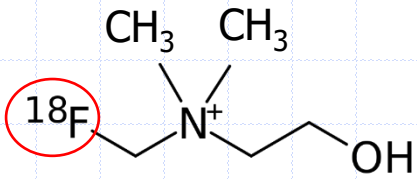
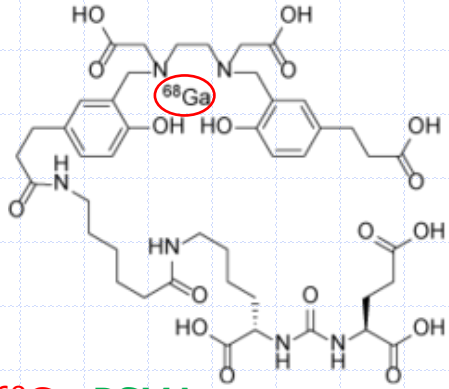
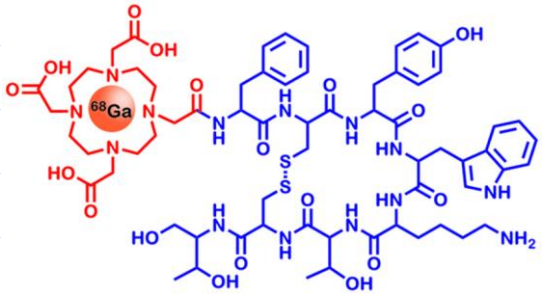
^{68}Ga-DOTA-Tyr-OCtréotide (edotréotide, Somakit)



^{18}F-CHOLINE

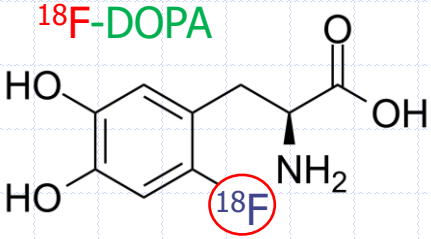


^{68}Ga-PSMA



^{68}Ga-DOTA

^{18}F-DOPA



Virginie Kouyoumdjian
Denis Mariano-Goulart

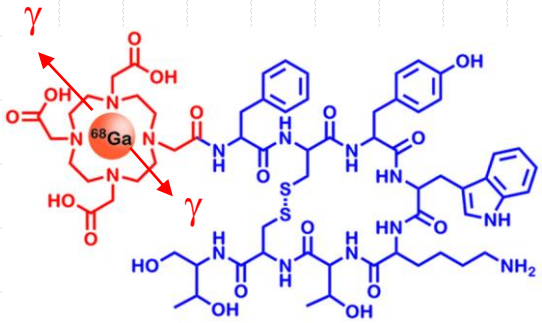
$^{68}_{31}Ga$, un équivalent TEP du ^{99m}Tc

- Cyclotron: $^{69}_{31}Ga + ^{1}_{1}p \rightarrow ^{68}_{32}Ge + 2.\,^{1}_{0}n$

- $^{68}_{32}Ge + ^{0}_{-1}e \xrightarrow[270\ j]{} \nu + ^{68}_{31}Ga \xrightarrow[68\ min]{} ^{68}_{30}Zn + ^{0}_{1}e + \nu$

- Emetteur β^+ (836; 1899 keV) à 88% + CE
  et γ (1,08 MeV)

- Ga^{3+}, complexation (DOTA, NOTA,…)



^{68}Ga-DOTA

Principaux MRP au ^{68}Ga:

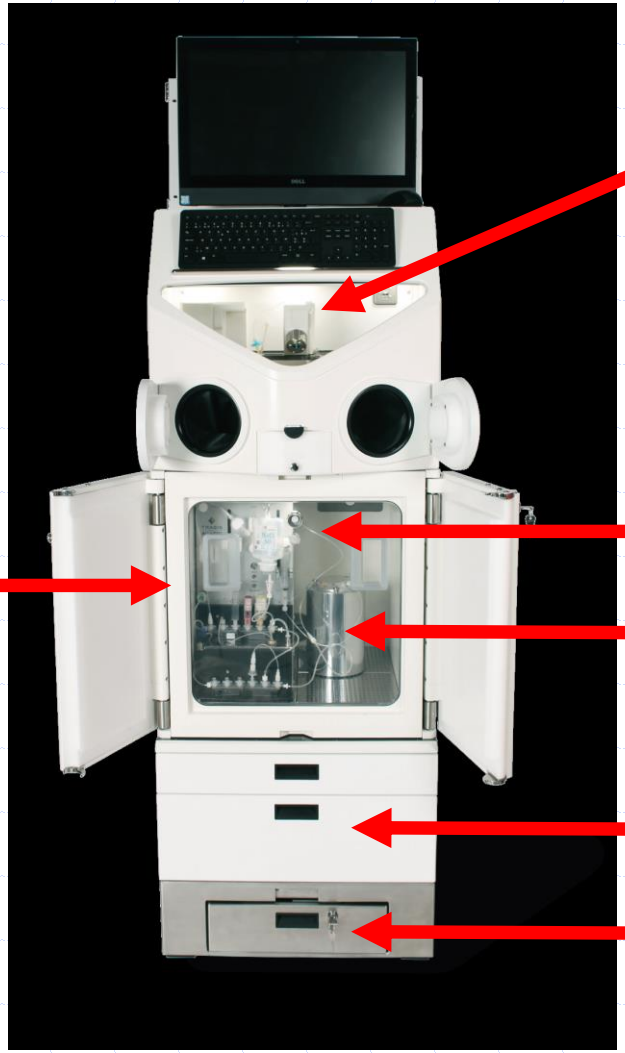
- SSTR: DOTA-TOC/NOC/TATE/(AT1S/AT2S) Agoniste SSTR 2 (5/TOC)
- PSMA

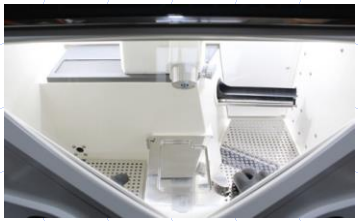
- En recherche clinique:
  - Bombésine (Gastrin Realising Peptide-R)
    - Gliomes, cancer de la prostate
  - α-Melanocyte Stimulating H (mélanome)
  - Cyclo-RGD (Arg-Gly-Asp) (néoangiogénèse tumorale)
  - Antagoniste des R type 4 aux chémokines: (leucémies, sein, prostate, poumons, ovaires, colorectal)
  - Affibody-^{68}Ga-HER_{2+} (sein)
  - Biphosphonates
  - Seul: Infection (Semin Nucl Med 2016; 46:436-447)

http://www.smno.fr/IMG/pdf/gallium-68.pdf

Enceinte H700 avec automate de synthèse

Société Trasis





Iso 5 Classe A avec ventilation et filtration autonome
Activimètre/ SAS ventilé entrée sortie matériel

