Is PET the future of Nuclear Medicine?

JN TALBOT and all the team of

Service de Médecine Nucléaire

Hôpital Tenon et Université Pierre et Marie Curie, Paris, France

Nuclear medicine imaging (NMI) uses
- radiolabelled tracers (« radiopharmaceuticals »)
- administered at a nanomolar amount (or even less)
- which are taken up by target organs and/or lesions according to a molecular biologic or metabolic process
to obtain, by non invasive external detection, images of their biodistribution.

Two different NMI techniques are available, according to the radionuclide of the radiopharmaceutical
- scintigraphy (SG) and tomoscintigraphy (SPECT)
-positron emission tomography (PET), the most recent modality of medical imaging in clinical practice.

Is PET the future of nuclear medicine = Does PET open new domains to NMI that were not accessible to SG & SPECT? can PET replace SG & SPECT in all current applications? Is it feasible?

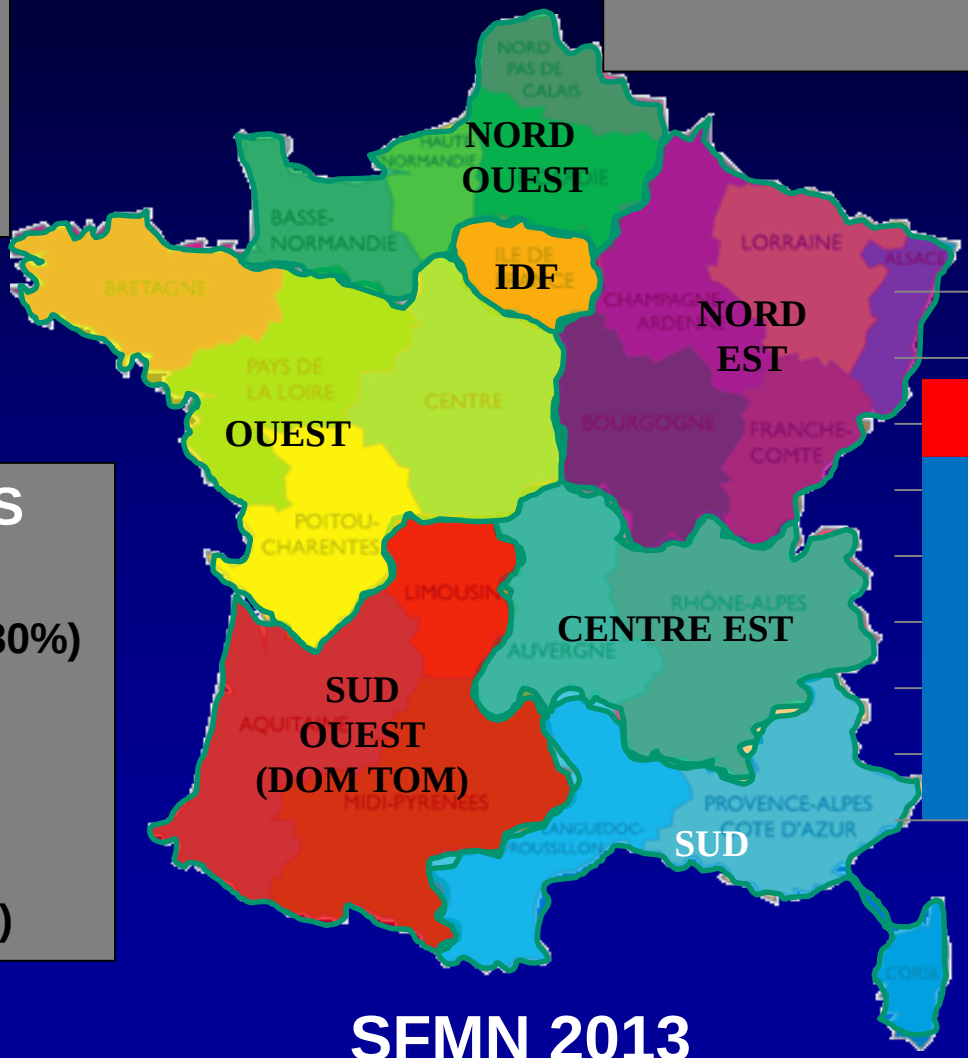
217 NM centres in France for 66 M inhabitants

623 NM
specialists
Men 63%
Women 37%

560 MACHINES

- **457 γ cameras (80%)**
  234 SPECT (51%)
  200 SPECT/CT (44%)
  23 CZT (5%)
- **113 PET/CT (20%)**

Diagnostic examinations 2013
Total: 1 272 274
(average 1.9% of inhabitants)
SG&SPECT: 962 640 (75%)
PET: 309 634 (25%)



