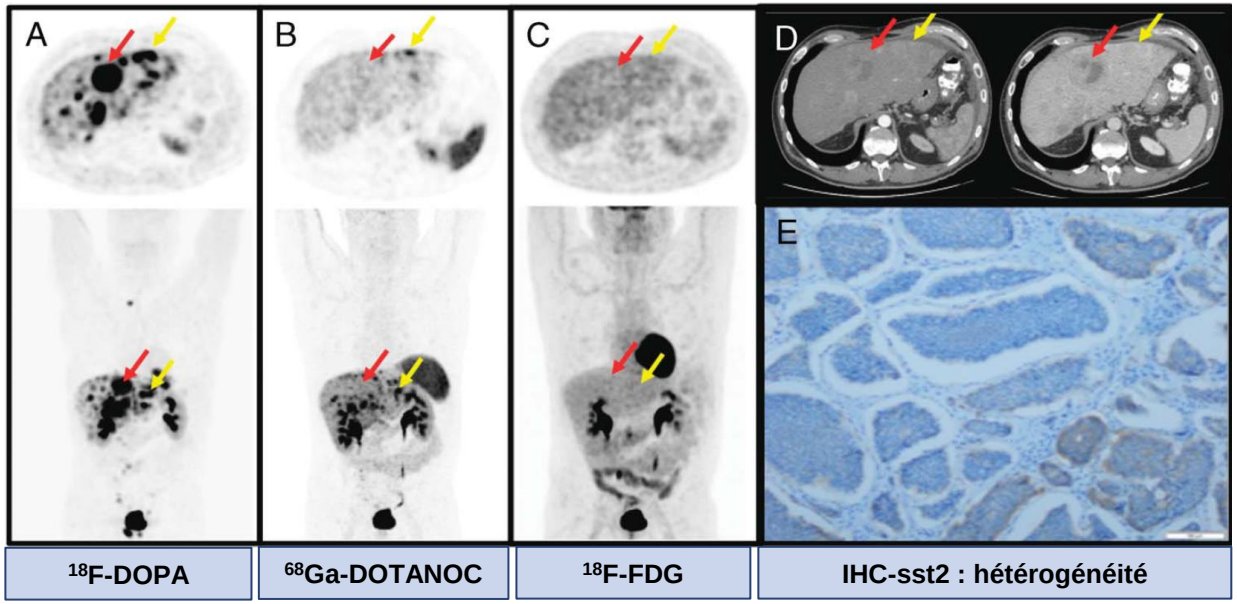
Region	[^{18}F]FDOPA	[68Ga]DOTATOC	Nb of lesions	*p*
Liver	267 (99)	214 (80)	269	**< 0.001**
Peritoneum	110 (90)	94 (77)	122	**0.011**
Abdominal LN	141 (99)	126 (88)	143	**< 0.001**
Left sup-clavicular LN	2 (67)	3 (100)	3	0.317
Supra-diaphragmatic	22 (100)	17 (77)	22	**0.025**
Bone	38 (83)	29 (63)	46	0.072
All	580 (96)	483 (80)	605	**< 0.001**

Head-to-Head Comparison of 18F-DOPA PET/CT and 68Ga-DOTANOC PET/CT in Patients With Midgut Neuroendocrine Tumors

Ansquer C, et al. Clin Nucl Med. 2021; 46:181-186.

- Etude rétrospective Nantaise
- 30 patients TNE midgut
- Examens positifs
  (F-DOPA 27 ; DOTANOC 25)
- Sensibilité par région (n = 81)
  (F-DOPA 95% vs DOTANOC 88% P<0.0001)
- F-DOPA > DOTATOC par lésion
  (F-DOPA 96% vs DOTANOC 88% P<0.0001)