Iso 7 Classe C avec ventilation et filtration autonome

Automate de synthèse :
Mini All in One

Emplacement pour 2 générateurs: Ger68/Ga68
Place pour bouteille de déchets liquides dans son blindage

Tiroirs de rangement

Marchepied

Activités de ^{68}Ga-DOTA-TOC

Somakit®: trousse de SSTR à marquer par le ^{68}Ga

RCP :

100 à 200 MBq pour un patient de 70 kg
soit entre 1,4 à 2,8 MBq/kg

Activité pratiquée par certains centres :

A Caen : 150 MBq fixe par patient, puis 120 MBq en fin de vie de générateur
A Bordeaux : 1,5 MBq/kg

Dose pédiatrique : 1,59 MBq/kg (11 à 111 MBq) (*Publication MDPI: 03/03/20)

Au CHU de Montpellier : Activité moyenne par patient : 150 MBq au T1 puis 120 MBq
Soit pour des poids moyens de 100 puis 80 kg à 1,5 MBq/kg,
A ajuster au fil de l'expérience et au poids pour les patients < 80 kg (1,5 MBq/kg)

*[68Ga]Ga-DOTA-TOC: The First FDA-Approved 68Ga-Radiopharmaceutical for PET Imaging, Ute Hennrich et al. Pharmaceuticals (Basel). 2020 Mar 3;13(3):38.

Synthèse du ^{68}Ga-DOTA-TOC

- $T(^{68}Ge) = 270\ j \Rightarrow A = A_0.2^{-t/270}$ en équilibre séculaire
- Rendement d'élution = 60%
- Perte de 4% lors du CQ
- Temps de synthèse + CQ = 50' : $2^{-50/68}$ = 60%
- A(Ga éluable) = $A_0(Ge).2^{-t/270}.(0,6).(0,96).(0,6)$
- Activité par patient : 150 MBq au *T1* puis 120 MBq

MOIS	0	1	2	3	4	5	6	7	8	9	10	11	12
A(Ga) éluable (MBq)	629	581	538	497	460	425	393	363	336	311	287	266	246
Nombre de patients	*4,2*	*3,9*	*3,6*	4,1	3,8	3,5	3,3	3,0	2,8	2,6	2,4	2,2	2,0
Nombre de patients	4	4	4	4	4	4	3	3	3	3	3	3	3
Poids moyen à 1,5 MBq/kg	105	97	90	83	77	71	87	81	75	69	64	59	55

Calibration Ge	1850	MBq	
A(Ge) 1° élution	1817	MBq	à 7 jours
REND ELUTION	0,6		
REND CQ	0,96		
TEMPS SYNTH	50	min	
MBq(Ga)/Patient	*150*	MBq	3 mois
MBq(Ga)/Patient	120	MBq	7 mois

donc changement de générateur tous les 10 mois

Programmation des examens

- Plutôt l'après-midi en fin de vacation: synthèse du Ga ajustable en fonction d'éventuels retards de planning de l'activité 18-FDG de la matinée.

- Utilisation des deux TEPs: 4 ^{68}Ga au max (2/TEP), puis 3
- Passage caméra 45' post IV (RCP de 40 à 90 min).
- Idéal = 58' et Activité maxi à 70±20 min post IV

- Maximum 18 ^{18}FDG + 2 ^{68}Ga sur chacun des 2 TEPs
- les lundis quand pas de choline (mais ↑ cholines), mercredi quand pas de DOPA, jeudi
- impossible les mardis (narcoglie) et vendredi (essais cliniques , synoviorthèses, volémies).
- Contrainte labo: dernière élution (« à blanc ») dans les 72h (impuretés).

TEP1 :
Injection 15h00 => passage 15h45
Injection 15h20 => passage 16h05 fin 16h25

TEP2:
Injection 15h00 => passage 15h45
Injection 15h20 => passage 16h05 fin 16h25

*Safety, tolerability and clinical implementation of 'ready-to-use' ^{68}gallium-DOTA0-Tyr3-octreotide (68Ga-DOTATOC) (SomaKIT TOC) for injection in patients diagnosed with gastroenteropancreatic neuroendocrine tumours (GEP-NETs) P Manoharan et al. ESMO Open. 2020 Mar;5(2):e000650.

PROTOCOLES

- Laxatif et jeûne non nécessaires
- ↕ octréotide discuté (RCP: ↕ le jour de l'examen)
- 1,5 (à 3) MBq/kg IVL ∉ Kt nutrition parentérale
- Attente 45' (< 90') post IV puis toilettes
  - Activité maxi à 70 ± 20 min post IV
- Acquisition cTAP de 20' sauf $PPGL_{métas/récidive}$
- Excrétion rénale
- E < 3 mSv

- Suspendre l'allaitement 12h post IV

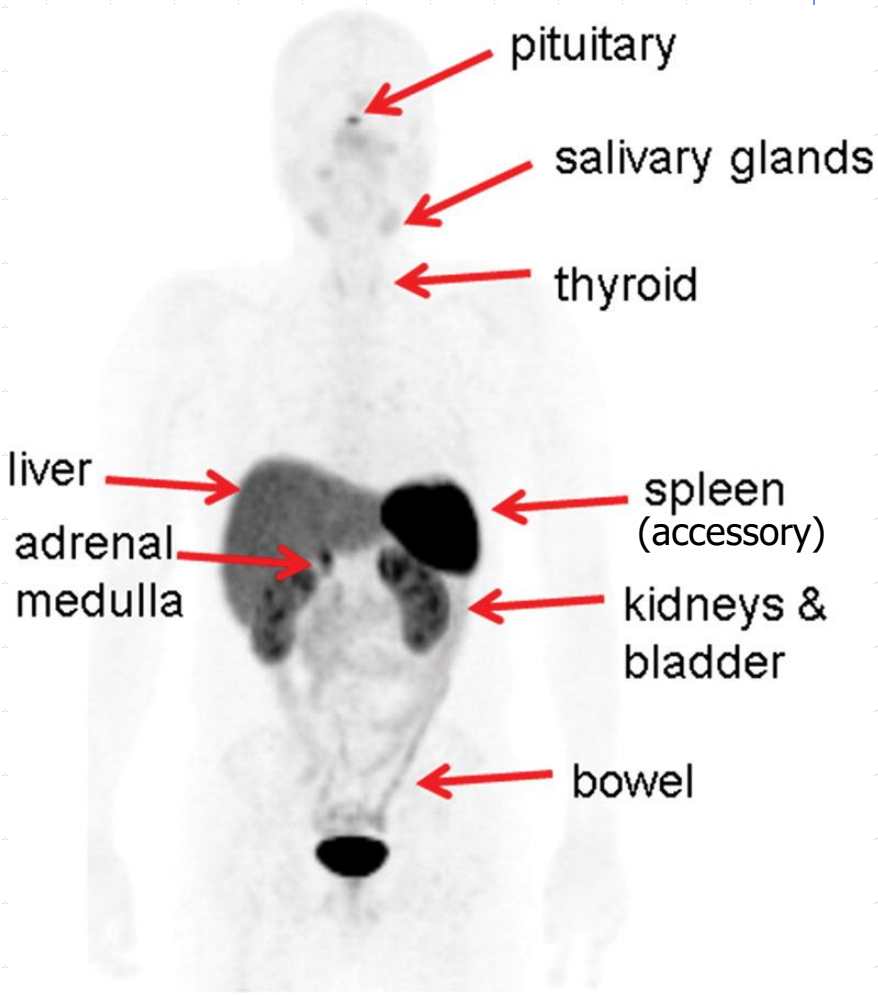
INTERPRETATION > BDF Foie

FN:

