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Approches Théranostiques au-delà du 177Lu-DOTATATE

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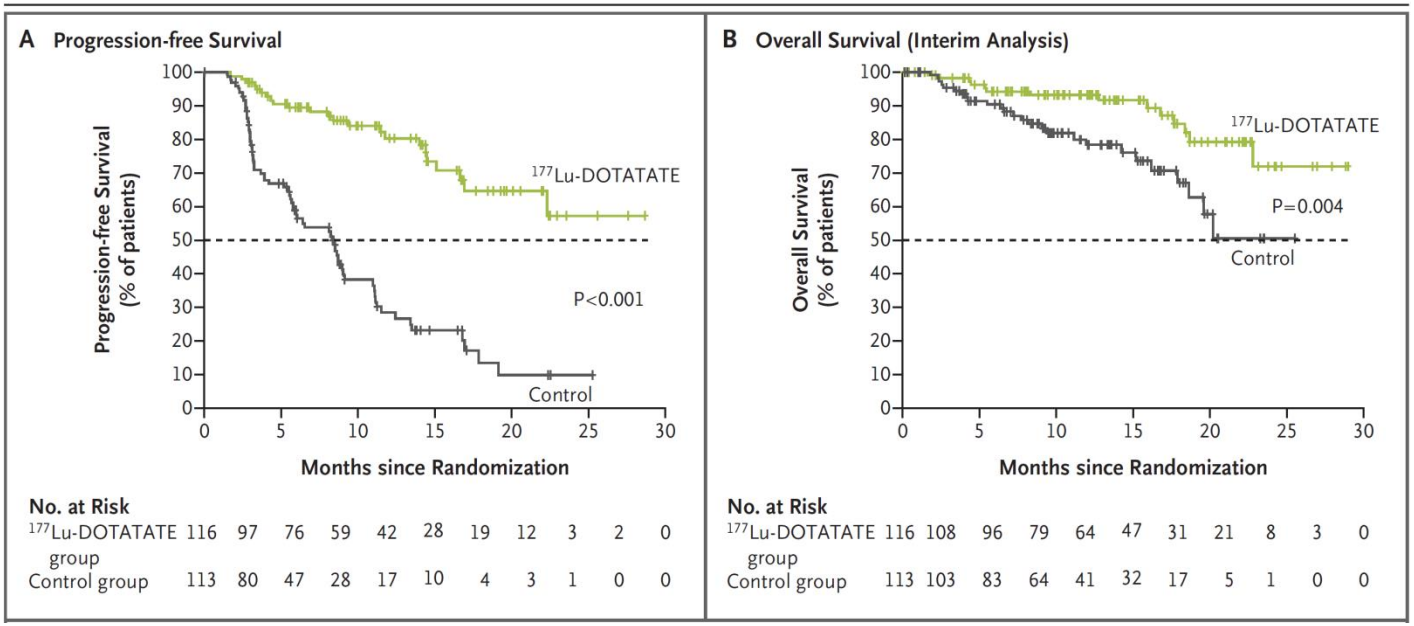
TRAIL Translational Research and Advanced Imaging Laboratory

INCIA Institut de Neurosciences Cognitives et Intégratives d'Aquitaine

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors.

Strosberg J, et al; **NETTER-1 Trial Investigators.**
N Engl J Med. 2017 Jan 12; 376:125-135.

The NEW ENGLAND JOURNAL of MEDICINE



- **Taux de PFS à 20 mois 65.2% dans groupe ^{177}Lu-Dotatate vs. 10.8% dans groupe control**
- Taux de réponse tumorale objective (critère RECIST): 18%
- Taux de toxicité Hématologique aigüe modéré (~10%)
- Taux de toxicité tardive rénale et hématologique faibles

Imagerie et Radiothérapie Interne Vectorisée par Ciblage de Récepteurs de Peptides

« The image and treat approach »

- **177Lu-DOTATATE : perspectives au-delà de NETTER-1**
- **Antagonistes radiomarqués de la somatostatine (JR11)**
- **Ciblage dans les TNE du GLP-1-R, GIP-R, CCK2/gastrin**

Ciblage du PSMA

- **Ciblage du GRP-R**
- **Ciblage de NTR1**
- **Ciblage CXCR4**

- *absence de conflit d'intérêt*

Disponibilités en France du 177Lu-Octreotate

- A travers l' ATU de cohorte (midgut)

- ATU nominative (TNE pancréas, carcinoïde bronchique,…)

Ezziddin S. Outcome of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced grade 1/2 pancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2014; 41:925-33.

Ianniello A. Peptide receptor radionuclide therapy with (177)Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and (18)F-FDG PET. Eur J Nucl Med Mol Imaging. 2016; 43:1040-6.

- Inclusion Etude Clinique

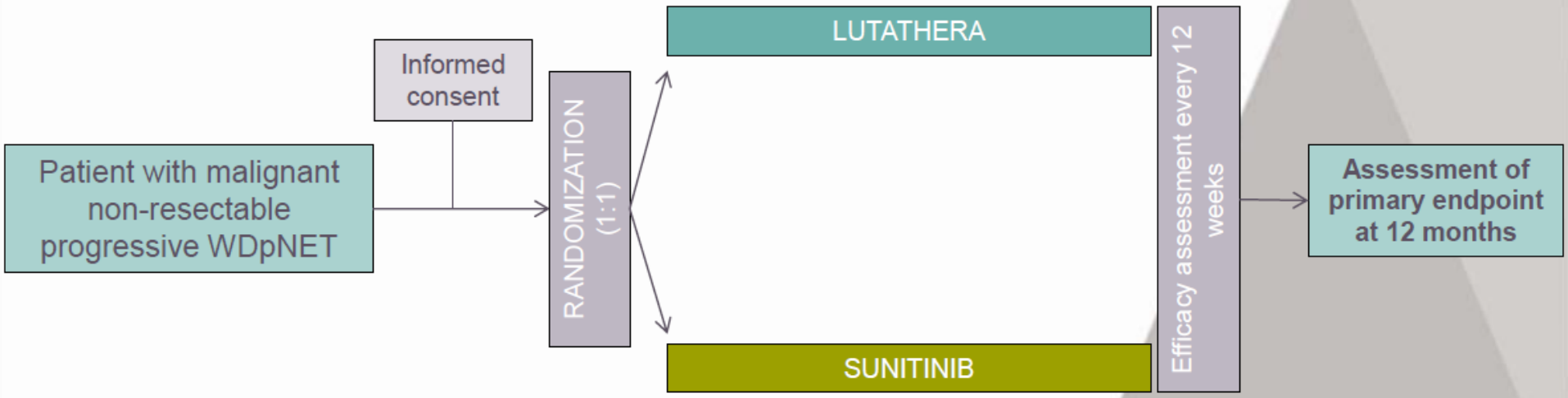
Étude OCCLURANDOM : Tumeurs pancréatiques

OCCLURANDOM

Objectif principal :

Déterminer la SSP à 12 mois de l'OCLU, défini par les critères RECIST1.1 chez des patients présentant une tumeur neuroendocrine du pancréas bien différenciée en progression

Design :



Investigateur principal : Dr Eric Baudin - IGR

Pistes pour augmenter le taux de réponse tumorale,

prenant en compte les paramètres individuels

Imagerie Moléculaire Pronostique

- **Imagerie des récepteurs à la somatostatine**

  Kratochwil C. SUV of [68Ga]DOTATOC-PET/CT Predicts Response Probability of PRRT in Neuroendocrine Tumors. Mol Imaging Biol. 2015;17:313-8.

- **18FDG-TEP**

  Sansovini M. Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with ^{177}Lu-D OTATATE. Eur J Nucl Med Mol Imaging. 2017;44:490-9

- **Association des 2 informations**

  Nilica B. Direct comparison of (68)Ga-DOTA-TOC and (18)F-FDG PET/CT in the follow-up of patients with neuroendocrine tumour treated with the first full peptide receptor radionuclide therapy cycle. Eur J Nucl Med Mol Imaging. 2016;43:1585-92.

Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with ^{177}Lu-DOTATATE.

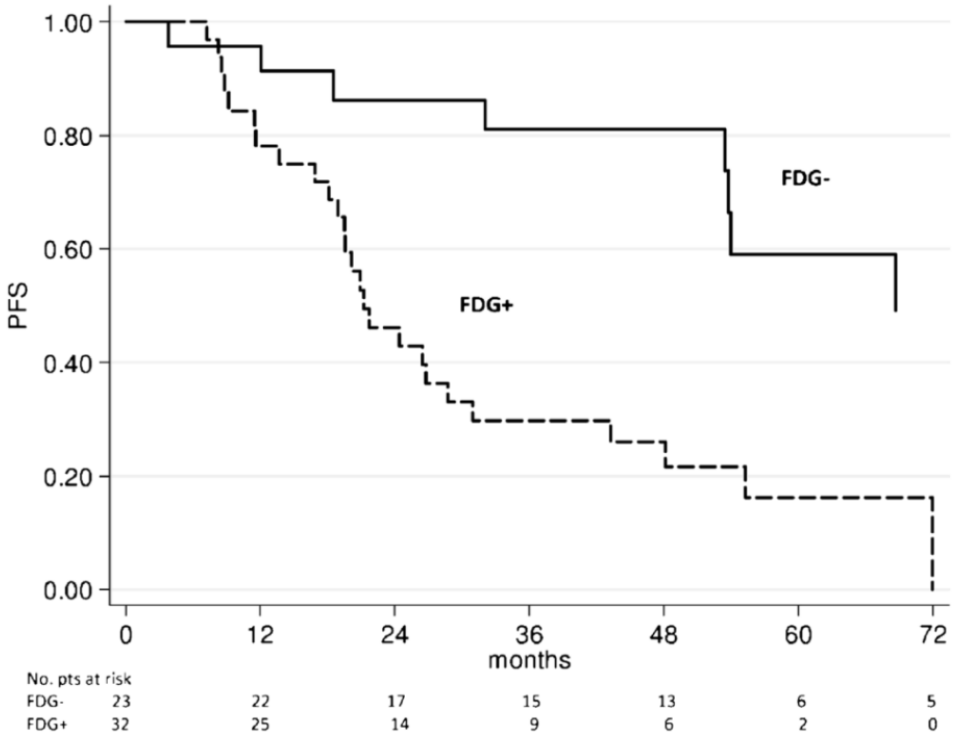
Sansovini M. Eur J Nucl Med Mol Imaging. 2017; 44:490-9.

60 patients avec P-NET traités par 177-Lu-DOTATATE

- TEP-FDG positive : 58%

PFS médiane

- FDG-positif : 21 mois
- FDG-négatif : 69 mois
- P <0.0002



Association PRRT et chimiothérapie pour contrer le mauvais pronostic des tumeurs FDG-positive

- **Modifying the Poor Prognosis Associated with 18F-FDG-Avid NET with Peptide Receptor Chemo-Radionuclide Therapy (PRCRT).**

Hofman MS, Michael M, Kashyap R, Hicks RJ. J Nucl Med. 2015; 56:968-9.

- **Phase I-II study of radiopeptide 177Lu-octreotate in combination with capecitabine and temozolomide in advanced low-grade neuroendocrine tumors.**

Claringbold PG, Price RA, Turner JH. Cancer Biother Radiopharm. 2012; 27:561-9.

Phase I-II study of radiopeptide 177Lu-octreotate in combination with capecitabine and temozolomide in advanced low-grade neuroendocrine tumors.

Claringbold PG. Cancer Biother Radiopharm. 2012; 27:561-9.

Essai phase I-II chez 35 patients de 177Lu-octreotate + capecitabine/temozolomide

4 cycles: 7.8 GBq ^{177}Lu-octreotate / 8 semaines + 14 jours capecitabine 1500 mg/m^2. Temozolomide les 5 derniers jours (durant la phase-II, posologie 200 mg/m^2.)

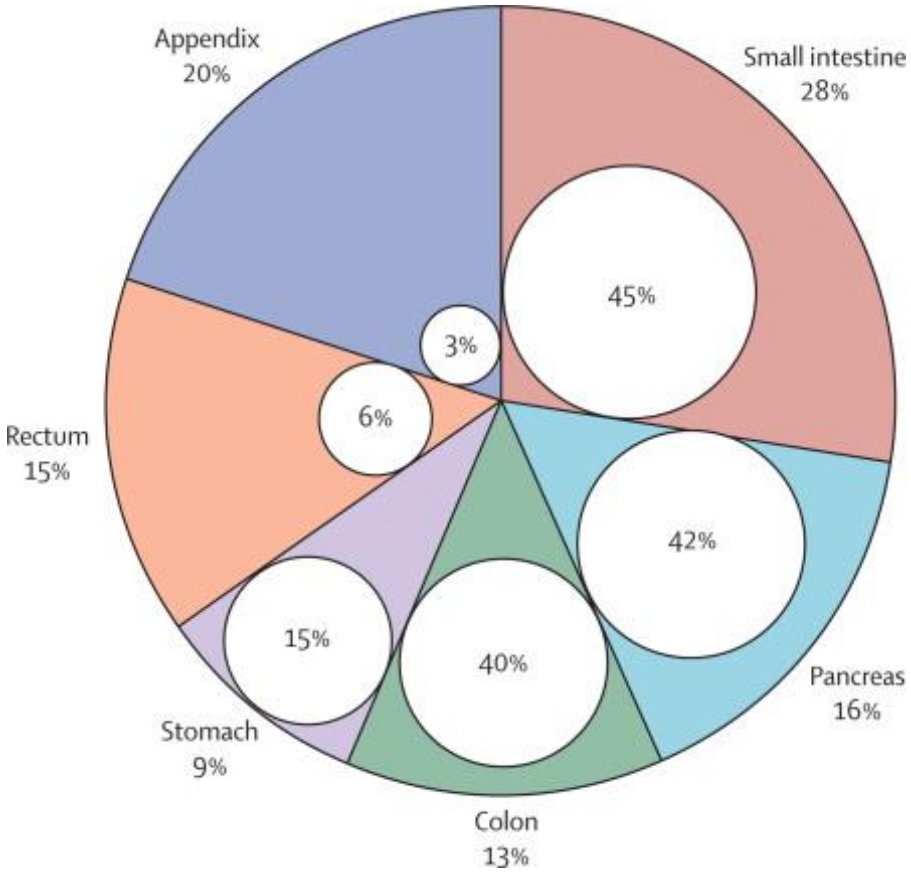
Pas de toxicité grade 4: nausée grade 2/3 (21%), thrombocytopénie grade 2 (24%), neutropénie grade 3 (6%)

Réponse complète 15% ; partielle 38% ; stable 38% ; progression 9%.