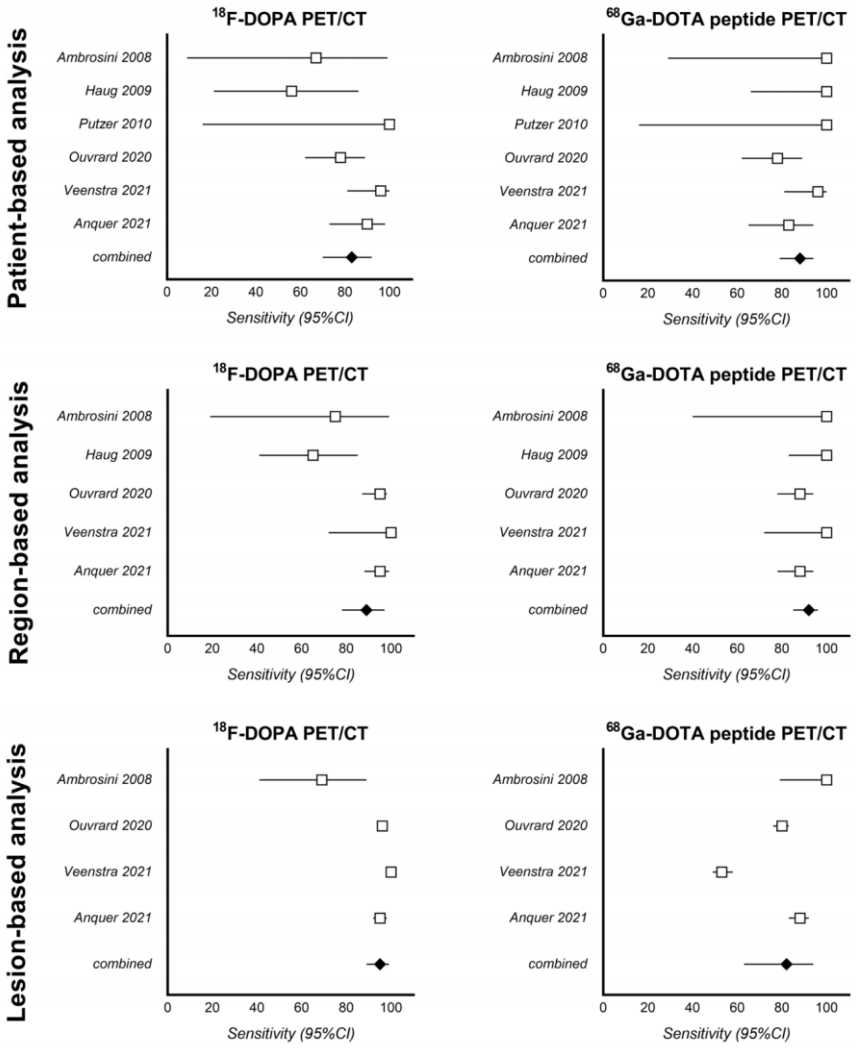
Well-differentiated grade 1, midgut NET



Head-to-head comparison between 18 F-DOPA PET/CT and 68 Ga-DOTA peptides PET/CT in detecting intestinal neuroendocrine tumours: A systematic review and meta-analysis.

Piccardo A, et al. Clin Endocrinol (Oxf). 2021 Oct;95(4):595-605.

- 6 articles published between 2008-21.
- Included 112 intestinal NETs patients.
- Sensitivity in terms of patient-based analysis (PBA), region-based analysis (RBA) and lesion-based analysis (LBA)
- The pooled sensitivity of 18F-DOPA PET/CT was 83%, 89% and 95% on PBA, RBA and LBA, respectively.
- 68Ga-DOTA peptides PET/CT showed sensitivity of 88%, 92% and 82% on PBA, RBA and LBA, respectively.
- **No significant differences were found between tracers on PBA and RBA. By contrast, a clear trend towards significance in favour of 18 F-DOPA PET/CT was identified on LBA.**
- The use of 18 F-DOPA PET/CT could be considered as a first-line molecular procedure in intestinal NETs.



Principles of Surgical Management of Small Intestinal NET.

Pasquer A, Walter T, Milot L, Hervieu V, Poncet G.
Cancers (Basel). 2021; 13:5473.

- Small-intestinal neuroendocrine tumors (siNETs) account for 25% of gastroenteropancreatic NETs.
- Multiple siNETs appear to develop in a limited segment of the small bowel (SB), 89% of them being located in the ileum, most often within 100 cm of the ileocecal valve (ICV).
- **All localized siNETs should be considered for radical surgical resection with adequate lymphadenectomy irrespective of the absence of lymphadenopathy or mesenteric involvement.**
- Morphological evaluation should include a CT scan including a thin-slice arterial CT, a PET/CT with 68 Ga, and a hepatic MRI in cases of suspected metastasis.

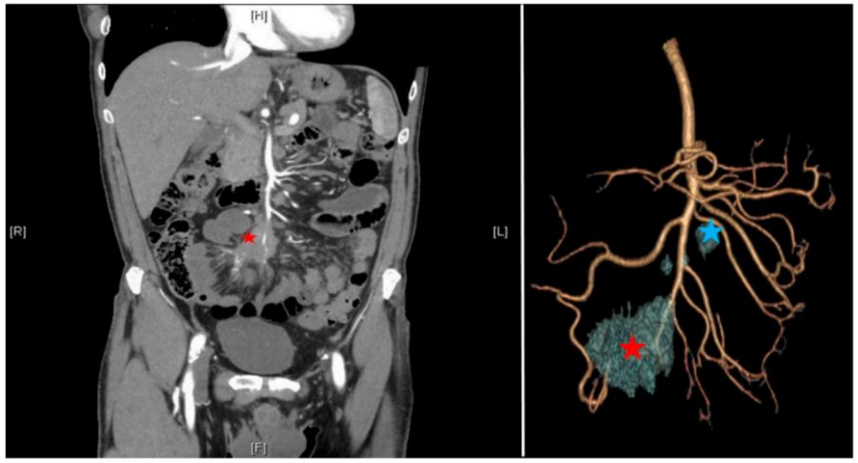
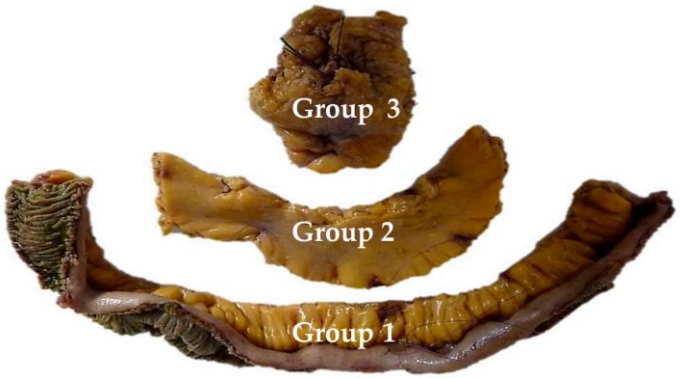