- ∅ < 2.LMH = 8 mm
- dédifférenciée (FDG)
- dans les fixations physiologiques (foie)
- hypercortisolisme (Cushing)

FP :

- lymphocytes activés/inflammation, pancréatite réactionnelle
- nodule autonome thyr, Hashimoto
- ilots (tête du) pancréas.
- Adénopathies/K,
- méningiomes, hémangioblastomes
- dysplasie fibreuse, fibrome utérin
- Carcinome mammaire,
- Tumeur hypophysaire
- K pulmonaire à petites cellules
- Tu de la crête neurale
  - CMT, paraGg, neuroblastome, phéo,
- Carcinome parotidien à cellules acineuses



± Estomac et pancréas

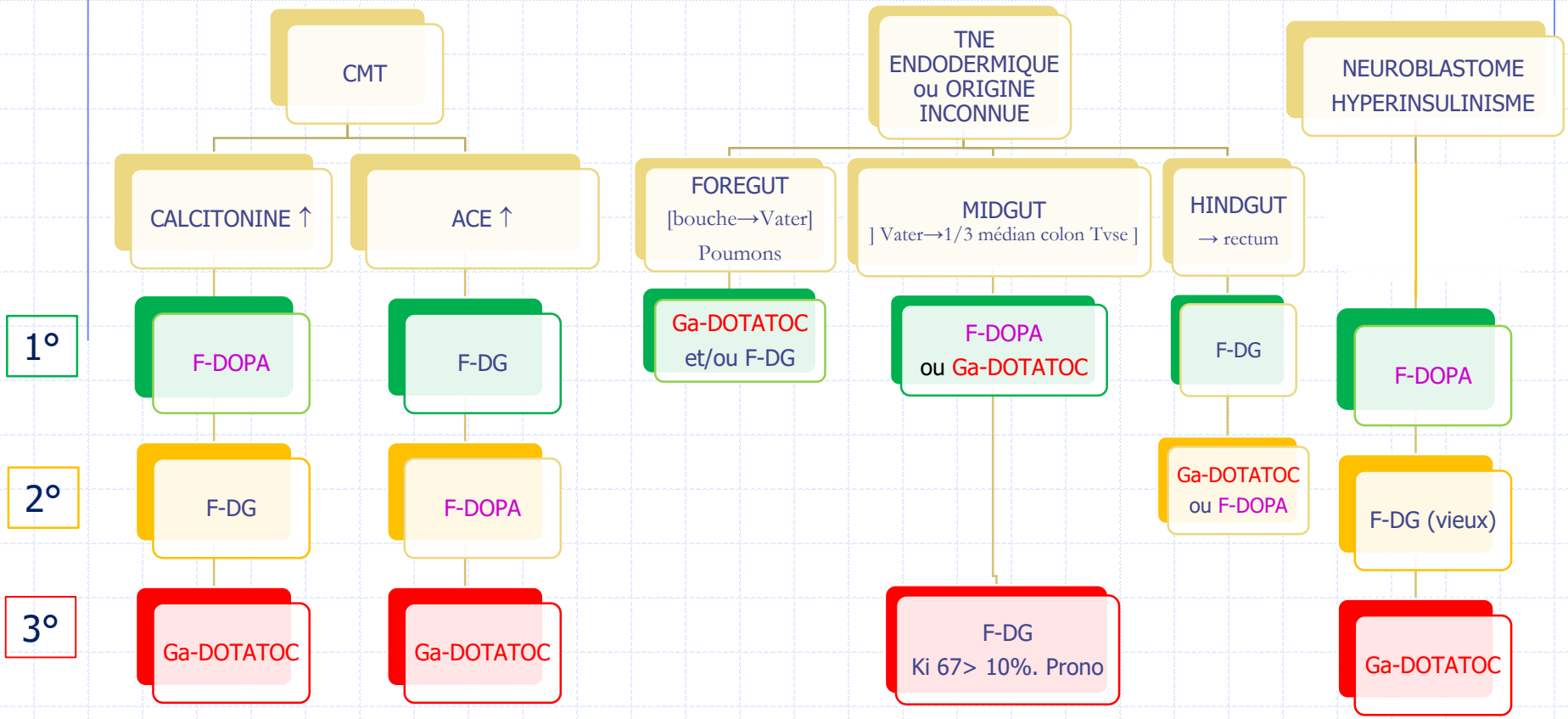
INDICATIONS: Tumeurs > endoderme

- ^{68}Ga-DOTA-TOC
  - BI TNE (foregut: bouche→Vater) ≠ carcinome (FDG)
    - TNE thymiques,
    - carcinoïdes bronchiques (^{18}FDG pour CP petites/grandes cellules)
    - digestives (estomac-D2, Foie, VB, pancréas, rate)
      - Gastrinome, insulinome, glucagonome, VIPome…
  - TNE jéjuno-iléale (midgut) si ^{18}F-DOPA négative
  - Paragangliomes
  - Phéochromocytomes si ^{18}F-DOPA négative
  - Méningiomes

- ^{68}Ga-PSMA-11 : ↑ PSA /K prostate ± choline normale

Med Nucl 42 (2019):9-31 - Eur J Nucl Med Mol Imaging. MF Bozkurt. 2017; 44:1588-1601

NEOPLASIES NEUROENDOCRINES HORS PPGL: QUEL TRACEUR ?