PFS médiane: 31 mois; Survie à 2 ans: 90%

Réponse plus élevée dans NET pancreatique/gastrique que intestin grêle: (CR+PR : 82 % *vs* 26 %)

GEP-NETs : distribution des sites primitifs et probabilité de métastases hépatiques selon le site



Recommendations for management of patients with neuroendocrine liver metastases.
Frilling A, et al; Working Group on Neuroendocrine Liver Metastases.
Lancet Oncol. 2014 ;15:e8-21.

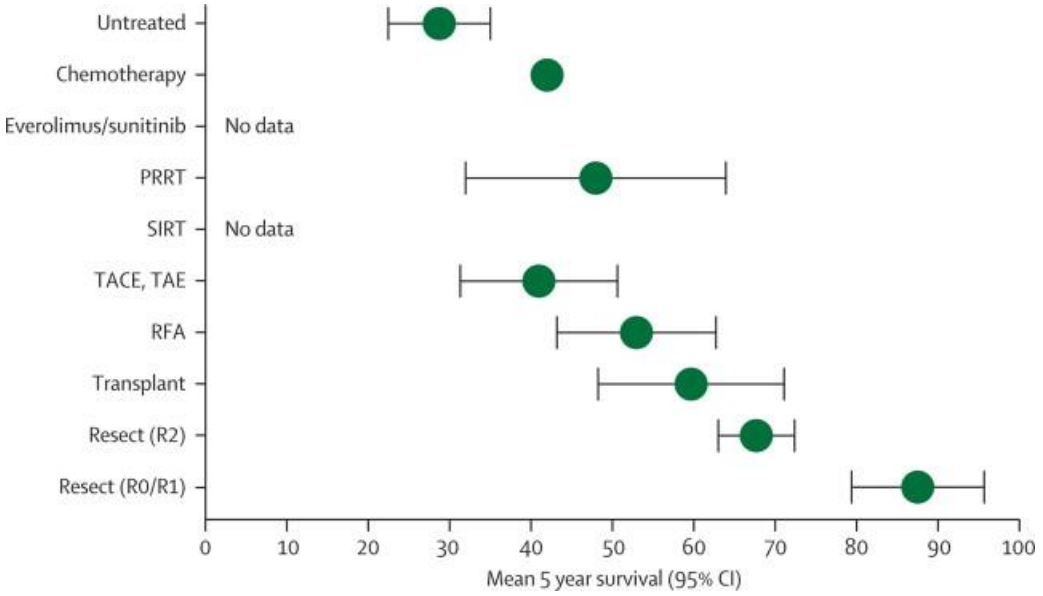
• Les traitements en intra-artériel hépatique en cas d'atteinte métastatique hépatique exclusive ou dominante

Rates of 5 year survival of patients with GEP-NET liver metastases by treatment method

TACE = transarterial chemoembolisation.
TAE = transarterial embolisation.
SIRT= selective internal radiotherapy.

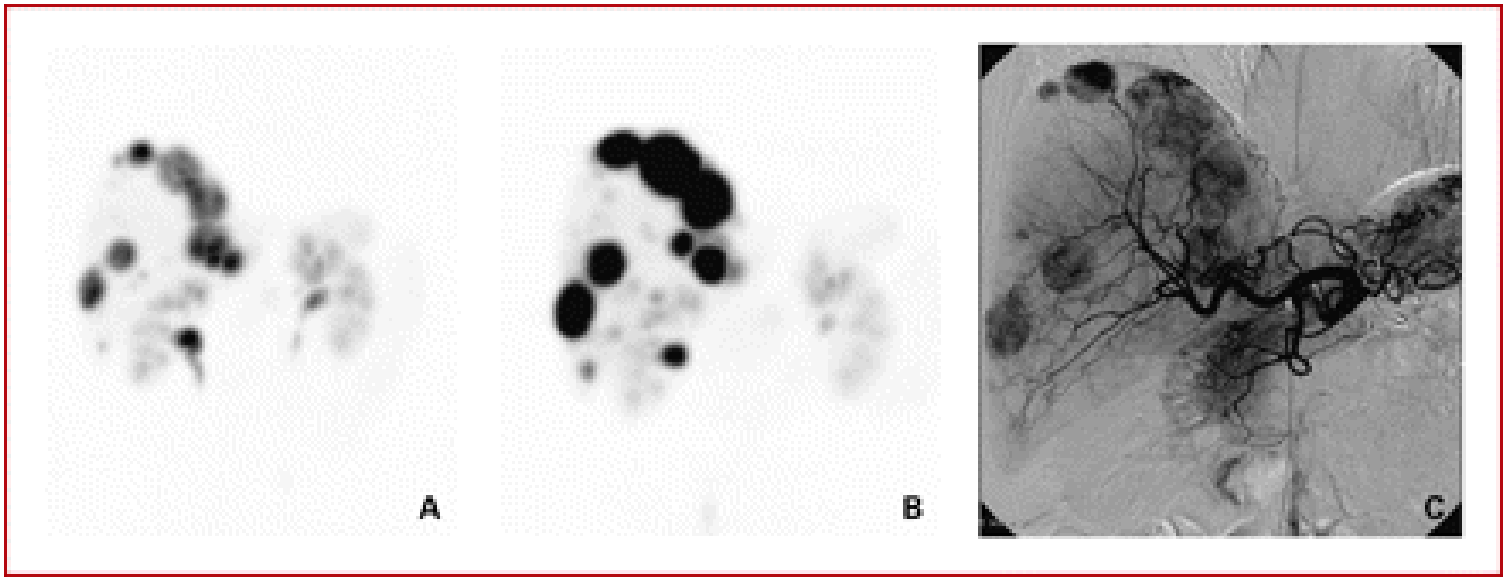
RFA=radiofrequency ablation.
Resect (R2)=cytoreduction.
Resect (R0/R1)=complete resection.

PRRT=peptide receptor radionuclide therapy.



Recommendations for management of patients with neuroendocrine liver metastases.
Frilling A, et al; Working Group on Neuroendocrine Liver Metastases.
Lancet Oncol. 2014;15:e8-21.

Comparaison administration par voie I.V. et par voie intra-artérielle hépatique (i.a.)



- Comparison of intraindividual 68Ga-DOTATOC PET/CT in a patient with liver metastases, presented as a maximum intensity projection after i.v. (A) versus i.a. (B) application.
- **Average SUV(max) presents a 3.2-fold higher value after i.a. 68Ga-DOTATOC infusion.**
- C, digital subtraction angiography illustrates the nearly exclusive arterial perfusion of neuroendocrine liver metastases.

Intraindividual comparison of selective arterial versus venous 68Ga-DOTATOC PET/CT in patients with gastroenteropancreatic neuroendocrine tumors.

Kratochwil C. Clin Cancer Res. 2010; 16:2899-905.

Intraindividual comparison of selective arterial versus venous 68Ga-DOTATOC PET/CT in patients with gastroenteropancreatic neuroendocrine tumors.

Kratochwil C. Clin Cancer Res. 2010; 16:2899-905.

- 11 patients avec métastases hépatiques
- SUVmax plus élevé en i.a. pour 117/122 lésions
- **En moyenne, SUVmax 3,75 fois supérieur (60,8 *vs*. 17,7)**

- Pas de différence au niveau du foie sain (5,9 *vs.* 4,7)

- Légère baisse du SUV des autres tissus
  - Rein : 5,6 *vs*. 7,4
  - Hypophyse : 3,7 *vs*. 4,9

La baisse pour lésions extra-hépatiques pourrait être du même ordre (~25%)

Hepatic arterial infusion enhances DOTATOC radiopeptide therapy in patients with neuroendocrine liver metastases.

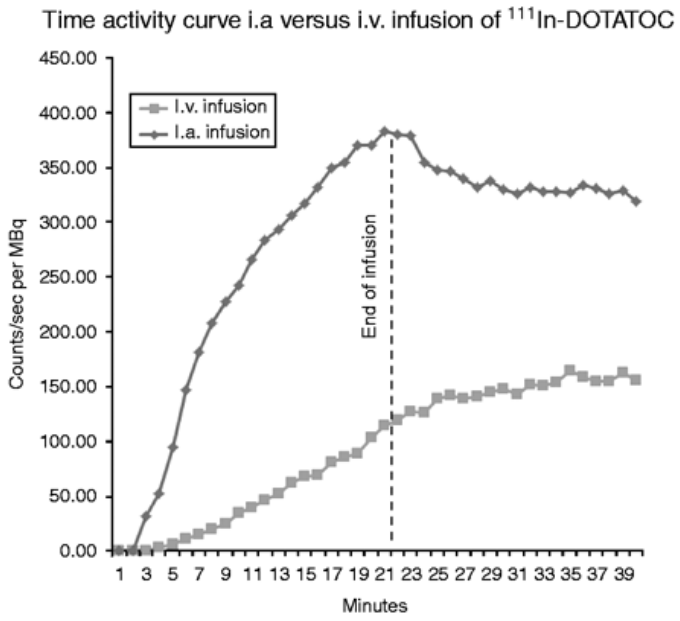
Kratochwil C, et al. Endocr Relat Cancer. 2011; 18:595-602.

Cet essai thérapeutique chez 15 patients a inclut une analyse ancillaire pharmacocinétique avec 111In-DOTATOC chez 4 patients.

L'augmentation de la fixation tumorale pour l'injection en I.A. par rapport à l'injection I.V. est de:

- **x 3,5 pendant la perfusion.**
- **x 2 à 4h**
- **x 1,3 à 72h**

  - **Donc effet lié à la saturation et à la redistribution**
  - **Privilégier une masse de peptide faible**

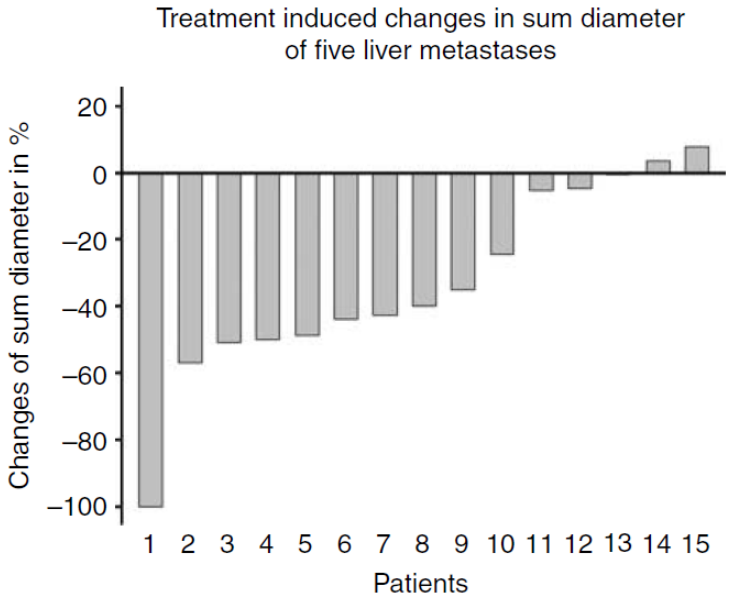


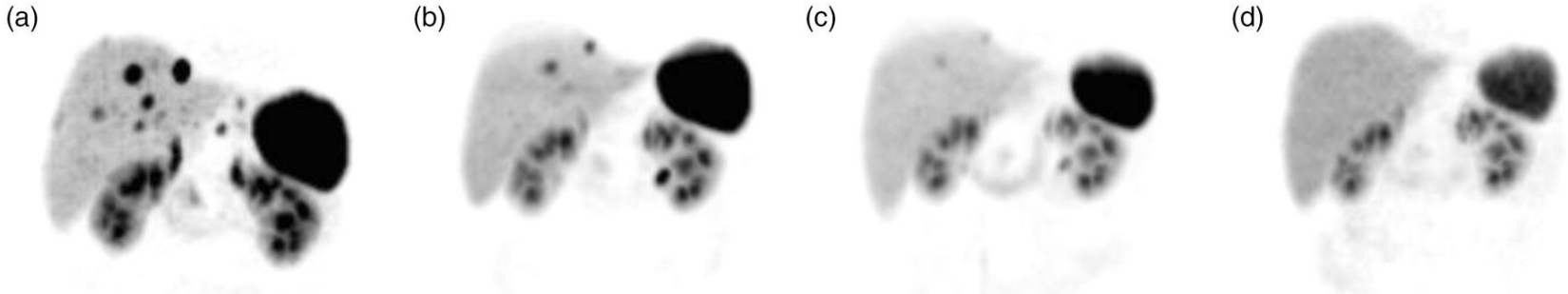
Hepatic arterial infusion enhances DOTATOC radiopeptide therapy in patients with neuroendocrine liver metastases.

Kratochwil C. Endocr Relat Cancer. 2011; 18:595-602.

15 patients traités par voie i.a. hépatique
(^{90}Y-DOTATOC + ^{177}Lu-DOTATOC)

- **Réponse objective : 60%** ***(RC 7% ; RP 53%)***
- Bonne tolérance hépatique, hémato, rénale



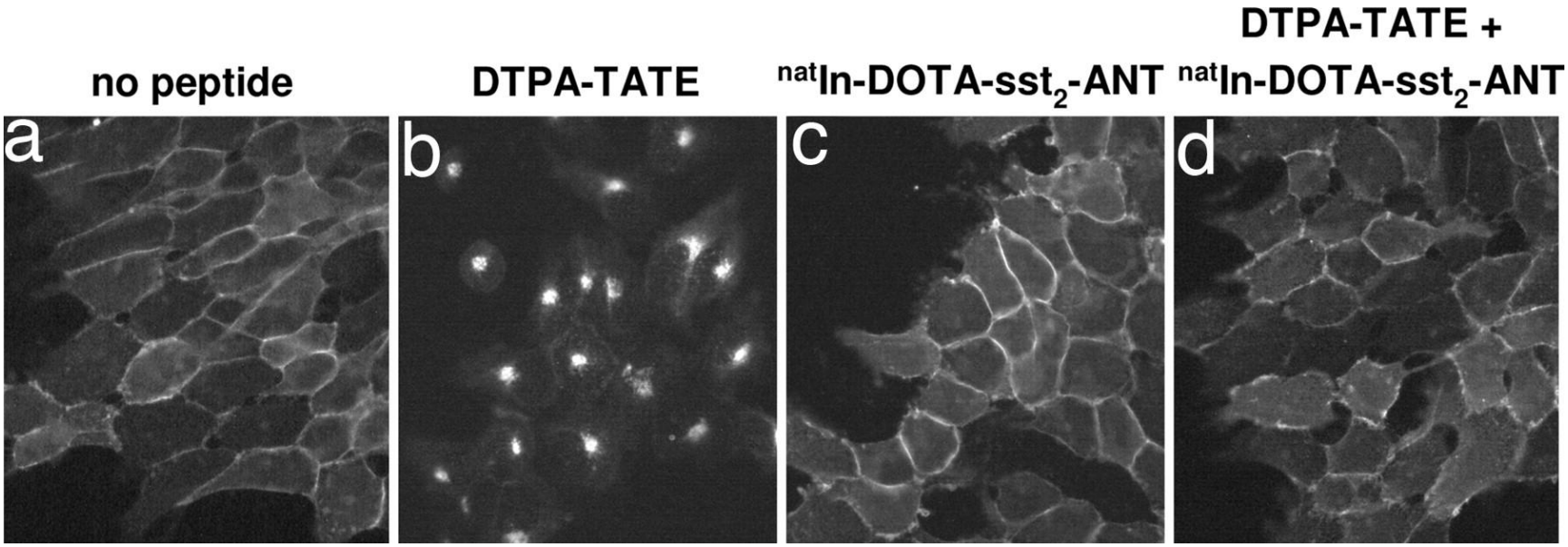


4 cycles de traitement : Cas de réponse complète persistante à 27 mois
(imagerie 68Ga-DOTATOC de base et après chacun des 3 premiers cycles)

Les Analogues Antagonistes Radiomarqués

Radiolabeled somatostatin receptor antagonists are preferable to agonists for in vivo peptide receptor targeting of tumors.