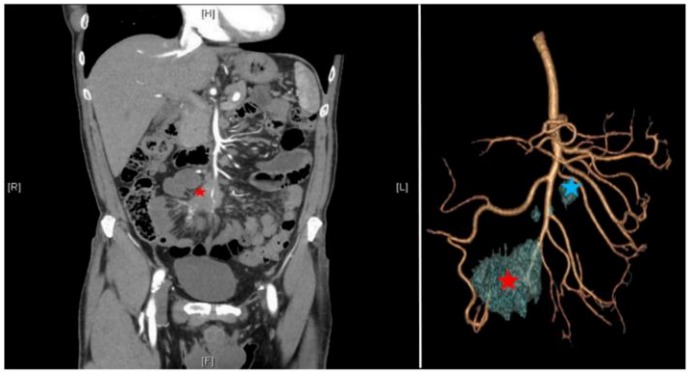
Figure 2. CT scan with arterial three-dimensional reconstruction; mesenteric mass (red star); proximal nodes (group 3 down from Deguelte et al. [13] in blue star).

Lymphadenectomy during Small Bowel Neuroendocrine Tumor Surgery: The Concept of Skip Metastases.

Pasquer A, Walter T, Rousset P, Hervieu V, Forestier J, Lombard-Bohas C, Poncet G.
Ann Surg Oncol. 2016; 23(Suppl 5):804-808.

- The resection and pathological analysis of LNs were standardized using three groups (group 1, along the small intestine; group 2, along the mesenteric vessel; and group 3, retropancreatic and mesenteric vessel origin).
- 20 patients with LNs involved:
  - 8 (38 %) in group 1,
  - 13 (62 %) in group 2, and
  - 12 (57 %) in group 3.
- **Skip metastases were found in 14 patients (67%): 4 (19%) with an invasion pattern of group 3+ without group 2+, and 12 (57%) with an invasion pattern of group 2+ or group 3+ without group 1+.**
- **Conclusion:** As a result of skip metastases, systematic, extensive LN resection in retropancreatic portion may be required to prevent unresectable locoregional recurrence.





Quand utiliser la 18F-DOPA ?

"analyse personnelle"

- Malgré le caractère rétrospectif (avec limites concernant les circonstances qui ont amené à prescrire les examens, la preuve histologique des lésions détectées, l'impact sur la prise en charge), ces études montrent une supériorité de la ^{18}F-DOPA en analyse par lésion.

- Une TEP ^{18}F-FDOPA me semble utile pour un bilan exhaustif, à chaque fois qu'il y a une sanction chirurgicale ; et dans la recherche d'un primitif grêlique.

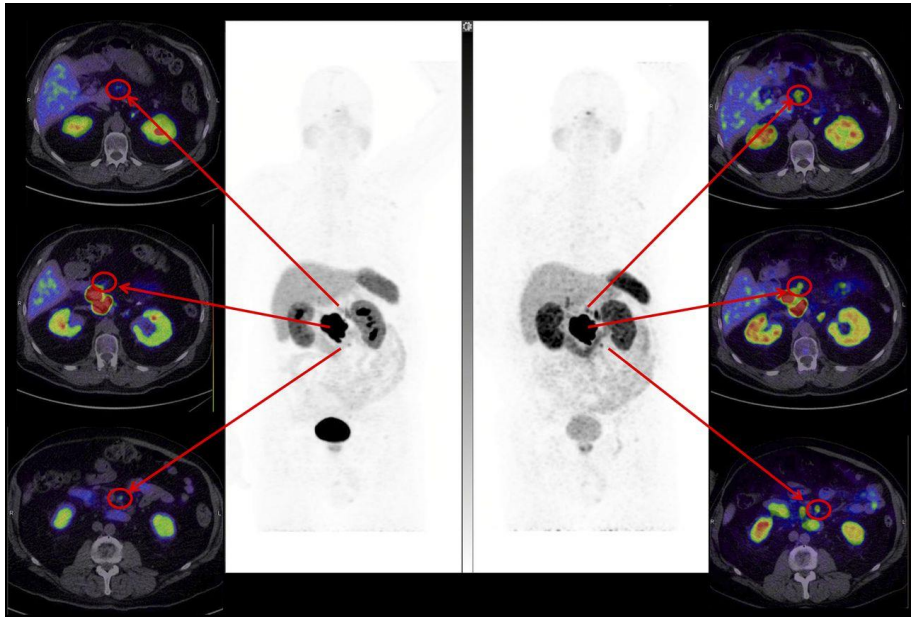
- Chez les patients multi-métastatiques, l'utilisation du ^{68}Ga-DOTATOC seul me parait raisonnable pour réduire les coûts.