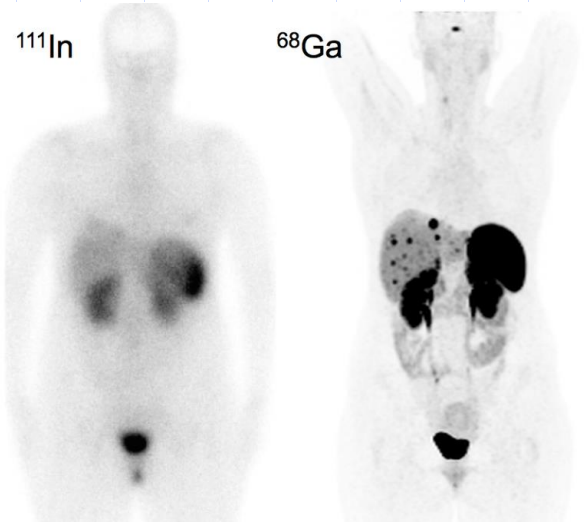


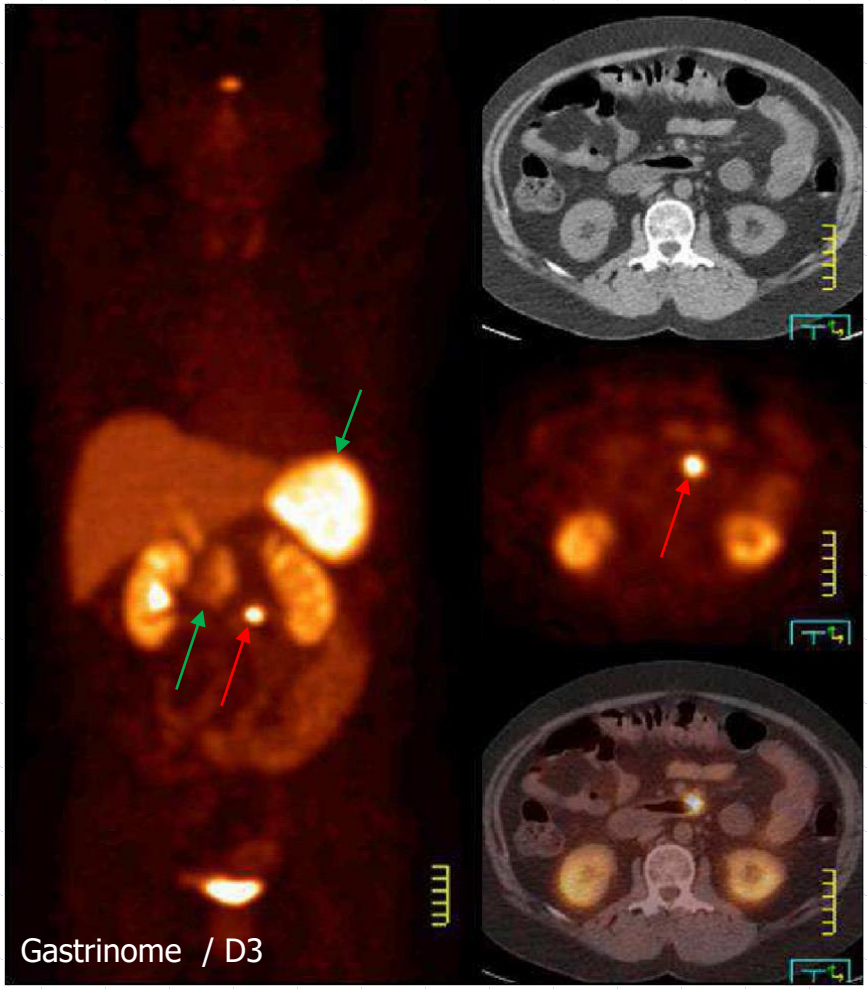
EJNM Guidelines for PET imaging of NEN with Ga and DOPA. MF Bozkurt et al. 2017. 44:1588-1601

OCTREOTIDE ET ^{68}Ga-DOTA-TOC

Méta-analyse vs. ^{111}In-OCTREOTIDE
sur 1561 TNE: 44% Δ (30% après In)

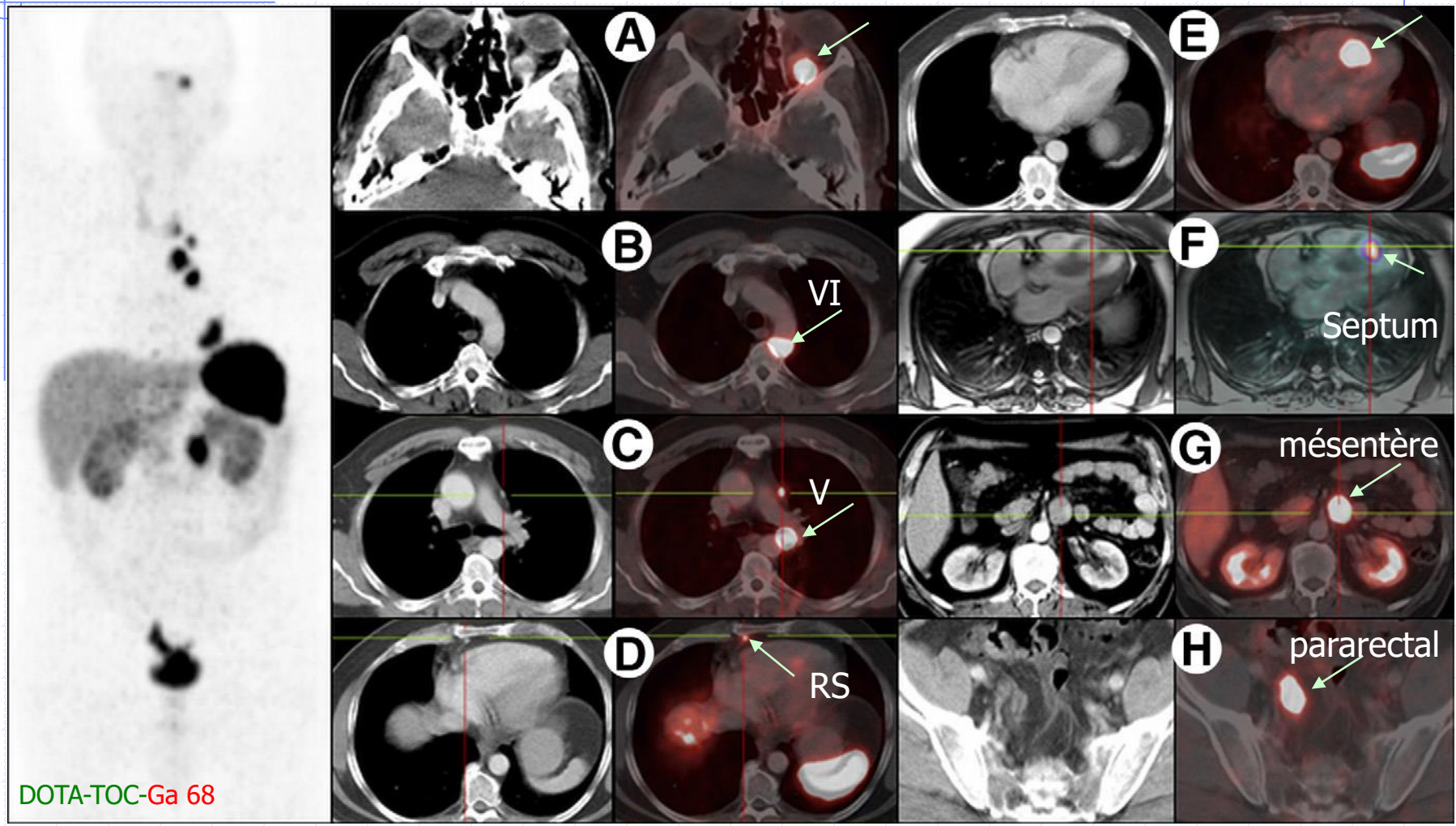
^{68}Ga-DOTA-TOC
3,6 fois moins irradiant
Résolution 15 → 4 mm
Plus sensible
Acquisition unique de 20'
Pas de laxatif
Pas d'obligation ↕ octréotide