Ginj M, Zhang H, Waser B, Cescato R, Wild D, Wang X, Erchegyi J, Rivier J, Mäcke HR, Reubi JC.
Proc Natl Acad Sci U S A. 2006; 103:16436-41.



Immunofluorescence du récepteur sst2 dans cellules HEK-sst$_2$ (anticorps R2–88)

- La liaison de l'agoniste DTPA-TATE provoque l'internalisation du récepteur (*b*)
- La liaison de l'antagoniste ^{nat}In-DOTA-sst$_2$-ANT n'entraîne pas l'internalisation (*c*)
- L'antagoniste à forte concentration aboli l'internalisation provoquée par l'agoniste (*d*).

Radiolabeled somatostatin receptor antagonists are preferable to agonists for in vivo peptide receptor targeting of tumors.

Ginj M. Proc Natl Acad Sci U S A. 2006; 103:16436-41.

Table 4. Biodistribution in HEK-sst_2 tumor bearing nude mice after injection of ^{111}In-DOTA-sst_2-ANT or ^{111}In-DTPA-TATE

	^{111}In-DOTA-sst_2-ANT				^{111}In-DTPA-TATE		
Organ	0.5 h	4 h	4 h, blocked*	24 h	0.5 h	4 h	24 h
Blood	2.76 ± 0.19	0.14 ± 0.03	0.13 ± 0.01	0.05 ± 0.01	0.99 ± 0.25	0.13 ± 0.1	0.06 ± 0.01
Stomach	7.82 ± 2.03	0.61 ± 0.18	0.19 ± 0.07	0.25 ± 0.06	13.93 ± 8.16	7.04 ± 2.02	4.86 ± 1.68
Kidney	22.92 ± 2.62	10.5 ± 1.0	9.67 ± 1.38	7.38 ± 0.09	29.25 ± 7.7	11.44 ± 0.86	7.08 ± 1.21
Bowel	1.72 ± 0.25	0.16 ± 0.03	0.15 ± 0.03	0.08 ± 0.03	1.7 ± 0.53	0.97 ± 0.31	0.62 ± 0.16
Pancreas	24.16 ± 6.58	0.71 ± 0.21	0.09 ± 0.02	0.13 ± 0.02	18.18 ± 12.59	6.06 ± 3.26	2.26 ± 0.09
Spleen	1.67 ± 0.23	0.23 ± 0.04	0.21 ± 0.02	0.15 ± 0.02	1.13 ± 0.32	0.39 ± 0.05	0.21 ± 0.05
Liver	1.74 ± 0.18	0.43 ± 0.07	0.49 ± 0.03	0.32 ± 0.02	0.46 ± 0.07	0.16 ± 0.04	0.17 ± 0.03
Heart	1.23 ± 0.05	0.11 ± 0.03	0.08 ± 0.01	0.04 ± 0.0	0.53 ± 0.21	0.18 ± 0.07	0.1 ± 0.01
sst_2 tumor	**22.33 ± 3.27**	**29.12 ± 3.9**	**3.62 ± 0.26**	**22.84 ± 0.4**	**18.36 ± 4.37**	**15.83 ± 3.94**	**12.3 ± 1.32**
Muscle	0.97 ± 0.36	0.11 ± 0.02	0.09 ± 0.02	0.06 ± 0.03	0.51 ± 0.15	0.09 ± 0.03	0.05 ± 0.01
Adrenal	4.74 ± 3.0	0.49 ± 0.12	0.24 ± 0.04	0.46 ± 0.26	4.68 ± 1.46	1.95 ± 0.26	2.28 ± 0.67
Bone	1.84 ± 0.38	1.29 ± 0.75	0.58 ± 0.22	0.48 ± 0.14	0.8 ± 0.27	0.87 ± 0.65	0.74 ± 0.37
Pituitary	27.7 ± 6.48	20.23 ± 6.38	3.14 ± 0.91	2.08 ± 1.72	21.99 ± 5.36	12.1 ± 5.01	6.99 ± 4.61

The results are expressed in percent of the %IA/g, mean ± SEM, $n \geq 3$. Bold text indicates the tumor as the most important of the listed tissues.
*Blocked with excess DOTA-sst_2-ANT coinjected with the radioligand.

Unexpected sensitivity of sst2 antagonists to N-terminal radiometal modifications.

Fani M, et al. J Nucl Med. 2012; 53:1481-9.

TABLE 1

Chemical Structure and IC_{50} Values of sst_2 Antagonists Based on JR10, JR11, and LM3 Family and Their Metallated Conjugates

Code number	Chemical structure	IC_{50} (nM) sst1	sst2	sst3	sst4	sst5
DOTA-JR11*	DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	0.72 ± 0.12	>1,000	>1,000	>1,000
Ga-DOTA-JR11	[^{nat}Ga]-DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	29 ± 2.7	>1,000	>1,000	>1,000
Y-DOTA-JR11	[^{nat}Y]-DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	0.47 ± 0.05	>1,000	>1,000	>1,000
Lu-DOTA-JR11	[^{nat}Lu]-DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	0.73 ± 0.15	>1,000	>1,000	>1,000
Cu-DOTA-JR11	[^{nat}Cu]-DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	16 ± 1.2	>1,000	>1,000	>1,000
In-DOTA-JR11	[^{nat}In]-DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	3.8 ± 0.7	>1,000	>1,000	>1,000
NODAGA-JR11	NODAGA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	4.1 ± 0.2	>1,000	>1,000	>1,000
Ga-NODAGA-JR11	[^{nat}Ga]-NODAGA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	1.2 ± 0.2	>1,000	>1,000	>1,000
Reference agonist, Ga-DOTATATE§	[^{nat}Ga]-DOTA-D-Phe-c[Cys-Tyr-D-Trp-Lys-Thr-Cys]-Thr	>1,000	0.2 ± 0.04	>1,000	300 ± 140	377 ± 18

OctreoPharm Sciences GmbH : Filiale IPSEN

Lu-DOTA-JR11 = OPS201 (SOMther®)
Ga-NODAGA-JR11 = OPS202 (SOMscan®): Received EMA Orphan Drug Designation

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Code number	Chemical structure	IC_{50} (nM) sst1	sst2	sst3	sst4	sst5
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Ga-DOTA-JR11	[^{nat}Ga]-DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	29 ± 2.7	>1,000	>1,000	>1,000
Y-DOTA-JR11	[^{nat}Y]-DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	0.47 ± 0.05	>1,000	>1,000	>1,000
Lu-DOTA-JR11	[^{nat}Lu]-DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	0.73 ± 0.15	>1,000	>1,000	>1,000
Cu-DOTA-JR11	[^{nat}Cu]-DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	16 ± 1.2	>1,000	>1,000	>1,000
In-DOTA-JR11	[^{nat}In]-DOTA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	3.8 ± 0.7	>1,000	>1,000	>1,000
NODAGA-JR11	NODAGA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	4.1 ± 0.2	>1,000	>1,000	>1,000
Ga-NODAGA-JR11	[^{nat}Ga]-NODAGA-Cpa-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2	>1,000	1.2 ± 0.2	>1,000	>1,000	>1,000

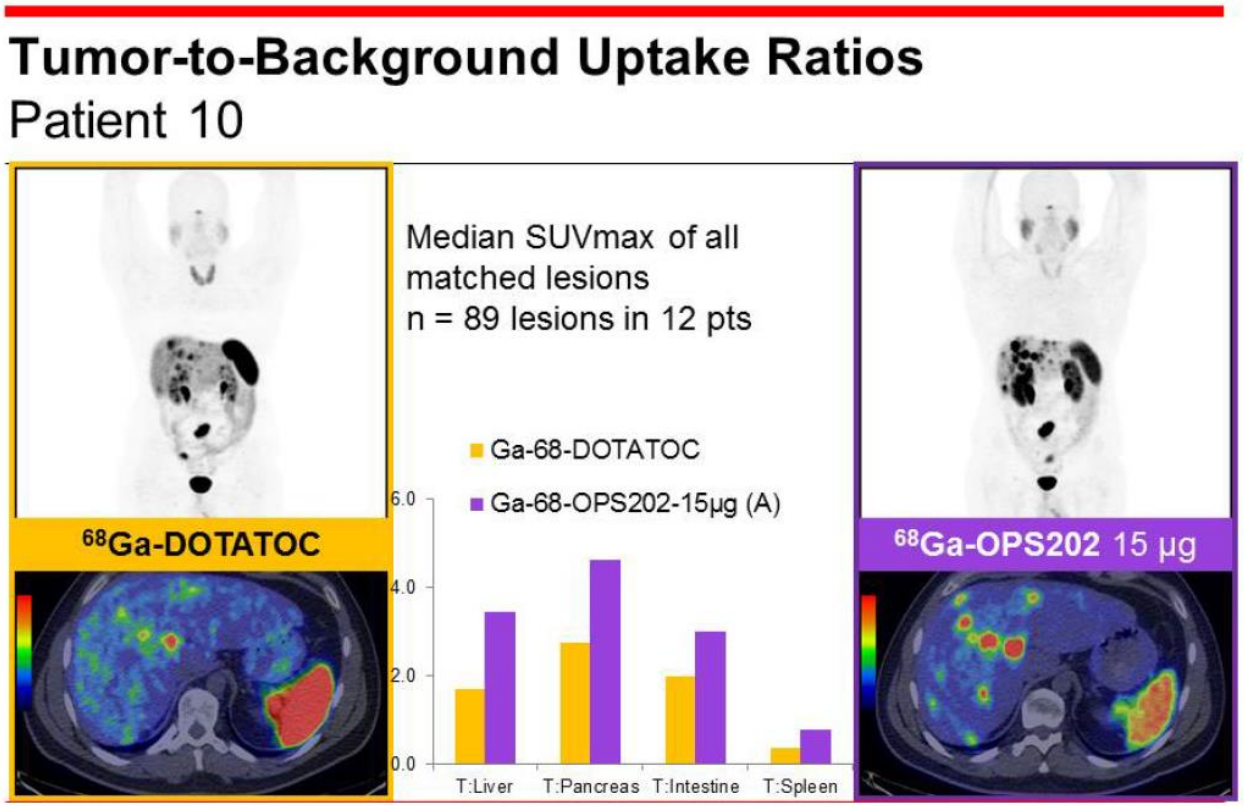
Unexpected sensitivity of sst2 antagonists to N-terminal radiometal modifications.
Fani M, et al. J Nucl Med. 2012; 53:1481-9.

PET/CT with the somatostatin receptor antagonist 68Ga-OPS202 is twice as accurate as with the agonist 68Ga-DOTATOC for detecting liver metastases: Results of a phase 1/2 study in gastroenteropancreatic NET patients.

Guillaume Nicolas, Nils Schreiter, Felix Kaul, John Uiters, Ramon Mena, Hakim Bouterfa, Helmut Maecke, Melpomeni Fani and Damian Wild

J Nucl Med May 1, 2016 vol. 57 no. supplement 2 154

- Etude phase I/II de biodistribution et tolérance chez 12 patients avec TNE G1/G2 métastatique



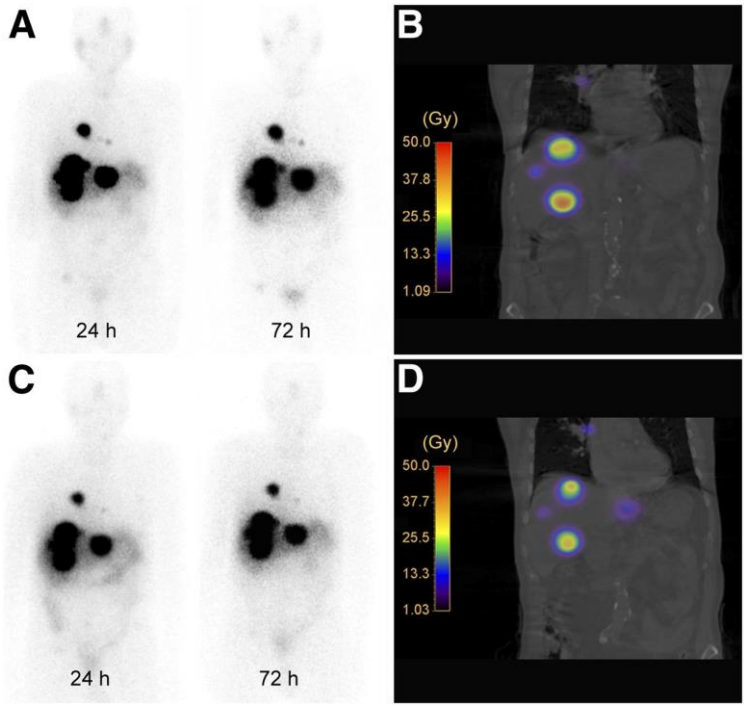
University Hospital Basel

Comparison of Somatostatin Receptor Agonist and Antagonist for Peptide Receptor Radionuclide Therapy: A Pilot Study.

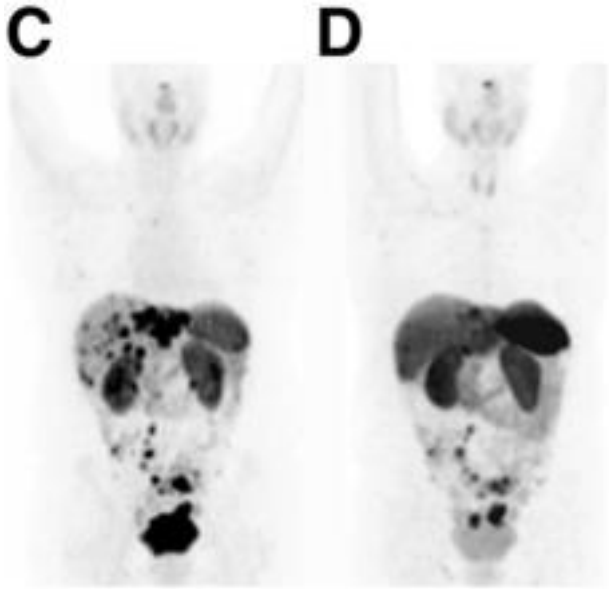
Wild D, et al. J Nucl Med. 2014; 55: 1248-1252.