- ^{18}F-FDOPA à ^{68}Ga-DOTATOC n'étant pas comparables, une homogénéité des examens au cours du suivi est souhaitable ; éviter le risque de pseudo-progression.

- Une TEP ^{18}F-FDOPA ne me semble pas nécessaire pour affiner la sélection avant tt par ^{177}Lu-DOTATATE des TNE midgut (sélection par TEP ^{68}Ga-DOTATOC +/- FDG)

Traceurs sst2 du futur ?

^{64}Cu-DOTATATE et ^{64}Cu-SARTATE une alternative à la plateforme ^{68}Ga

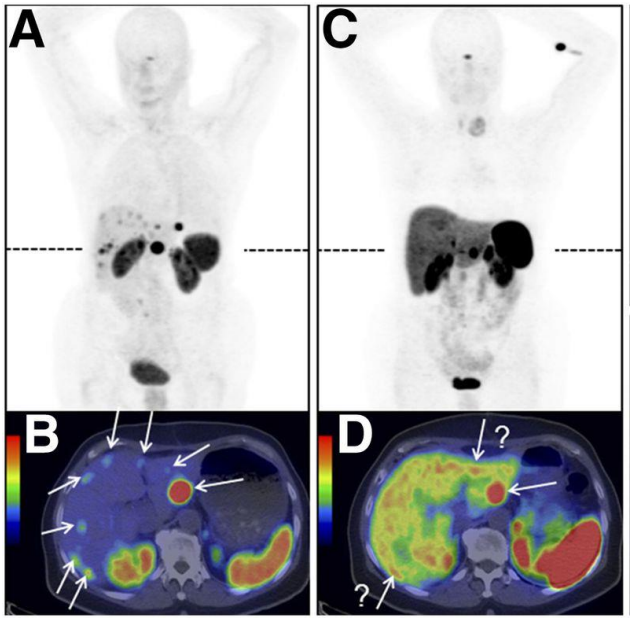


High lesion contrast on ^{64}Cu-SARTATE at 4 h (right) better defines regional nodal disease than ^{68}Ga-DOTATATE at 1 h (left) in patient with large pancreatic primary tumor.

[^{64}Cu-SARTATE PET Imaging of Patients with Neuroendocrine Tumors Demonstrates High Tumor Uptake and Retention, Potentially Allowing Prospective Dosimetry for Peptide Receptor Radionuclide Therapy.]

Hicks RJ, et al. Nucl Med. 2019;60:777-85.

Les analogues antagonistes de sst2 comme le ^{68}Ga-NODAGA-JR11

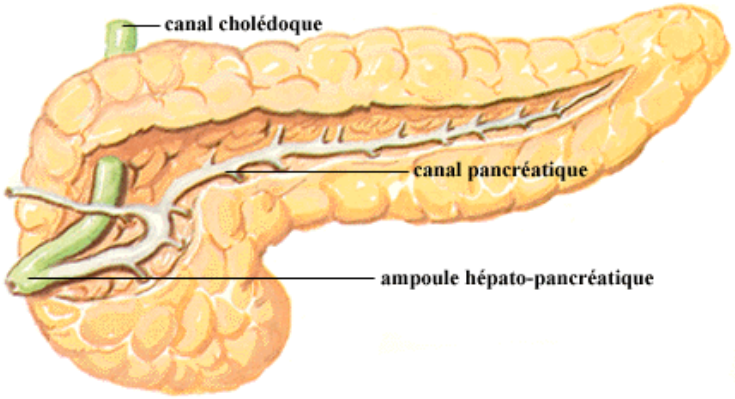


Patient with ileal NET and liver metastases: ^{68}Ga-OPS202 PET/CT (A and B), ^{68}Ga-DOTATOC PET/CT (C and D). Background activity was lower with ^{68}Ga-OPS202.

[Sensitivity Comparison of ^{68}Ga-OPS202 and ^{68}Ga-DOTATOC PET/CT in Patients with Gastroenteropancreatic Neuroendocrine Tumors: A Prospective Phase II Imaging Study.]

Nicolas GP, et al. J Nucl Med. 2018;59:915-21.