J Nucl Med 2017;58:756-761 – Med Nucl 38(2014) 235-239

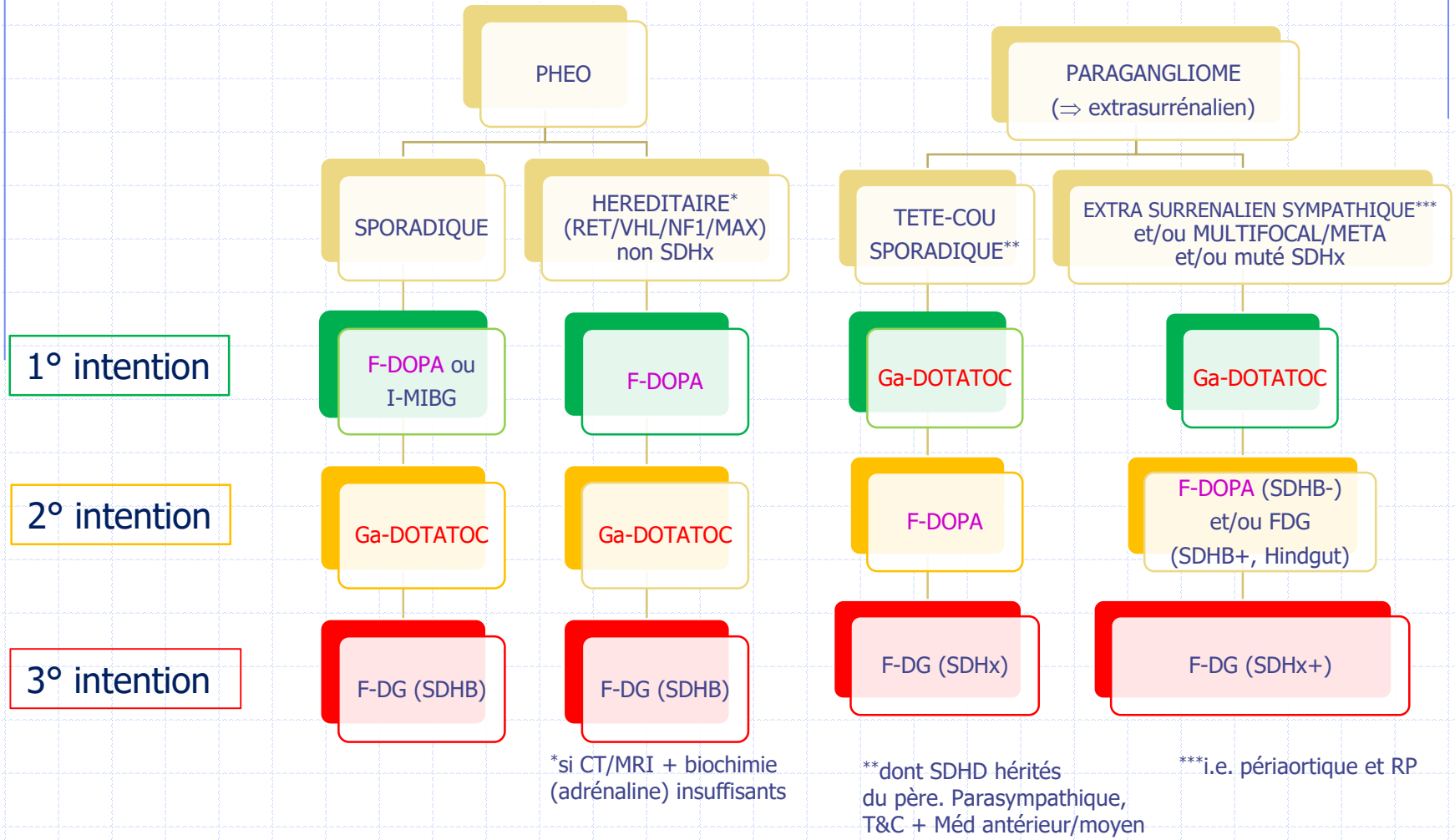
^{68}Ga-DOTA-TOC & TNE ILEALE



Rechercher: Médiastin, RP, surrénales + orbites, m. hypoglosse, thyroïde, cœur & péricarde, foie & VB, queue de cheval, paroi vessie (furosémide)…

Semin Nucl Med, 2012; 42:190-207

PHEOCHROMOCYTOME & PARAGANGLIOME: QUEL TRACEUR ?



EJNM 2019. EANM/SNMMI Guidelines. D Taïeb 46:2112-2137 et 2017 MF Bozkurt; 44:1588-1601

Table 1 Characteristics of the various hereditary forms of phaeochromocytomas and paragangliomas

	First manifestation	Context at presentation (in index cases)	PHEO at presentation	Additional extra-adrenal PGL	Biochemical phenotype	Malignancy risk	Other tumour types
MEN2	MTC	Adult Possible phenotypic features of MEN2 Family history of MTC/PHEO is common	Uni- or bilateral	Very rare	EPI	Very low	Parathyroid adenoma/hyperplasia (MEN2A)
NF1	Neurofibromas	Adult Phenotypic features of neurofibromatosis type 1 Family history of neurofibromatosis type 1 is possible	Often unilateral	Very rare	EPI	Very low	Peripheral nerve sheath tumours, optical glioma[a]
MAX	PHEO	Young adult Family history of PHEO is common	Bilateral	Uncommon	EPI and NE	Moderate	Renal oncocytoma
VHL	PHEO/PGL	Young adult Family history of PPGL is common	Uni- or bilateral	Moderate (retroperitoneum)	NE	Low	Multiple[b]
SDHA	PHEO/PGL	Adult Family history of PPGL is extremely rare	Rare	Moderate (retroperitoneum or head and neck)	NE and/or DA	Moderate/high	GIST [c], RCC
SDHB	PHEO/PGL	Adult Family history of PPGL is possible	Often unilateral	Common (retroperitoneum)	NE and/or DA	High	GIST[c], pituitary adenoma, RCC
SDHD	PHEO/PGL	Adult Family history of HNPGL is common	Uni- or bilateral	Common (head and neck)	NE and/or DA	Moderate	GIST[c], pituitary adenoma, RCC
SDHC	PHEO/PGL	Adult Family history of PHEO/PGL is rare	Rare	Common (mediastinum)	NE	Low/Moderate	GIST[c], RCC
HIF2A	Polycythaemia (often at birth or in early childhood)	Adolescent girls or young adult women Family history of PPGL is absent	Rare	Expected (retroperitoneum)	NE	High	Somatostatinoma