- **4 patients avec TNE métastatiques**
- **Comparaison de l'analogue antagoniste 177Lu-JR11 (1 GBq) à l'agoniste 177Lu-DOTATATE (1GBq), Dosimétrie tumorale et aux organes sains par SPECT/CT**
- **Tenant compte du degré de captation et temps de résidence, dose à la tumeur du 177Lu-DOTA-JR11 x1,7 à x10,6 la dose délivrée par 177Lu-DOTATATE**
- **Ratio dose tumeur/dose rein amélioré d'un facteur 2,1** (3,3 vs 1,6)
- **Ratio dose tumeur/dose moelle amélioré d'un facteur 2,6** (56 vs 22)
- **Effets secondaires mineurs réversibles après administration de 177Lu-DOTA-JR11 (flush chez 1 patient)**

Analogues Antagonistes Radiomarqués



- **177Lu-DOTA-JR11 planar scans (A) and isodose curves (B)**
- **177Lu-DOTATATE planar scans (C) and isodose curves (D)**



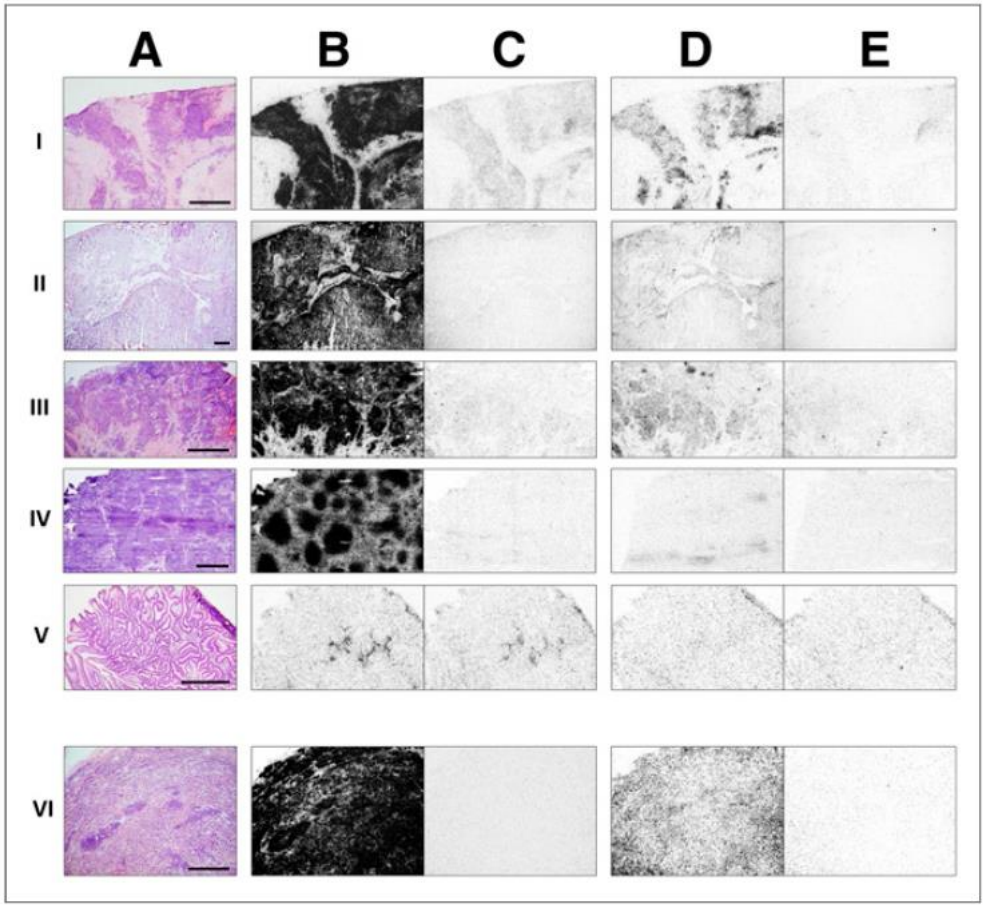
- 68Ga-DOTATATE PET images of patient 3 before (C) and 12 mo after (D) treatment with 5.9 GBq of 177Lu-DOTA-JR11

Comparison of Somatostatin Receptor Agonist and Antagonist for Peptide Receptor Radionuclide Therapy: A Pilot Study.

Wild D, et al. J Nucl Med. 2014; 55: 1248-1252.

Highly Increased 125I-JR11 Antagonist Binding In Vitro Reveals Novel Indications for sst2 Targeting in Human Cancers.

Reubi JC, Waser B, Mäcke H, Rivier J. **J Nucl Med. 2017**; 58:300-306.



Autoradiographie du récepteur sst2 dans diverses tumeurs.

Comparaison de l'antagoniste ^{125}I-JR11 (B) et l'agoniste ^{125}I-Tyr3-octreotide (D)

Colonnes C et E (en présence d'un excès de ligand froid).
Barre = 1 mm.

(I) Cancer du sein
(II) Cancer du rein (RCC).
(III) Cancer médullaire de la thyroïde
(IV) Lymphome non-hodgkinien
(V) Cancer du colon (négatif)

Incubation: 30 000 cpm/100 µL d'antagonist ou agonist.

(VI) TNE iléale

Incubation: 10 000 cpm/100 µL).

Avantages et Inconvénients des Antagonistes

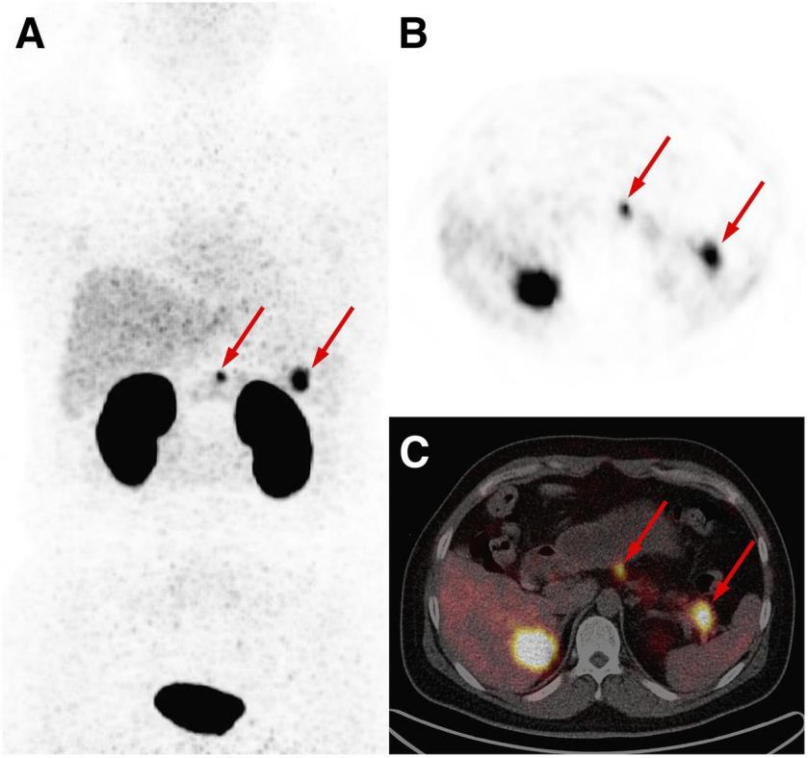
Avantages:

- **Plus forte captation; et plus forte rétention tumorale**
- **Ouvre le champs à des applications hors TNE**

- **Inconvénients:**
  - L'absence d'internalisation cellulaire réduit légèrement la dose au noyau (certains électrons Auger ou de faible parcours)
  - **Des effets secondaires aux doses pharmacologiques peuvent être rencontrès, notamment dans les TNE**
  - **Des Etudes de phase I/II démarrent**

Ciblage GLP-1 dans l'insulinome

^{68}Ga-NOTA-exendin-4



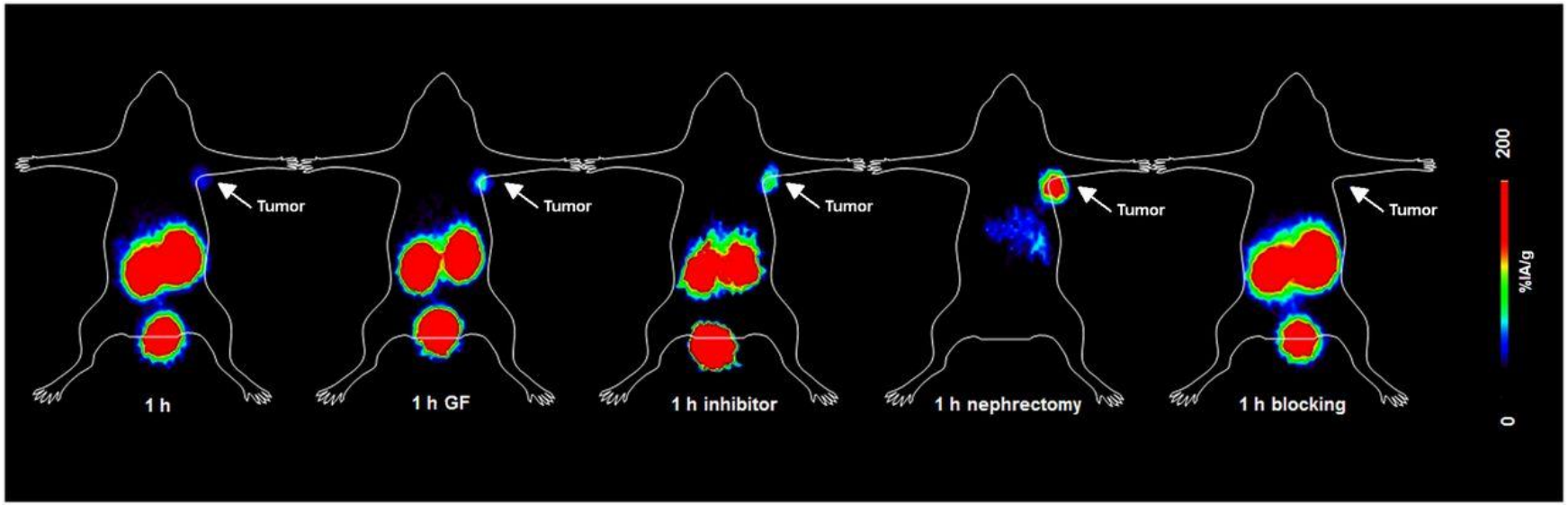
- Images chez un patient de 37 ans, 40 min après injection de 18 MBq de ^{68}Ga-NOTA-exendin-4.
- Deux foyers intenses sont visibles au niveau du pancréas (insulinomes confirmés à la chirurgie).
- Patient porteur de NEM-1

Glucagon-Like Peptide-1 Receptor PET/CT with 68Ga-NOTA-Exendin-4 for Detecting Localized Insulinoma: A Prospective Cohort Study.

Luo Y, Pan Q, Yao S, Yu M, Wu W, Xue H, Kiesewetter DO, Zhu Z, Li F, Zhao Y, Chen X.
J Nucl Med. 2016; 57:715-20.

The glucose-dependent insulinotropic polypeptide receptor: a novel target for neuroendocrine tumor imaging-first preclinical studies.

Gourni E, Waser B, Clerc P, Fourmy D, Reubi JC, Maecke HR.
J Nucl Med. 2014; 55:976-82.



- Imagerie PET ^{68}Ga-EG4 du récepteur GIP-R PET (greffe tumorale INR1G9-hGIPR).
- Imagerie à 1 h avec ou sans blocage, ou après nephréctomie.

- After administration of Gelofusine or vildagliptin, kidney uptake was lower, resulting in better delineation of tumor.

Cancer médullaire de la thyroïde:

Ciblage du récepteur CCK2

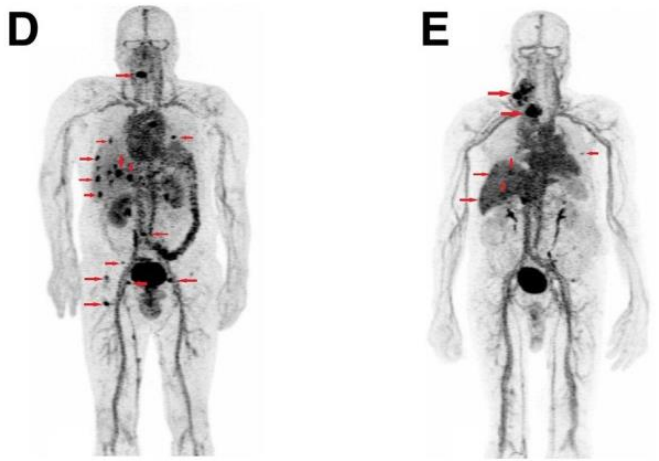
Ciblage de l'ACE

From preclinical development to clinical application: Kit formulation for radiolabelling the minigastrin analogue CP04 with In-111 for a first-in-human clinical trial.

Pawlak D. Eur J Pharm Sci. 2016; 85:1-9.

Immuno-PET Using Anticarcinoembryonic Antigen Bispecific Antibody and 68Ga-Labeled Peptide in Metastatic Medullary Thyroid Carcinoma: Clinical Optimization of the Pretargeting Parameters in a First-in-Human Trial.