TNE-GEP bien différenciées non Midgut



^{68}Ga-SSA >>^{18}F-DOPA

Exception insulinome bénin : TEP ^{68}Ga-exendine > ^{68}Ga-SSA ≈ ^{18}F-DOPA

NB: 18F-DOPA avec carbidopa et acquisition précoce (Imperiale et al. EJNMMI 2015)

Insulinome : TEP ^{68}Ga-exendine

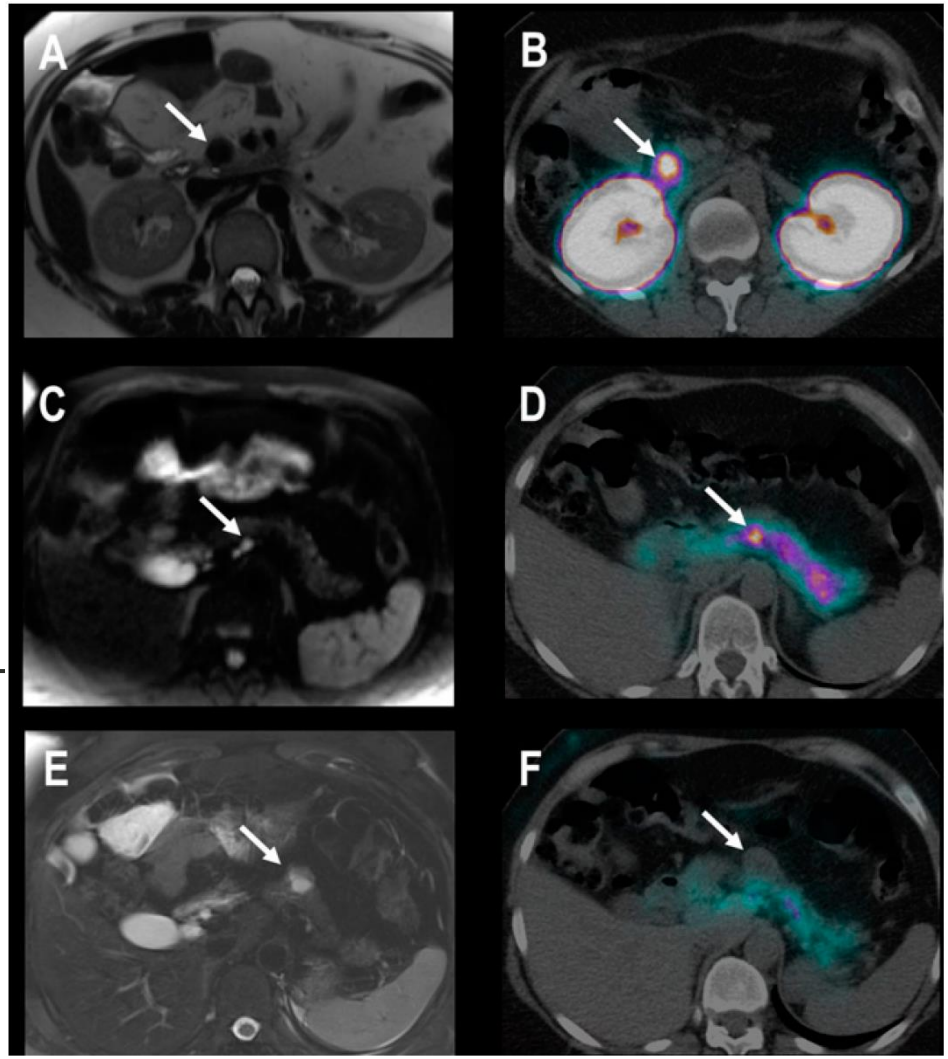
Ciblant les récepteurs de GLP-1

Importance toute particulière chez les patients NEM-1 pour différencier l' insulinome des autres TNE concomitantes

68Ga-Exendin-4 PET/CT Detects Insulinomas in Patients With Endogenous Hyperinsulinemic Hypoglycemia in MEN-1.

Antwi K, et al.

J Clin Endocrinol Metab. 2019;104:5843-52.



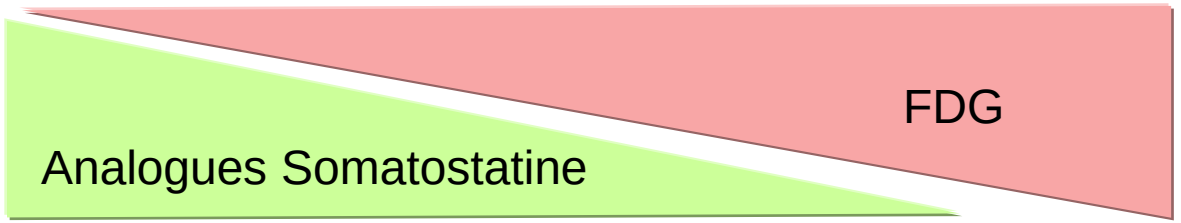
N.B. ^{68}Ga-SSA PET plus sensible que ^{68}Ga-exendin-4 pour insulinome malin

L’ imagerie métabolique au 18FDG en tant qu’indice pronostique

Classification OMS 2019 et présentation scintigraphique des TNE-GEP

Grade	Tumeurs NE G1	Tumeurs NE G2	Tumeurs NE G3a	Carcinomes NE G3b
Indice mitotique (pour 10 CFG)	< 2	2-20	> 20	
Indice de prolifération Ki67 (%)	< 3	3- 20	> 20	souvent >55%
Différentiation	……..bien différenciées……			**peu différenciées** (à grandes ou petites cellules)
Evolution	lente →			rapide/mauvais pronostic

Présentation scintigraphique



Faut-il étendre l’utilisation de la TEP-FDG à l’ensemble des TNE digestives G1/G2 métastatiques avant prise en charge?