MAX: myc-associated factor X, MEN: multiple endocrine neoplasia, NF1: neurofibromin 1, VHL: von Hippel–Lindau, SDHA, -B, -C, and -D: succinate dehydrogenase subunits A, B, C, and D, HIF2A: hypoxia-inducible factor 2α, PPGL: phaeochromocytoma and paraganglioma, PHEO: phaeochromocytoma, PGL: paraganglioma, MTC: medullary thyroid carcinoma, HNPGL: head and neck paraganglioma; GIST: gastrointestinal stromal tumour, RCC: renal cell carcinoma, EPI: epinephrine, NE: norepinephrine, DA: dopamine

[a] *NF1*-associated PGEOs/PGLs are characterised by the presence of multiple neurofibromas, café-au-lait spots, Lisch nodules of the iris, and other rare disorders

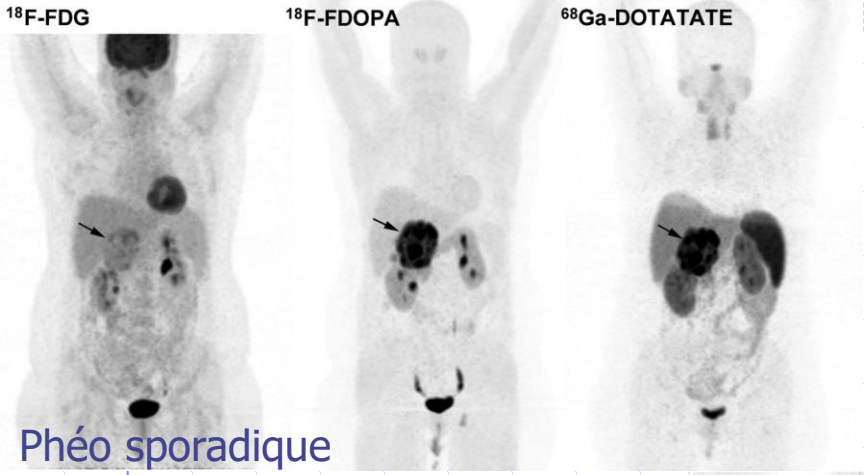
[b] VHL disease is an autosomal dominant disorder that also predisposes to renal tumours and clear cell carcinoma, pancreatic serous cystadenomas, pancreatic neuroendocrine tumours, testicular tumours, and haemangioblastoma of the eye and central nervous system

[c] Non-*KIT/PDGFRA* GISTs may be caused by mutations in the SDHA-D genes and could be associated with PGLs in patients with Carney–Stratakis syndrome

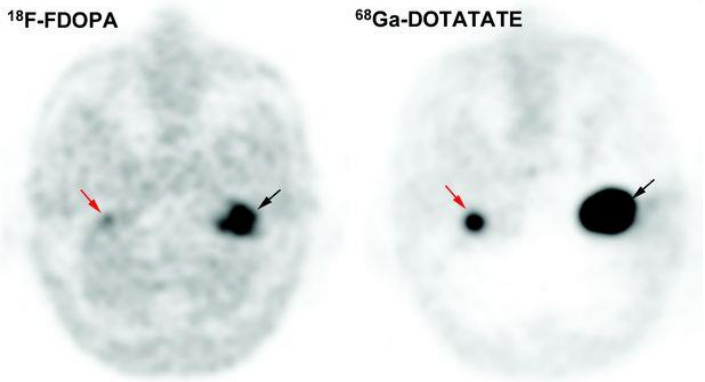
[d] *HIF2A*-related PHEOs/PGLs are associated with the presence of duodenal somatostatinoma and retinal abnormalities (Pacak–Zhuang syndrome)