Bodet-Milin C. J Nucl Med. 2016; 57:1505-1511



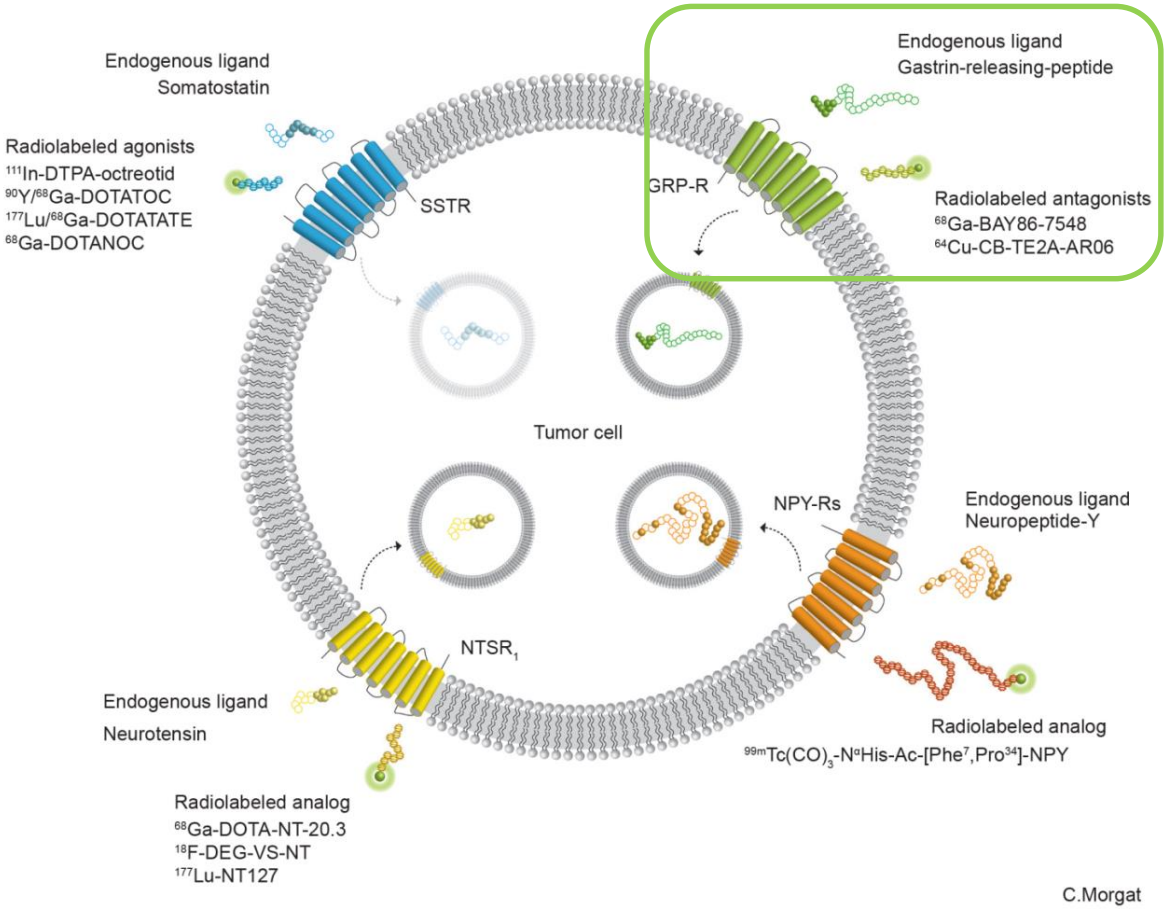
- **Immuno-PET**

(D) supradiaphragmatic nodes, lung, liver, and bone foci in C4

(E) supradiaphragmatic nodes and liver foci in C5.

Gastrin-Releasing Peptide Receptor (GRP-R)

Famille bombésine



Cancer prostate

Cancer du sein

Cancer du poumon à petites cellules

Targeting neuropeptide receptors for cancer imaging and therapy: perspectives with bombesin, neurotensin, and neuropeptide-Y receptors.

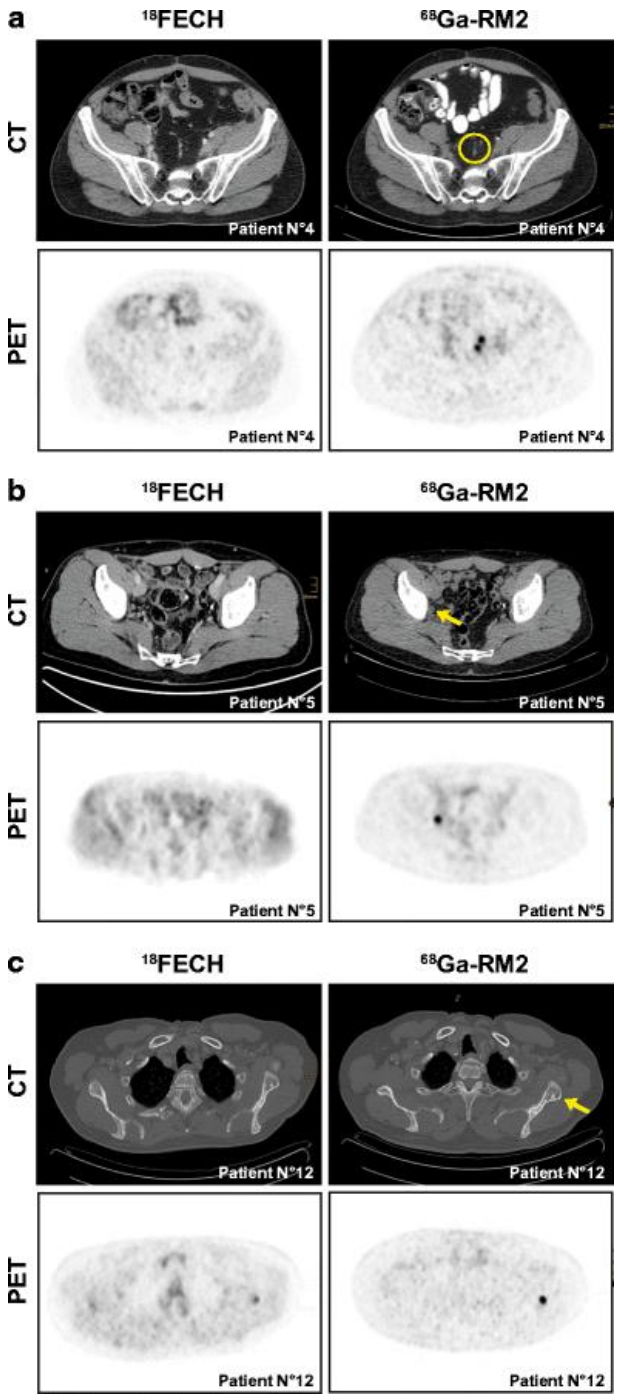
Morgat C, Mishra AK, Varshney R, Allard M, Fernandez P, Hindié E.

J Nucl Med. 2014; 55:1650-7.

Diagnosis of recurrent prostate cancer with PET/CT imaging using the gastrin-releasing peptide receptor antagonist 68Ga-RM2: Preliminary results in patients with negative or inconclusive [18F]Fluoroethylcholine-PET/CT.

Wieser G. Eur J Nucl Med Mol Imaging. 2017 Apr 18. [Epub ahead of print]

- 16 patients avec récidive biochimique de cancer de la prostate et imagerie ^{18}F-fluoroethylcholine négative (n = 14) ou inconclusive (n = 2)
- 14/16 patients avaient déjà reçu un traitement de rattrapage
- PSA moyen au moment de la TEP au ^{68}Ga-RM2 : 19 ng/ml (1,1 - 226)
- la TEP-TDM au ^{68}Ga-RM2-PET/CT est positive chez 10 patients (62,5%)
- Confirmée chez 7



^{18}FECH-PET et ^{68}Ga-RM2-PET/CT chez 3 patients

(**a**) ^{68}Ga-RM2-PET: ganglion présacré

(**b**) ^{68}Ga-RM2-PET: ganglion iliaque.

(**c**) ^{68}Ga-RM2-PET: multiples lésions osseuses

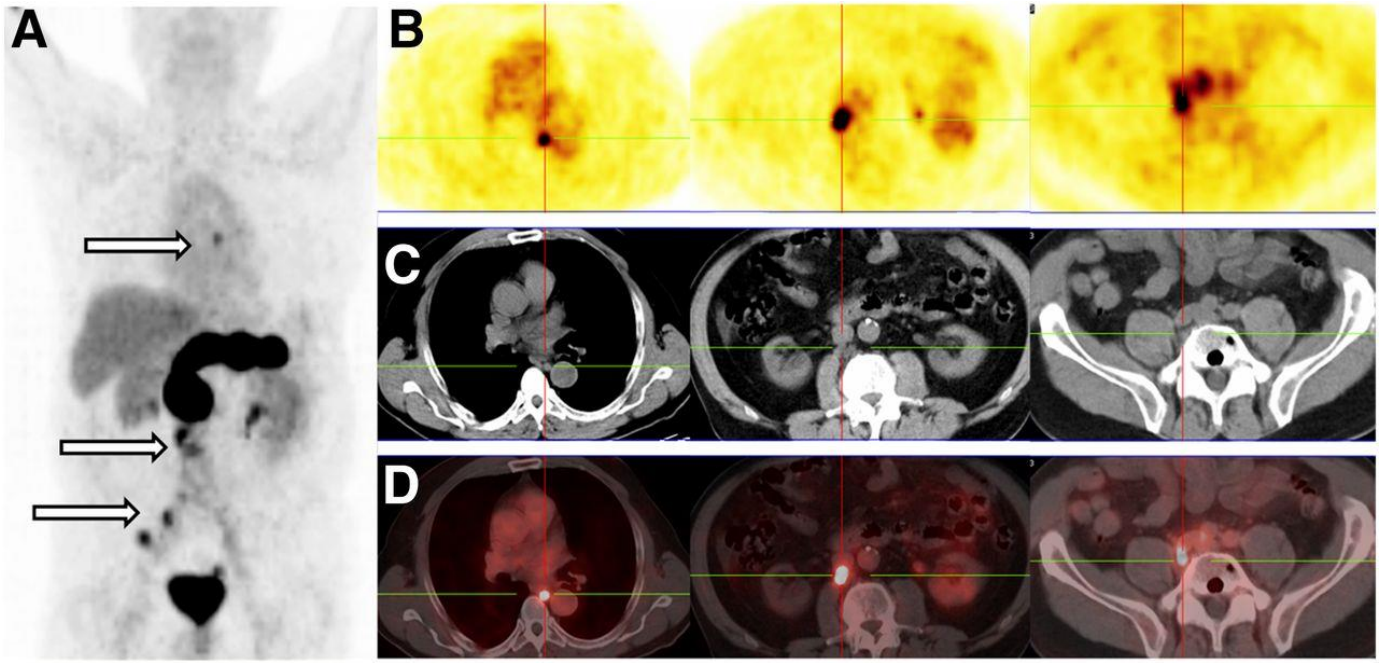
(^{18}FECH montre une seule lésion: omoplate gauche)

Wieser G, et al. Eur J Nucl Med Mol Imaging. 2017 Apr 18

Theranostic Perspectives in Prostate Cancer with the Gastrin-Releasing Peptide Receptor Antagonist **NeoBOMB1**: Preclinical and First Clinical Results.

Nock BA, et al.

J Nucl Med. 2017 Jan;58(1):75-80.

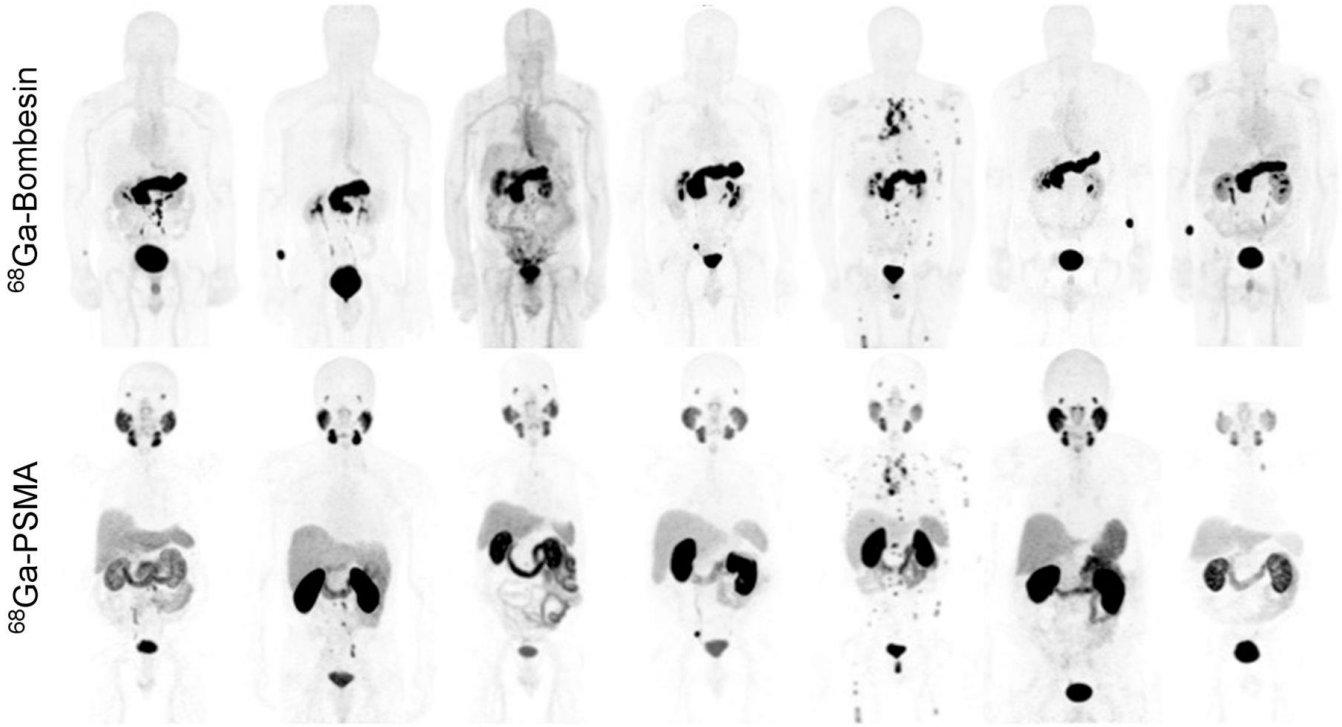


Patient with prostate adenocarcinoma, postradical prostatovesiculectomy with pelvic lymphadenectomy, intensity-modulated radiotherapy, and androgen-deprivation therapy (PSA: 22 ng/mL).

^{68}Ga-NeoBOMB1 PET: Multiple mediastinal, abdominal, paraesophageal, and pelvic lymph node.

Pilot Comparison of **^{68}Ga-RM2 PET and ^{68}Ga-PSMA-11 PET** in Patients with Biochemically Recurrent Prostate Cancer.

Minamimoto R, et al. J Nucl Med. 2016; 57:557-62.