^{18}F-FDG PET is Superior to WHO Grading as a Prognostic Tool in Neuroendocrine Neoplasms and Useful in Guiding PRRT: A Prospective 10-Year Follow-up Study.

Binderup T, et al.

J Nucl Med. 2021; 62: 808-15.

- Prospective cohort study evaluating the prognostic value of 18F-FDG PET imaging and histologic grading.

- 166 patients of all grades and with histologically confirmed NENs of gastroenteropancreatic origin.
- The primary endpoint was overall survival (OS).
- In addition, OS in relation to peptide receptor radionuclide therapy was analyzed as an exploratory endpoint.

^{18}F-FDG PET is Superior to WHO Grading as a Prognostic Tool in Neuroendocrine Neoplasms and Useful in Guiding PRRT: A Prospective 10-Year Follow-up Study.

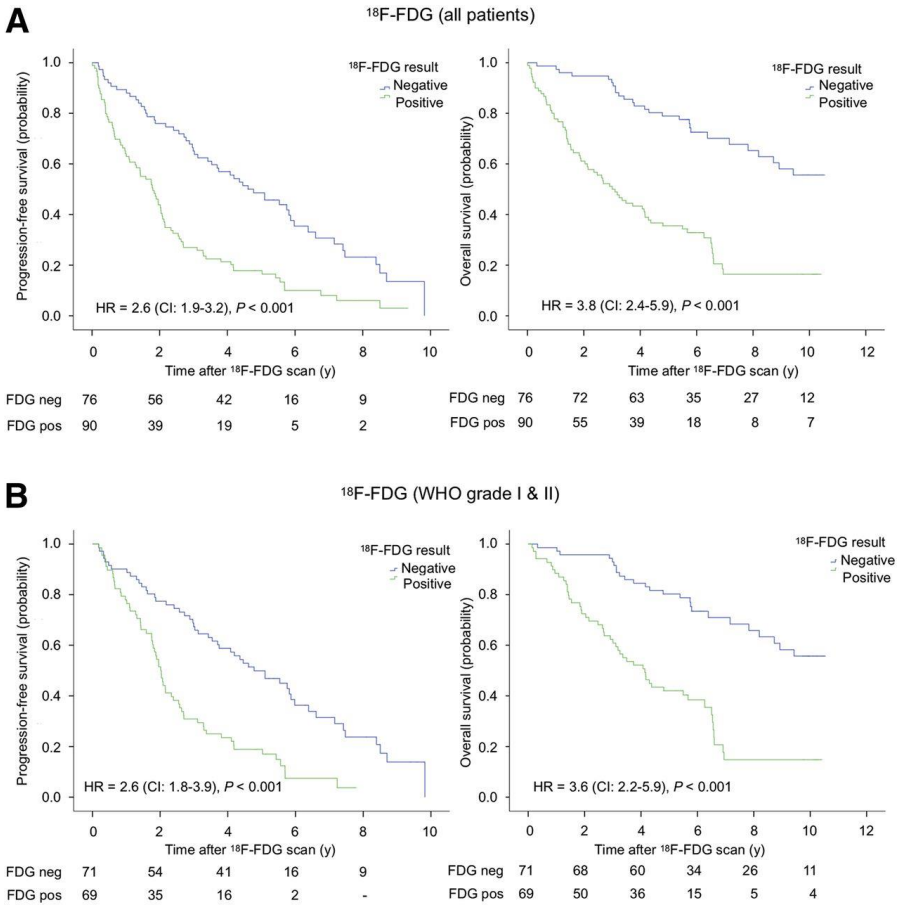
Binderup T, et al. J Nucl Med. 2021; 62: 808-15.

- In the whole cohort, a positive 18F-FDG PET scan was associated with a shorter OS (hazard ratio: 3.8; 95% CI: 2.4-5.9; P < 0.001).
- In multivariate analysis, 18F-FDG PET, G3 tumor, ≥2 liver metastases, and ≥2 prior therapies were independent prognostic factors for OS.
- **In G1 and G2 patients (n = 140), a positive 18F-FDG PET scan was the only identifier of high risk for death (hazard ratio: 3.6; 95% CI, 2.2-5.9; P < 0.001).**

- For patients receiving PRRT, 18F-FDG-negative cases had a significantly longer survival than 18F-FDG-positive cases, whereas no difference was identified for tumor grading.
- **18F-FDG-positive patients receiving PRRT had a significantly longer median survival than patients not receiving PRRT (4.4 vs. 1.4 y, P = 0.001), whereas no difference was seen for 18F-FDG-negative patients.**

^{18}F-FDG PET is Superior to WHO Grading as a Prognostic Tool in Neuroendocrine Neoplasms and Useful in Guiding PRRT: A Prospective 10-Year Follow-up Study.