EJNM 2019. EANM/SNMMI Guidelines. D Taïeb 46:2112-2137

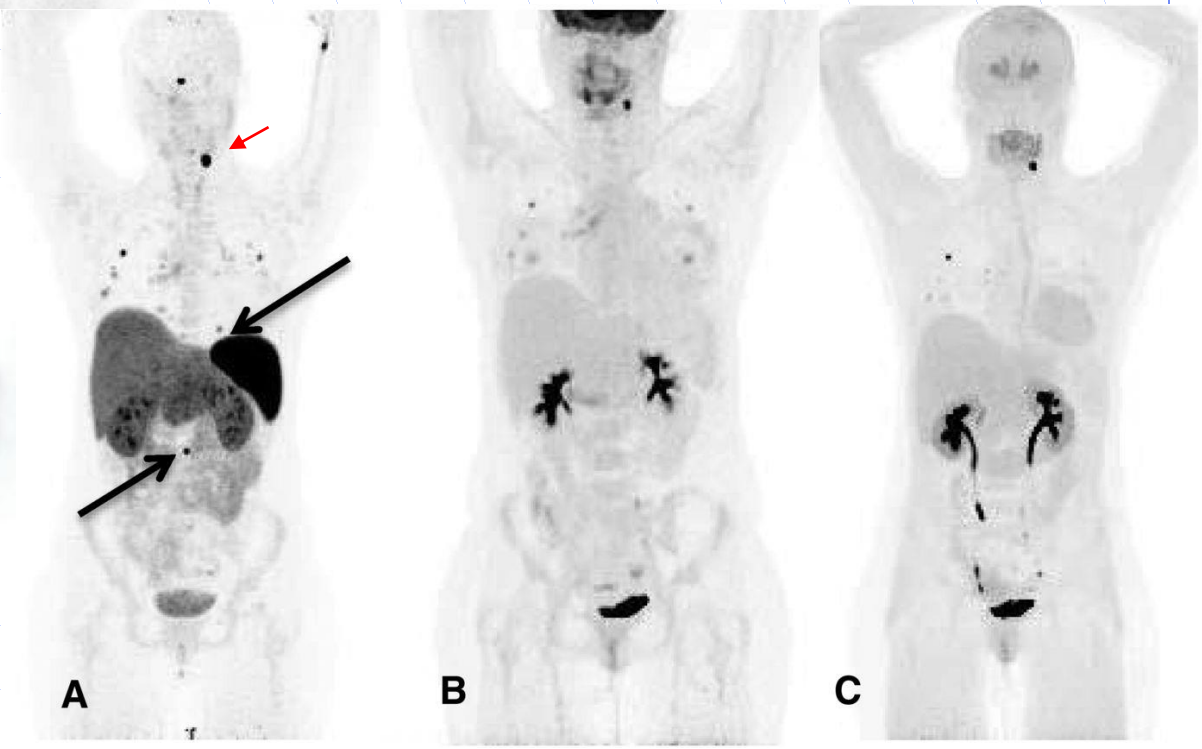
EXEMPLES



Phéo sporadique



PGL muftifocal SDHD-

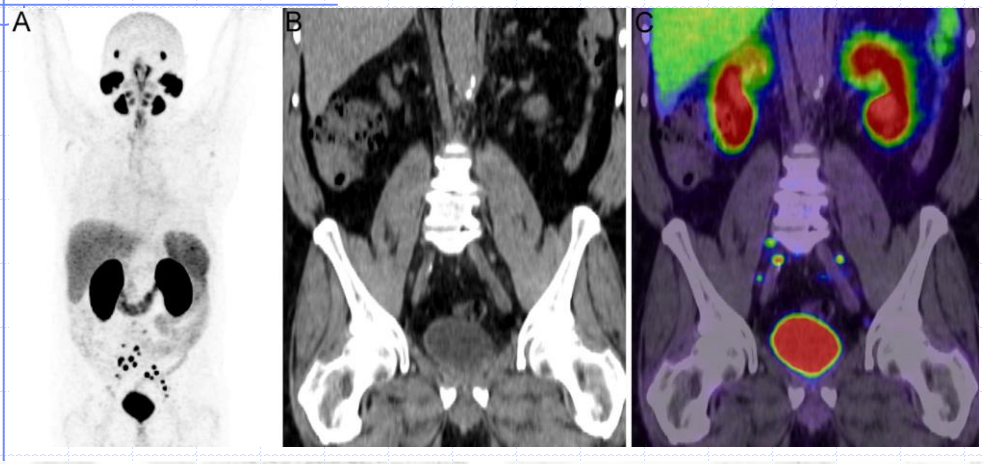


[^{68}Ga]-DOTATATE [^{18}F]-FDG PET [^{18}F]-FDOPA

PGL métastatique (poumon, os) SDHB +

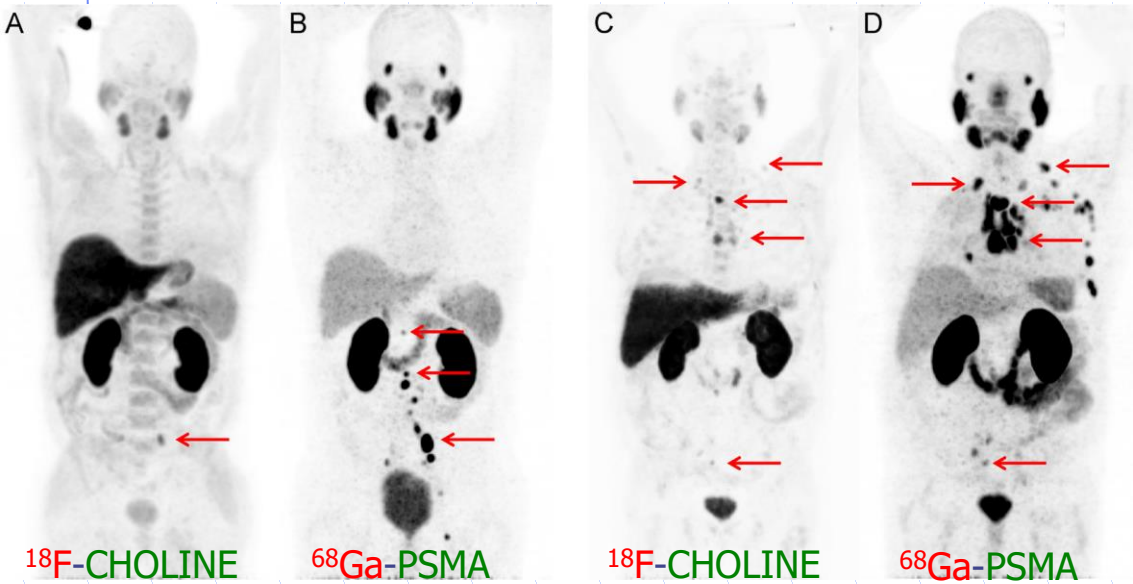
I Janssen et al. Clin Cancer Res; 21(17); 3888–95. 2015

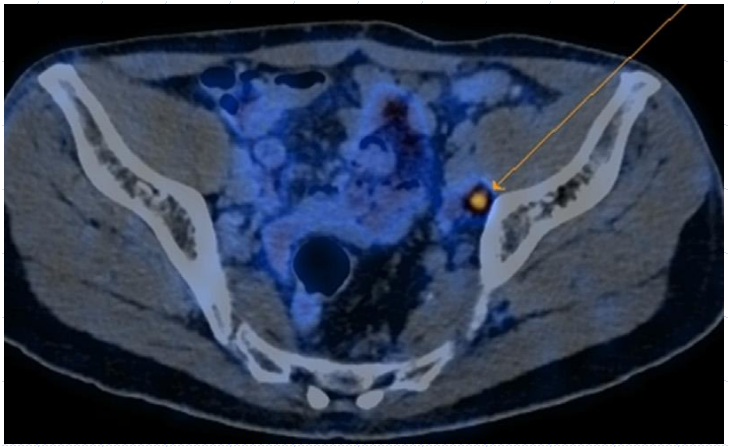
^{18}F-CHOLINE ET ^{68}Ga-PSMA



^{68}Ga-PSMA-11: ligand inhibiteur du PSMA, protéine transmembranaire ↑ ADC prostate ∝ Gleason, gravité
Pas si spé: grêle, pancréas, SNP, glandes salivaires…

ATU 2018: ↑ PSA ± choline normale
10 % d'examens TEP-Ga-PSMA normaux
30-50% changement thérapeutique