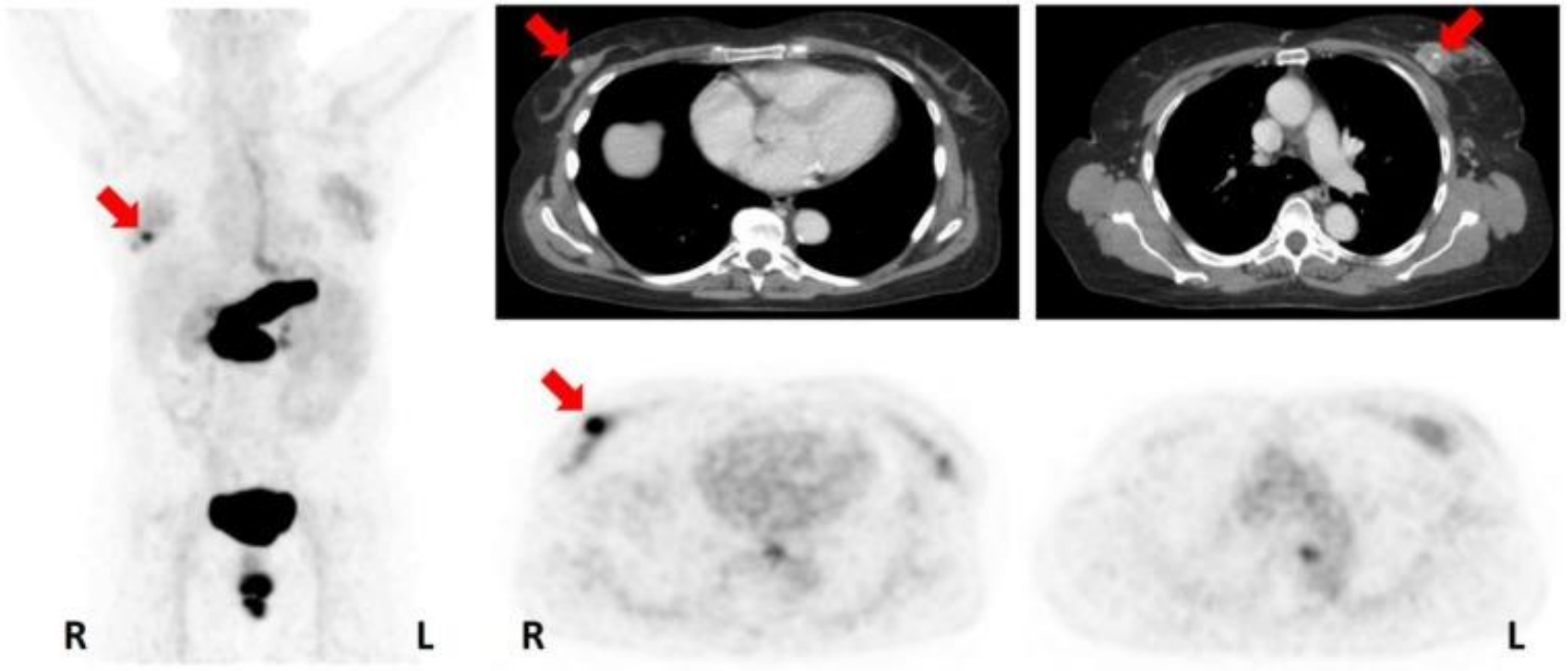


MIP du ^{68}Ga-RM2 et ^{68}Ga-PSMA-11 des 7 patients inclus

- Distribution physiologique très différente : information parfois complémentaire
- Place de l'imagerie GRP-R par rapport au PSMA à définir

Gastrin-releasing Peptide Receptor Imaging in Breast Cancer Using the Receptor Antagonist ^{68}Ga-RM2 And PET.

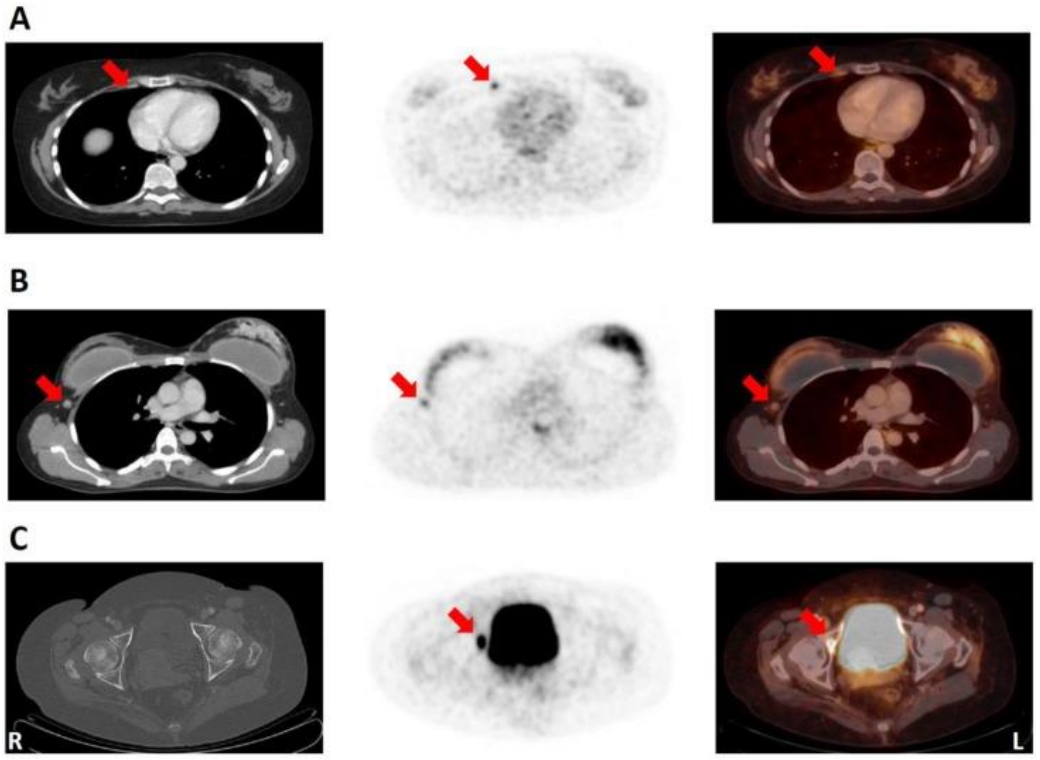
Stoykow C, et al. Theranostics. 2016 ; 6:1641-50.



- **74-year-old patient with an ER/PR-positive tumor on the right side (SUVMAX 8.32) and an ER/PR-negative tumor on the left side (PET-negative; SUVMAX 2.68).**
- Note the physiological uptake in the pancreas, esophagus and rectum.

Gastrin-releasing Peptide Receptor Imaging in Breast Cancer Using the Receptor Antagonist (68)Ga-RM2 And PET.

Stoykow C, et al. Theranostics. 2016 ; 6:1641-50.

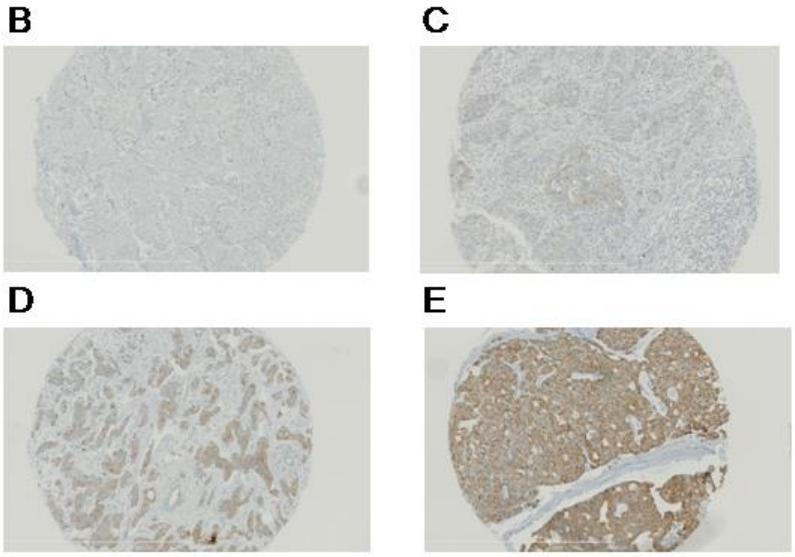


- **A.** 50-year-old patient with bilateral ER/PR-positive BC. Detection of a very small (3x3 mm) internal mammary lymph node with intensive 68Ga-RM2-uptake (SUVmax = 3,8)
- **B:** 43-year-old patient with a ER/PR-positive BC of the left breast. Contralateral axillary lymph node metastasis with increased GRPR expression (verified by biopsy; SUVmax = 2,6)
- **C:** 80-year-old patient with an ER/PR-positive BC of the right breast. Focal 68Ga-RM2 uptake in the right acetabulum (bone metastasis) (SUVmax 14.3)

Expression of Gastrin-Releasing Peptide Receptor (GRPR) in Breast Cancer and its Association with Pathological, Biological and Clinical Parameters: A Study of 1432 Primary Tumors.

Morgat C, MacGrogan G, Brouste V, Vélasco V, Sevenet N, Bonnefoi H, Fernandez P, Debled M, Hindié E.

J Nucl Med. 2017 Mar 9. [Epub ahead of print]



Analyse TMA: 1438 tumeurs

- Surexpression du GRP-R (modérée à forte) dans ~76% des tumeurs

Lorsque la tumeur primitive est positive, les ganglions métastatiques expriment également GRP-R

Distribution of low and high GRPR expression within different categories of breast cancers

Characteristic	Category	No. of Patients	GRPR expression Low %	GRPR expression High %	*P*-value
Age	≤40 y	85	45.9	54.1	*P*< 0.00001
	>40 y	1347	22.9	77.1	
Histology *	IDC	1221	25.4	74.6	*P*= 0.09
	ILC	161	19.3	80.7	
Pathological size	<20mm	961	20.9	79.1	*P*= 0.00003
	≥20mm	471	31.0	69.0	
SBR grade *	I	358	10.6	89.4	*P*< 0.00001†
	II	661	16.9	83.1	
	III	397	48.6	51.4	
Ki-67	<20%	1115	17.0	83.0	*P*< 0.00001
	≥20%	317	49.8	50.2	
Lymph node status*	N_0	848	23.3	76.7	*P*= 0.03
	N^+	472	28.8	71.2	
Estrogen receptor	0%	150	88.0	12.0	*P*< 0.00001
	≥1%	1282	16.8	83.2	
Progesteron receptor	0%	266	60.9	39.1	*P*< 0.00001
	≥1%	1166	15.9	84.1	
Androgen receptor	<10%	184	63.0	37.0	*P*< 0.00001
	≥10%	1248	18.5	81.5	
HER2 overexpression	No	1286	22.8	77.2	*P*= 0.0001
	Yes	146	37.0	63.0	

Perspectives de thérapie par antagonistes radiomarqués du GRP-R

- **^{177}Lu-RM2 /** ^{68}Ga-RM2 ***Produits de recherche Piramal Imaging***

Dumont RA, et al: Targeted radiotherapy of prostate cancer with a gastrin-releasing peptide receptor antagonist is effective as monotherapy and in combination with rapamycin.

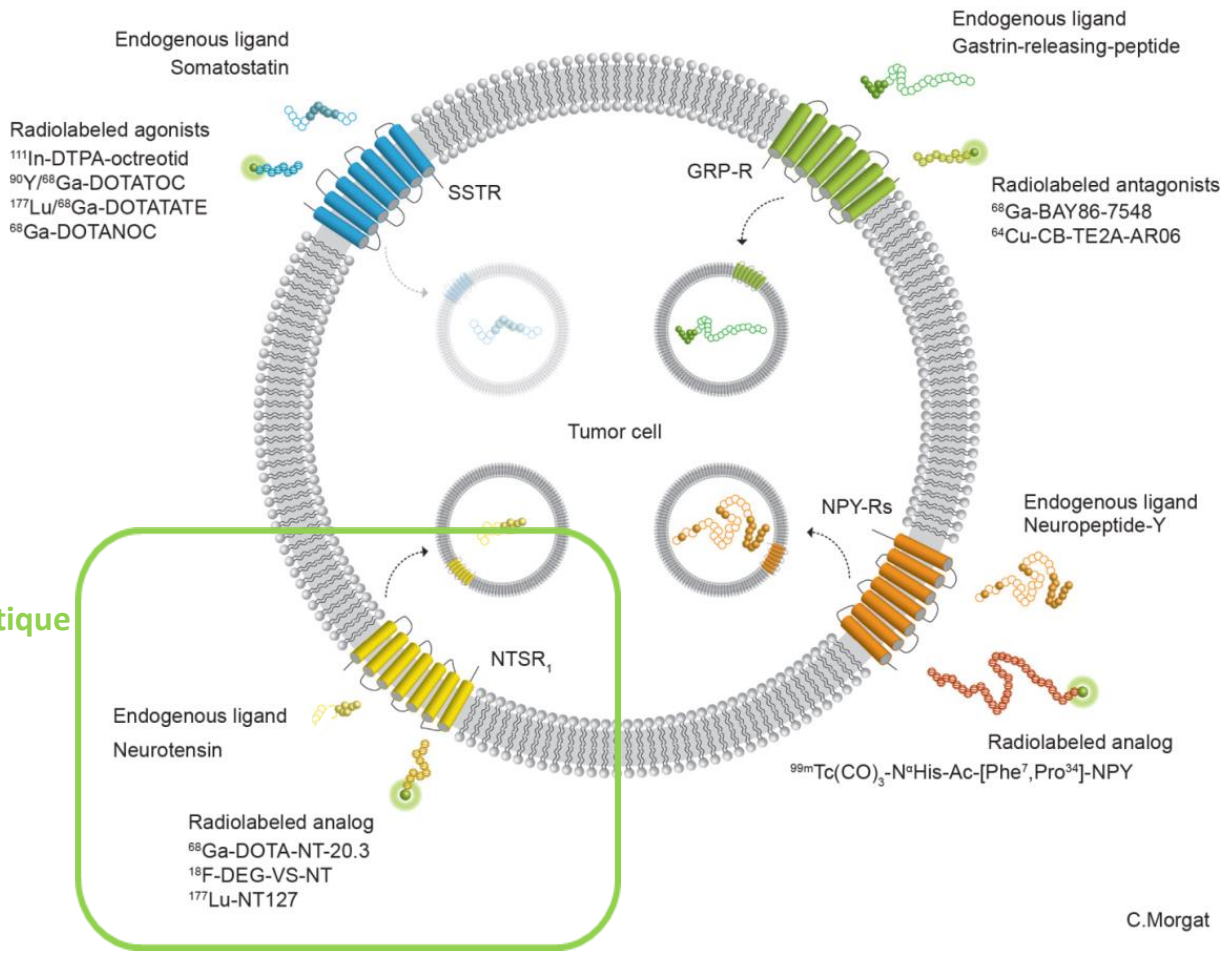
J Nucl Med. 54:762-9, 2013

- **^{177}Lu-NeoBOMB1 /** ^{68}Ga-NeoBOMB1 ***Produits recherche AAA***

Dalm SU, et al: 68Ga/177Lu-NeoBOMB1, a Novel Radiolabeled GRPR Antagonist for Theranostic Use in Oncology.

J Nucl Med. 2017 Feb;58(2):293-299.

Neurotensin Receptor-1 (NTR1)



Adénocarcinome pancréatique

Cancer du Colon

Cancer pulmonaire NSCLC

Cancer du sein

Targeting neuropeptide receptors for cancer imaging and therapy: perspectives with bombesin, neurotensin, and neuropeptide-Y receptors.