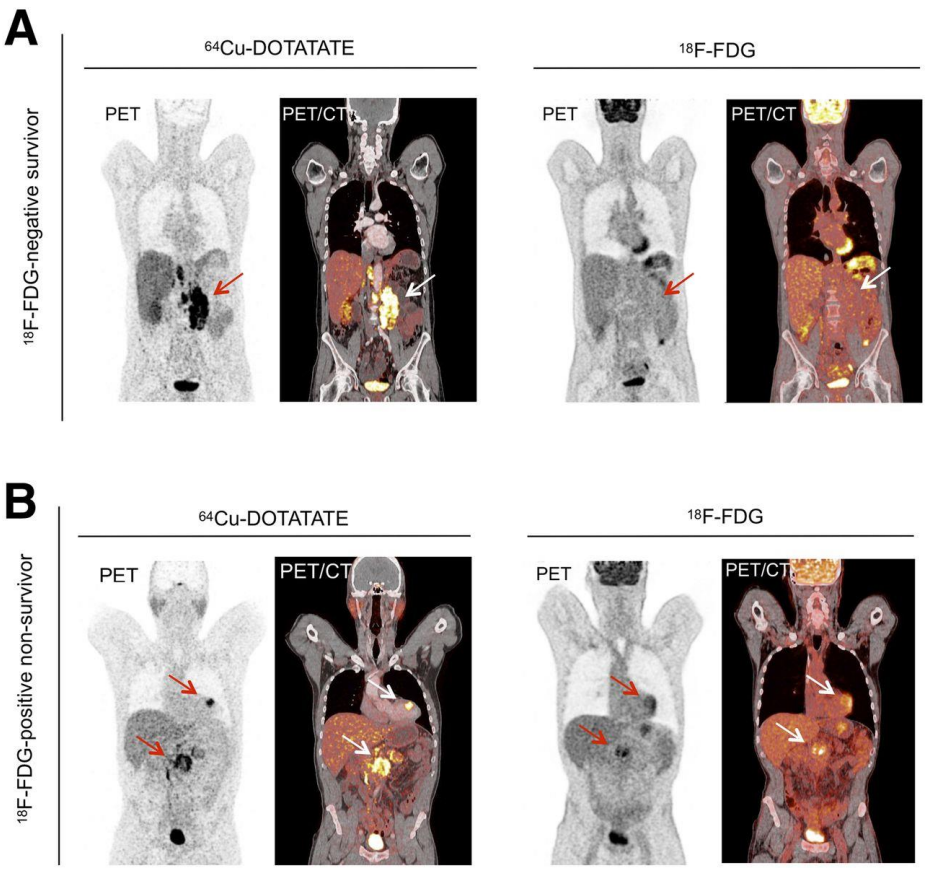
Binderup T, et al. J Nucl Med. 2021; 62: 808-15.



- Risk stratification of NEN patients based on 18F-FDG PET results. PFS (A and B, left) and OS (A and B, right) are shown for all patients (A) and G1 and G2 patients (B).

^{18}F-FDG PET is Superior to WHO Grading as a Prognostic Tool in Neuroendocrine Neoplasms and Useful in Guiding PRRT: A Prospective 10-Year Follow-up Study.

Binderup T, et al. J Nucl Med. 2021; 62: 808-15.



Examples of 18F-FDG PET and somatostatin receptor imaging results:

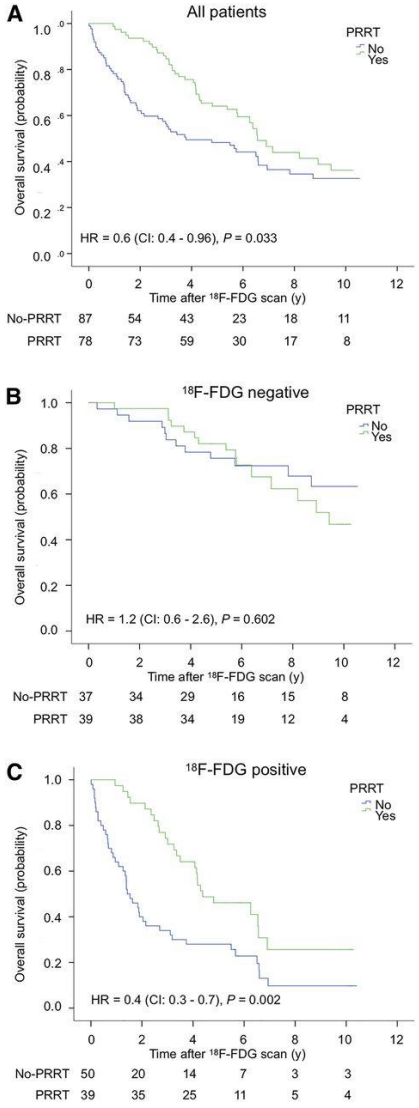
- (A) Patient with G2 NEN tumor, Ki-67 index of 14%, a positive 64Cu-DOTATATE reading (left), and a negative 18F-FDG PET reading (right), and alive at the end of follow-up (73 mo after 18F-FDG PET scan).
- (B) Patient with G2 NEN, Ki-67 index of 5%, a positive 64Cu-DOTATATE reading (left), a positive 18F-FDG PET reading (right), and dead 18 mo after 18F-FDG PET scan.