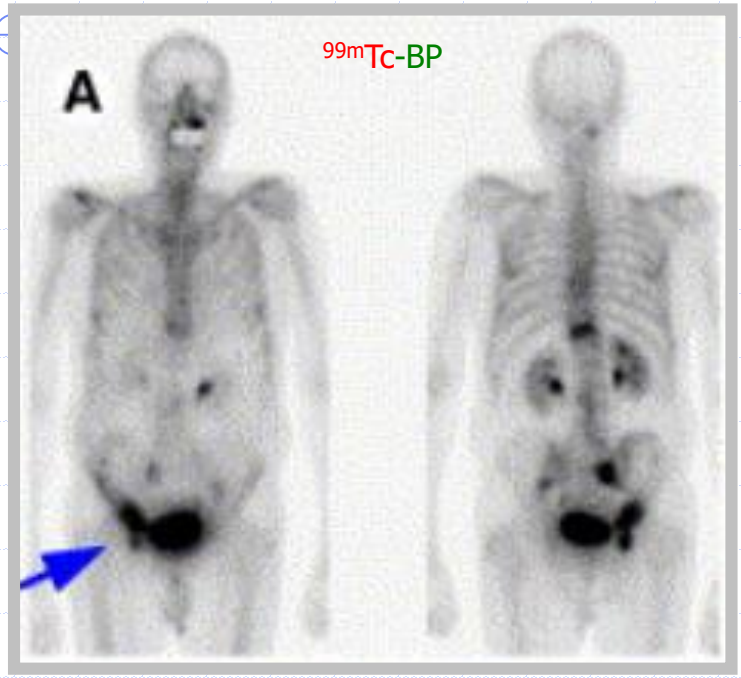


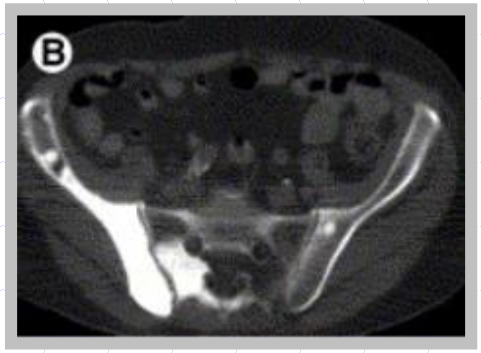


^{68}Ga-PSMA après ^{18}F-CHOLINE négative

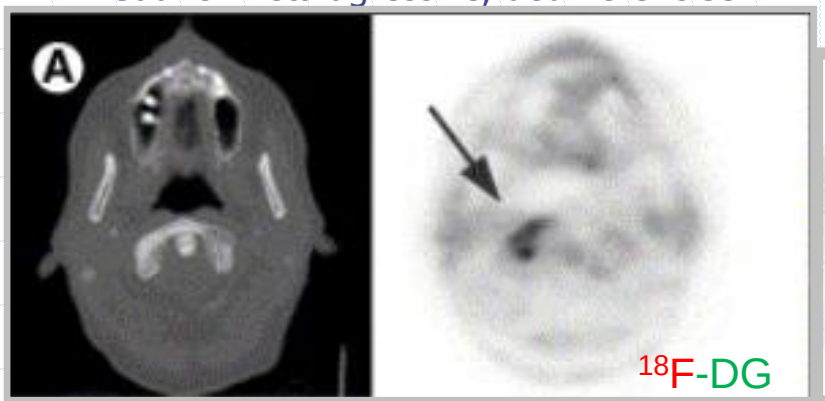
Semin Nucl Med 2016;46:405-418, Médecine Nucléaire 2017; 41: 453-457

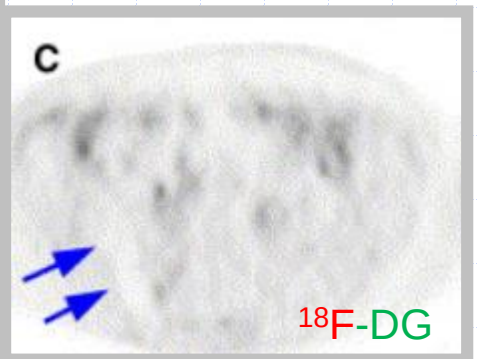
FDG & CANCERS DEDIFFERENCIES

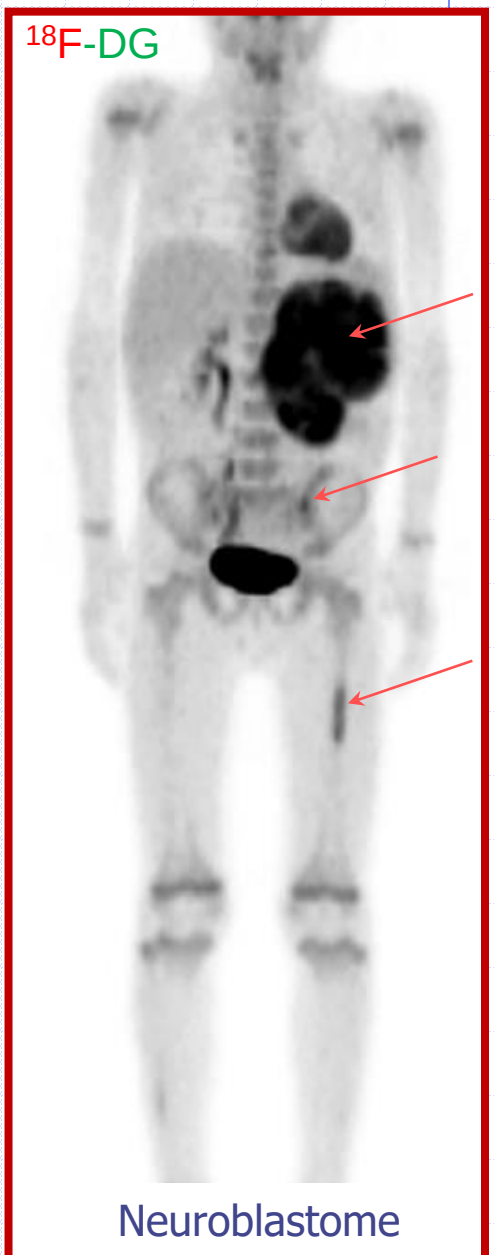




Se (99mTc-BP) >> Se(18F-DG)
Sauf si méta agressive, dédifférenciée

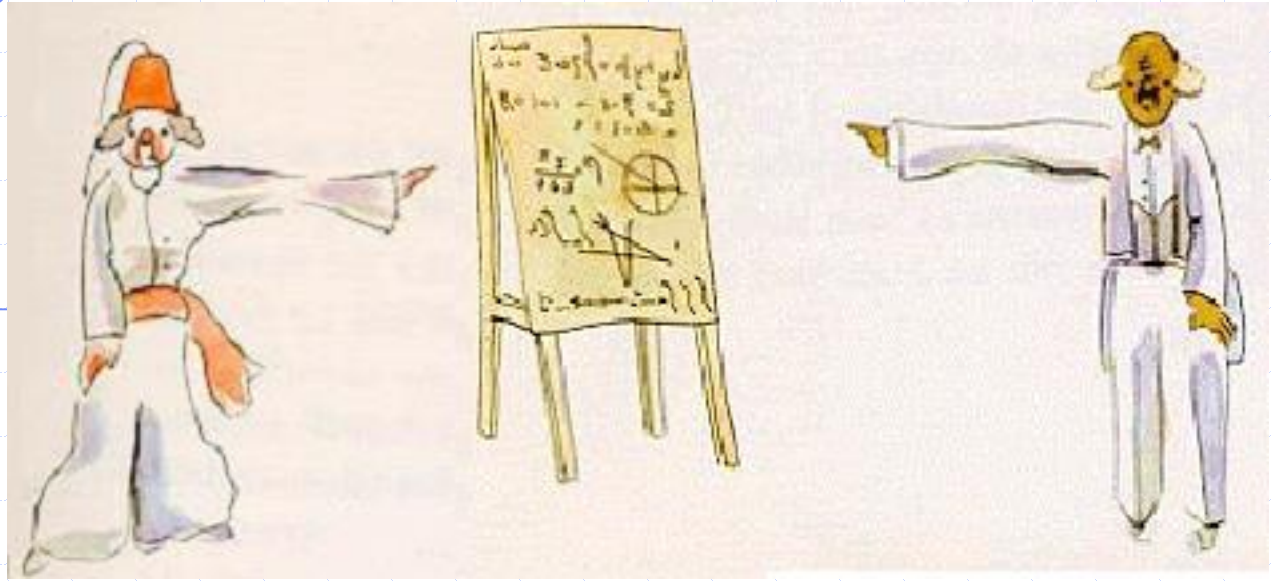






Neuroblastome

MERCI POUR VOTRE ATTENTION



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