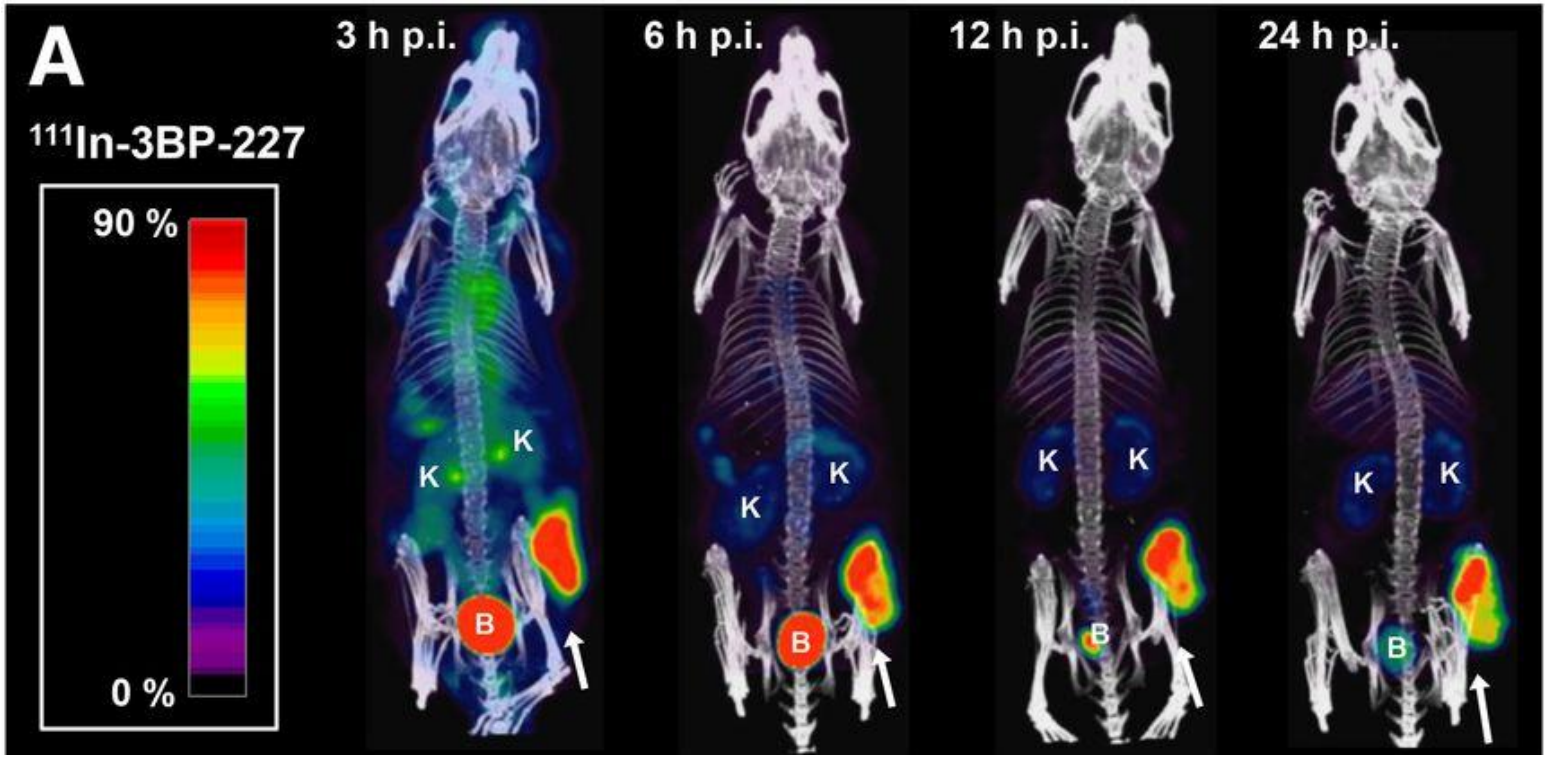
Morgat C, Mishra AK, Varshney R, Allard M, Fernandez P, Hindié E.

J Nucl Med. 2014 Oct;55(10):1650-7.

Comparative Evaluation of the Biodistribution Profiles of a Series of Nonpeptidic Neurotensin Receptor-1 Antagonists Reveals a Promising Candidate for Theranostic Applications.

Schulz J, et al.

J Nucl Med. 2016 Jul;57(7):1120-3.



Female nude mice bearing HT29 xenograft (arrows).

SPECT/CT at 3, 6, 12, and 24 h after injection (p.i.) of 22 MBq of ^{111}In-3BP-227

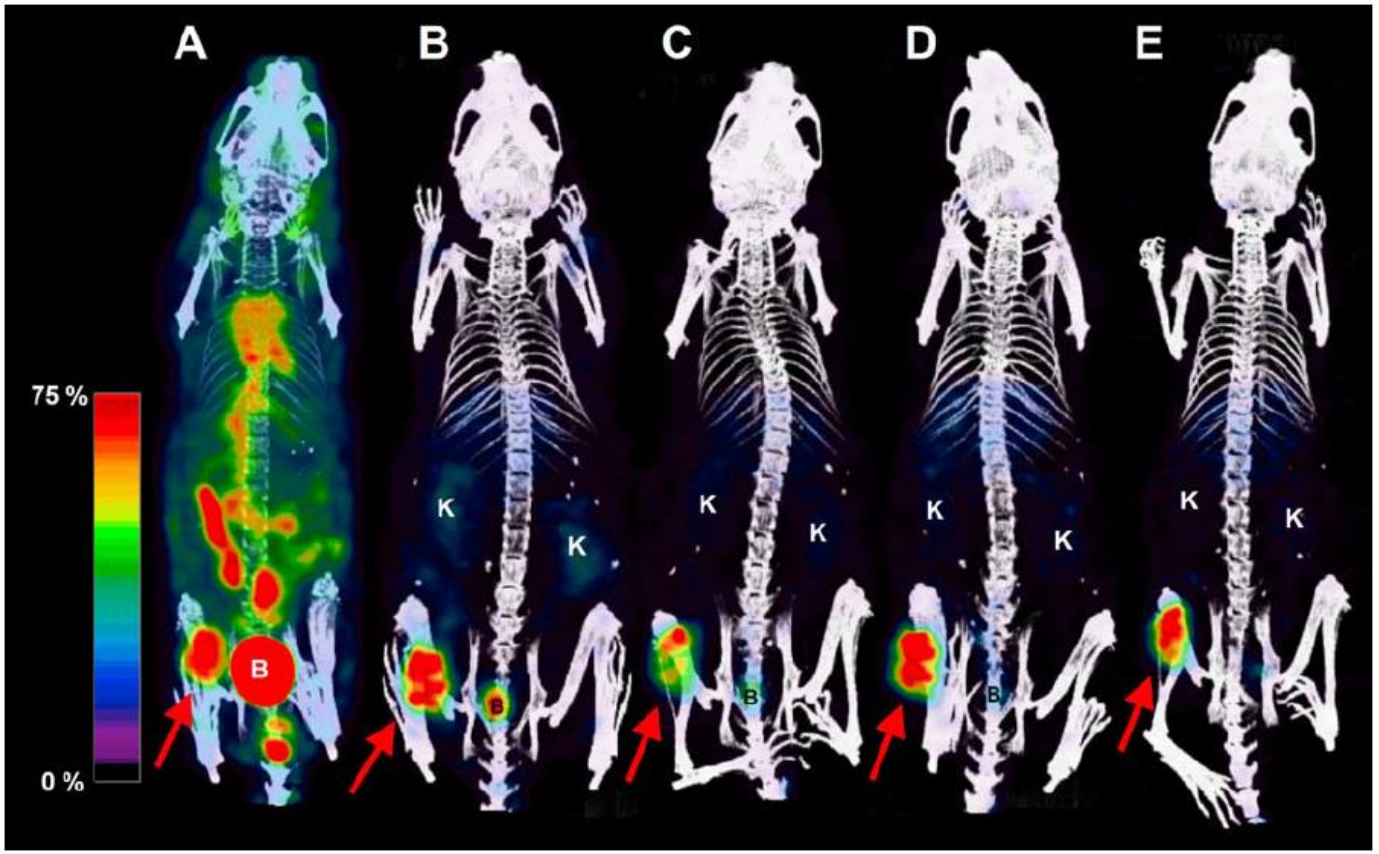
SPECT data were scaled to 0%–90% of maximum count values in HT29 tumors.

B = urinary bladder; K = kidney.

Proof of Therapeutic Efficacy of a Novel ^{177}Lu-Labeled Neurotensin Receptor 1-Antagonist in a Colon Carcinoma Xenograft Model.

Schulz J, et al.

J Nucl Med. 2017 Mar 2. [Epub ahead of print]



Co-registered SPECT/CT scans of a female nude mouse grafted with HT29 tumor cells acquired 3h (A), 20h (B), 45h (C), 69h (D), and 93h (E) p.i. of 130.7 MBq of **177Lu-3BP-227.**

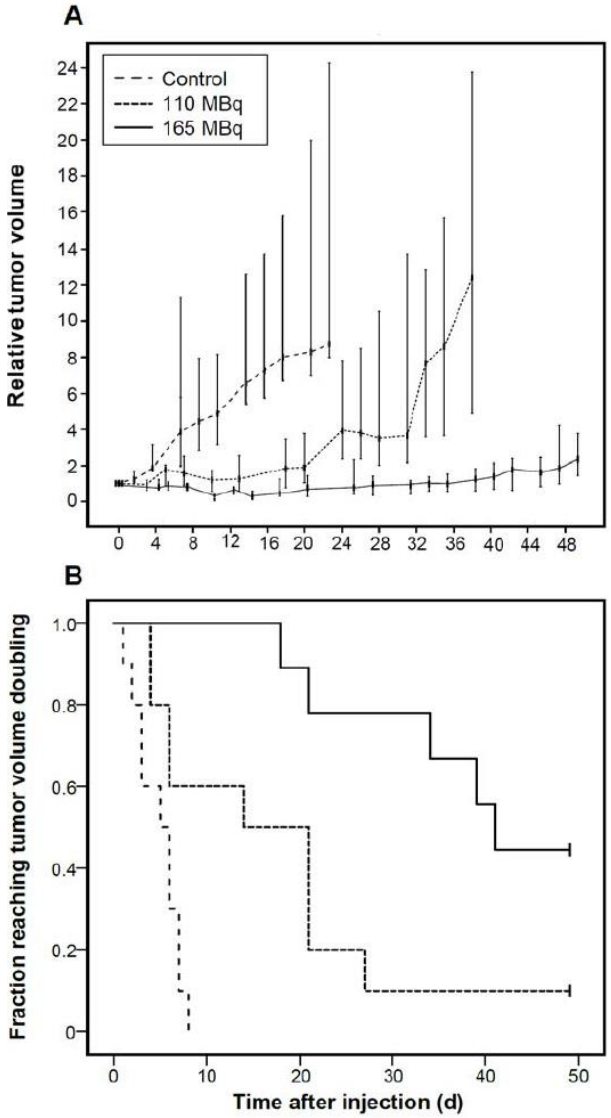
Arrows show HT29 tumors.

SPECT data were scaled to 0-75% of max

Proof of Therapeutic Efficacy of a Novel ^{177}Lu-Labeled Neurotensin Receptor 1-Antagonist in a Colon Carcinoma Xenograft Model.

Schulz J, et al.

J Nucl Med. 2017 Mar 2. [Epub ahead of print]



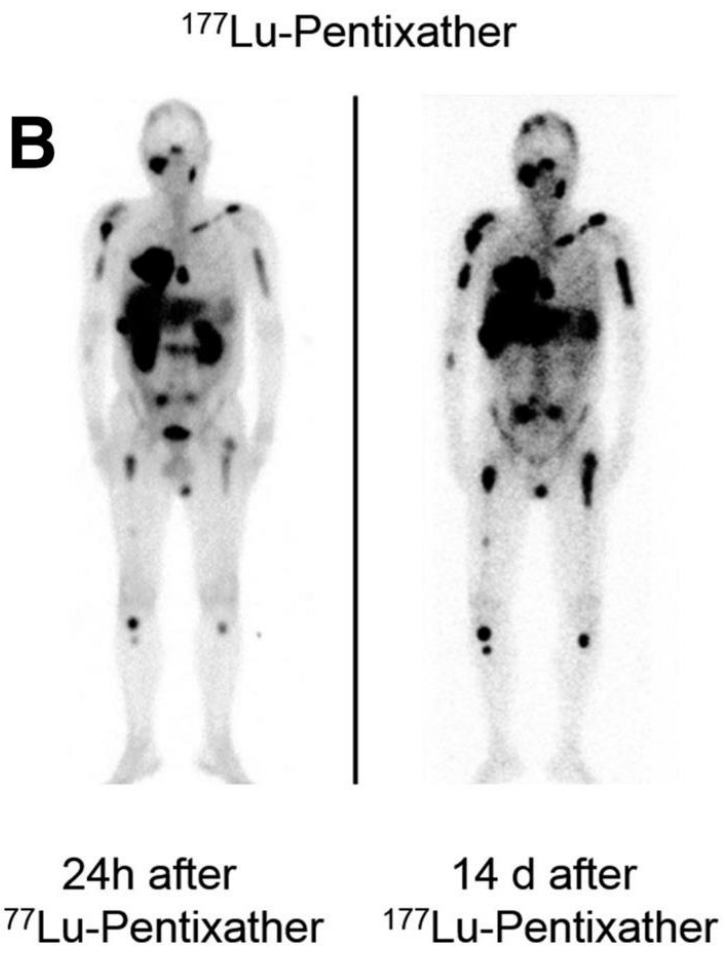
- Therapeutic effect of 177Lu-3BP-227 in female nude mice grafted with HT29 cells (A).
- Tumor volume data are normalized to the measurement at the day of 177Lu-3BP-227 injection and represented as median and interquartile range.
- Kaplan-Meier plot (B) showing tumor progression of HT29 in the same study. The end point was set at reaching a relative tumor volume of ≥ 2.

- Control: n = 10
- 110 MBq group: n = 10
- 165 MBq group: n = 9

Ciblage du CXCR4 (Chemokine receptor4)

First-in-Human Experience of CXCR4-Directed Endoradiotherapy with 177Lu- and 90Y-Labeled Pentixather in Advanced-Stage Multiple Myeloma with Extensive Intra- and Extramedullary Disease.

Herrmann K. J Nucl Med. 2016; 57:248-51.