^{18}F-FDG PET is Superior to WHO Grading as a Prognostic Tool in Neuroendocrine Neoplasms and Useful in Guiding PRRT: A Prospective 10-Year Follow-up Study.

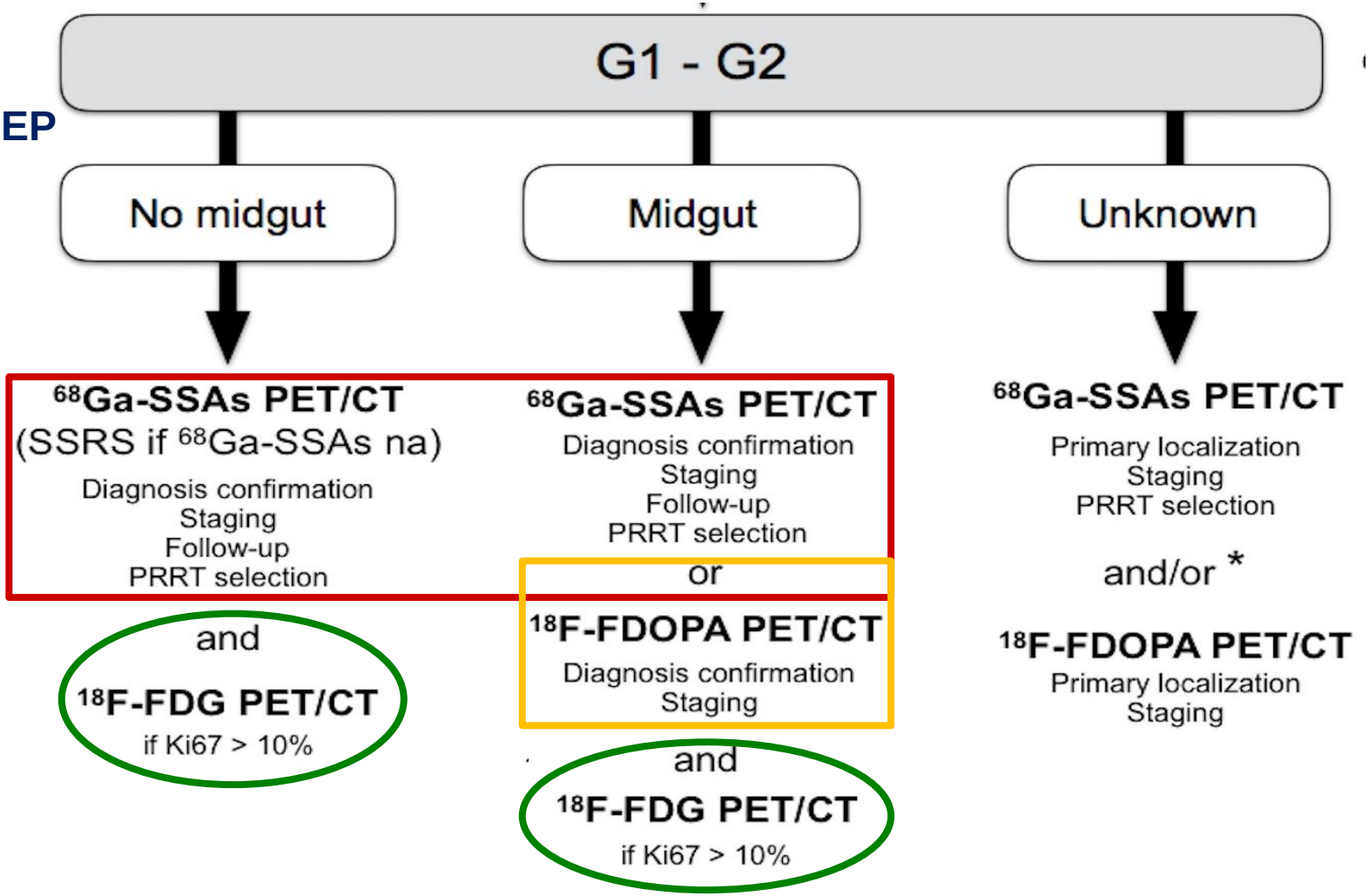
Binderup T, et al. J Nucl Med. 2021; 62: 808-15.

Kaplan–Meier curves for patients receiving PRRT vs. patients not receiving PRRT.

All patients enrolled in the study (A), 18F-FDG–negative patients (B), and 18F-FDG–positive patients (C) stratified by PRRT status.



TNE - GEP



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Merci pour votre attention!