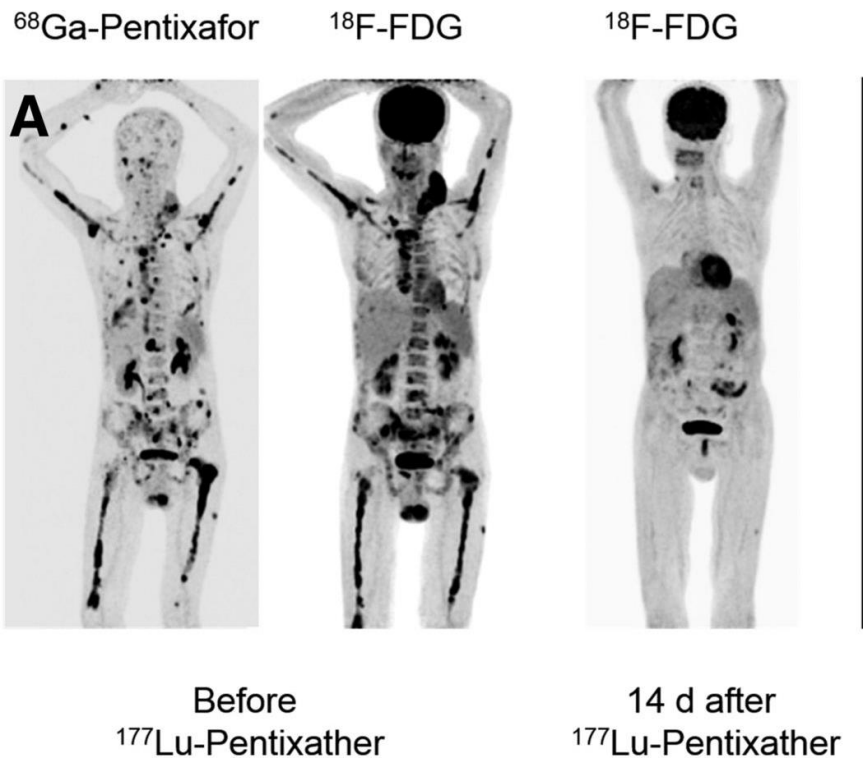


Myélome multiple avancé

- **Imagerie ^{177}Lu à 24h et J15 après administration de 15 GBq de ^{177}Lu-pentixather**
- **Expression du CXCR4 au niveau des lésions et bon ciblage même sur les images tardives.**

Ciblage du CXCR4 (Chemokine receptor4)

- **Ligand imagerie: 68Ga-Pentixafor**
- **Thérapie: 90YPentixather / 177Lu-Pentixather** *(Produits de Scintomics)*



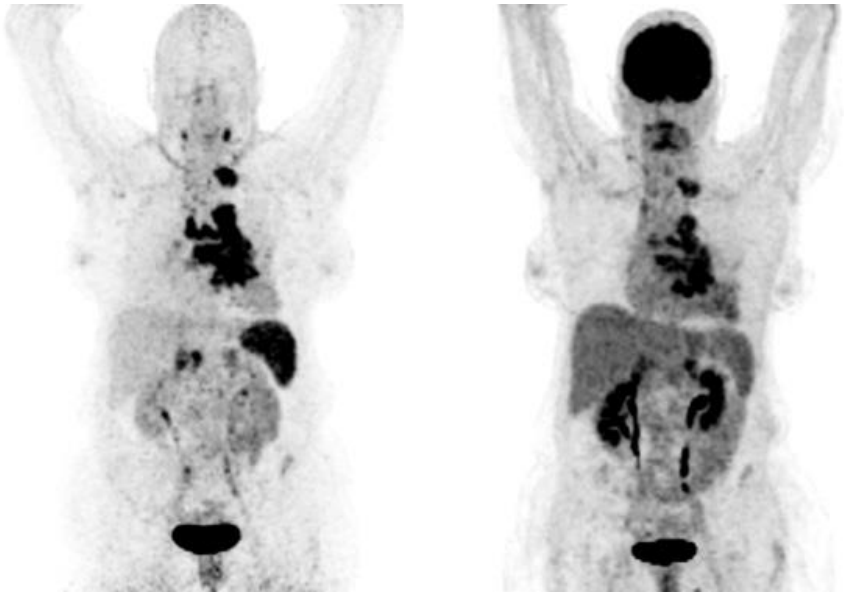
Myélome Multiple avec atteinte osseuse et extramédullaire

- Imagerie TEP (MIP) au ^{68}Ga-pentixafor et au ^{18}FDG montrant une bonne expression du CXCR4 dans les lésions
- TEP-FDG 2 semaines après radiothérapie intrerne vectorisée.

First-in-Human Experience of CXCR4-Directed Endoradiotherapy with 177Lu- and 90Y-Labeled Pentixather in Advanced-Stage Multiple Myeloma with Extensive Intra- and Extramedullary Disease.
Herrmann K. J Nucl Med. 2016; 57:248-51.

[68Ga]Pentixafor-PET/CT for imaging of chemokine receptor 4 expression in small cell lung cancer--initial experience.

Lapa C. Oncotarget. 2016; 7:9288-95.



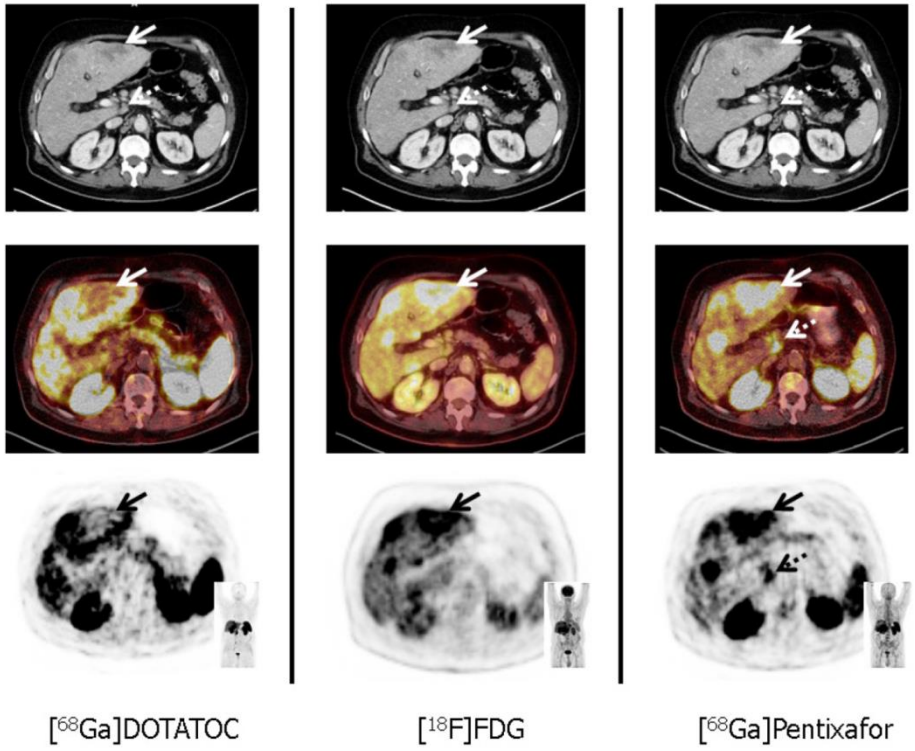
TEP au 68Ga-Pentixafor (à gauche) et TEP-FDG chez un patient avec récidive de cancer de poumon à petites cellules

Comparaison du 68Ga-Pentixafor et du 18FDG chez 6 patients avec cancer du poumon à petites cellules

- **68Ga-Pentixafor < 18FDG chez 4 (négatif chez 2)**
- **68Ga-Pentixafor > 18FDG chez 2 patients**

Imaging of Chemokine Receptor 4 Expression in Neuroendocrine Tumors - a Triple Tracer Comparative Approach

Werner RA. *Theranostics* 2017; 7(6): 1489-1498.



Etude pilote d'imagerie du CXCR4 (68Ga-Pentixafor) dans les TNE: 12 patients

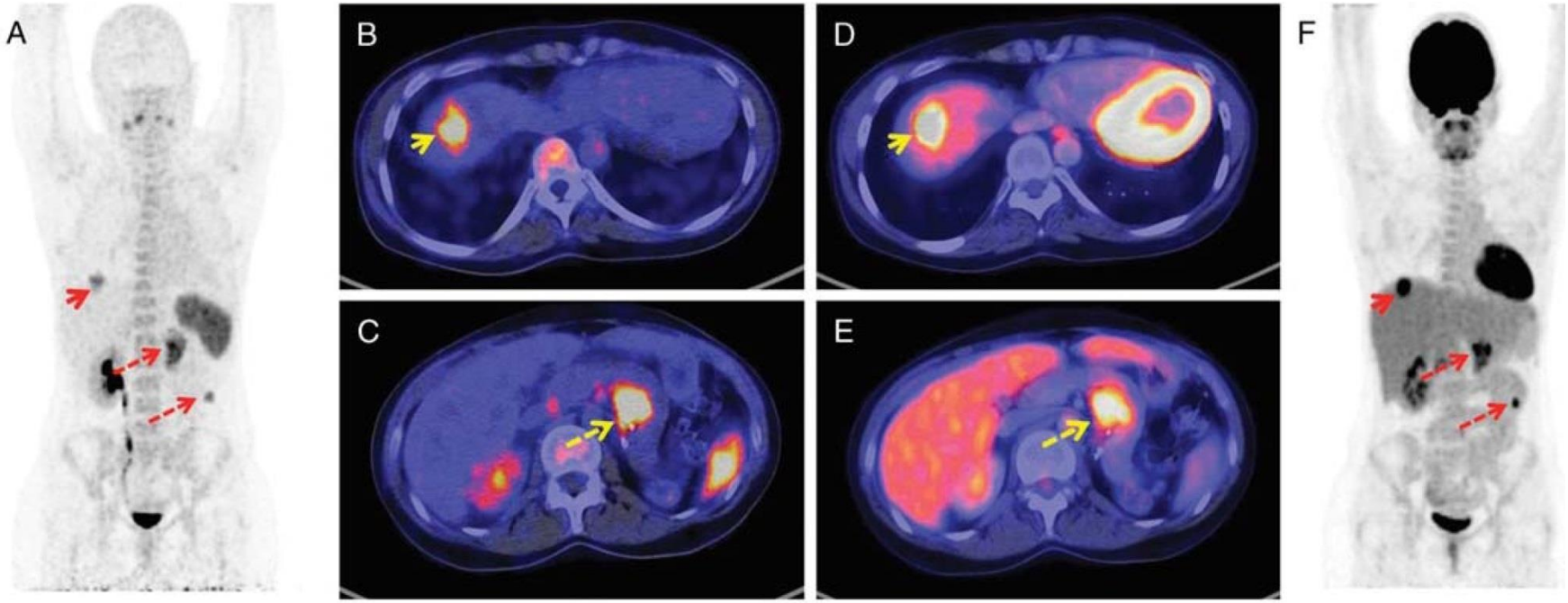
- **Négative dans les tumeurs G1**
- **Positive dans ~50% des G2 et ~80 des G3**

Tumeur neuroendocrine gastrique (G3; Ki67: 90%) avec métastases hépatiques.

- **Métastases négatives en imagerie des récepteurs de la somatostatine**
- **Hypermétaboliques en 18FDG, et**
- **Exprimant CXCR4 sur l'imagerie 68Ga-Pentixafor**

Investigating the Chemokine Receptor 4 as Potential Theranostic Target in Adrenocortical Cancer Patients.

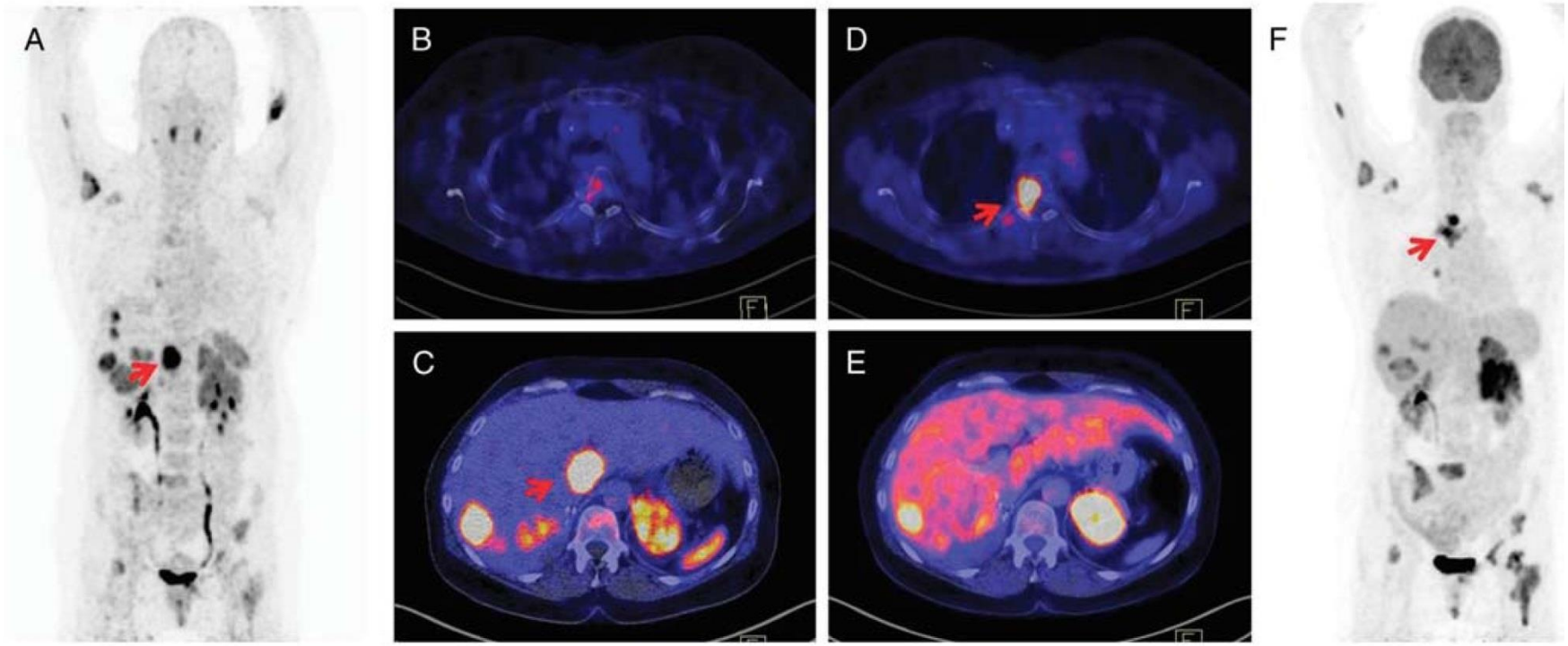
Bluemel C. Clin Nucl Med. 2017; 42:e29-e34.



- **Imagerie 68Ga-pentixafor et 18FDG PET/CT chez une patiente de 26 ans avec corticosurrénalome métastatique : Expression du CXCR4 au niveau de l'ensemble des cibles**

Investigating the Chemokine Receptor 4 as Potential Theranostic Target in Adrenocortical Cancer Patients.

Bluemel C. Clin Nucl Med. 2017; 42:e29-e34.



- **Imagerie ^{68}Ga-pentixafor et 18FDG PET/CT chez une patiente de 53 ans avec corticosurrénalome métastatique: Une des lésions osseuse exprime faiblement le CXCR4**

Merci pour votre attention !