Trend

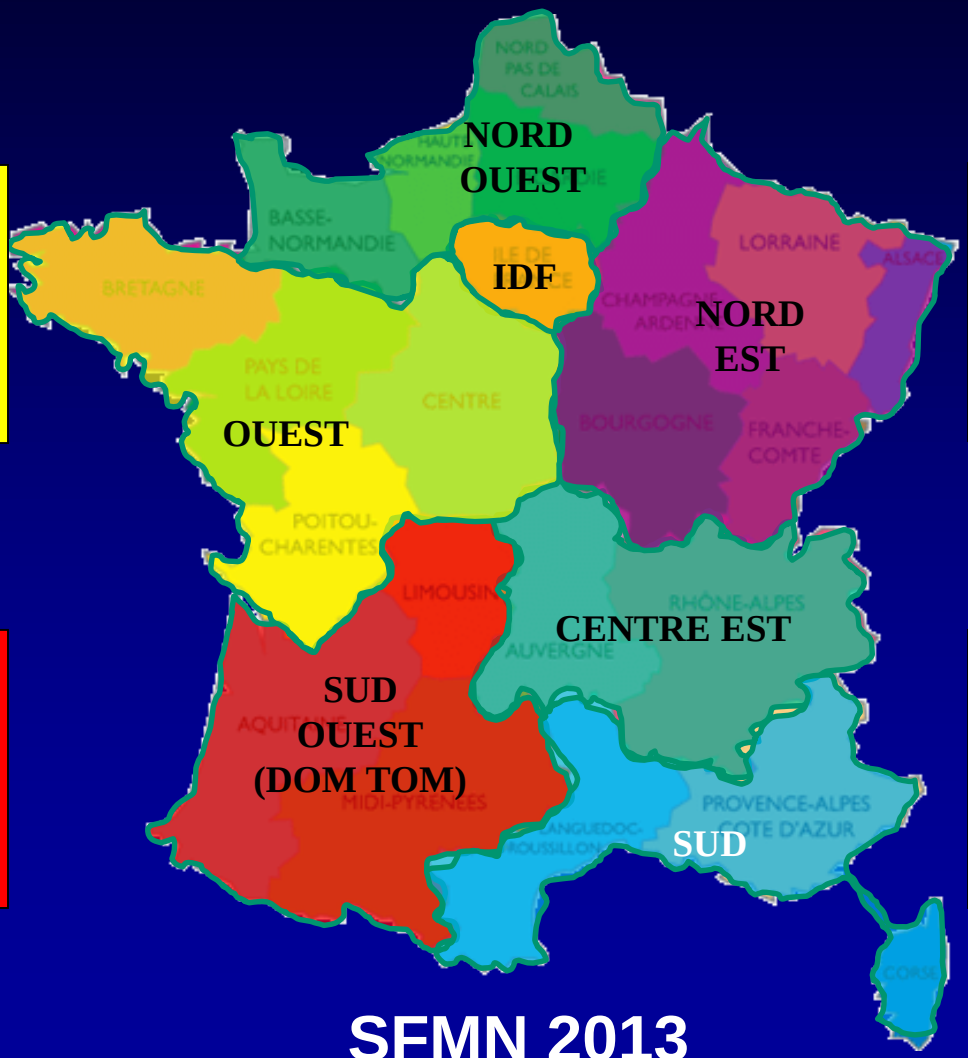
SFMN 2013

IDF
(12 M inhabitants)
43 centres
133 MN
85 SPECT
22 PET

NORD OUEST
34 centres
81 MN
67 SPECT
20 PET

NORD EST
33 centres
89 MN
66 SPECT
14 PET

OUEST
32 centres
89 MN
56 SPECT
17 PET



CENTRE EST
20 centres
66 MN
57 SPECT
12 PET

SUD OUEST
26 centres
77 MN
57 TEMP
12 PET

SUD
26 centres
88 MN
63 TEMP
15 PET

SFMN 2013

Technical comparison of PET vs. SG&SPECT

- Resolution of tomographic images: PET better than SPECT

- Simultaneous acquisition but separate imaging with dual tracers: possible only with SG&SPECT, but possible sequentially 11C-18F or 68Ga-18F

- Duration of acquisition: PET shorter than SPECT
- (SPECT of the whole body is not feasible in a reasonable time)

- Number of patients per working day: PET typically twice more than SG&PET

- Duration of the whole procedure, including waiting time:
- PET better than SPECT for comparable indications e.g. bone PET (45 min) vs. bone SG&SPECT (>120 min)

- Radiation exposure of the patient: similar

- Limitation of contacts, children caring, travels, for the patient: shorter with PET (half life of 18F=110 min) than with SPECT (half life of 99mTc=360min)

- Radioactivity release to the environment: less with PET

Can PET open new domains to Nuclear Medicine imaging (NMI) that were not accessible to scintigraphy & SPECT?

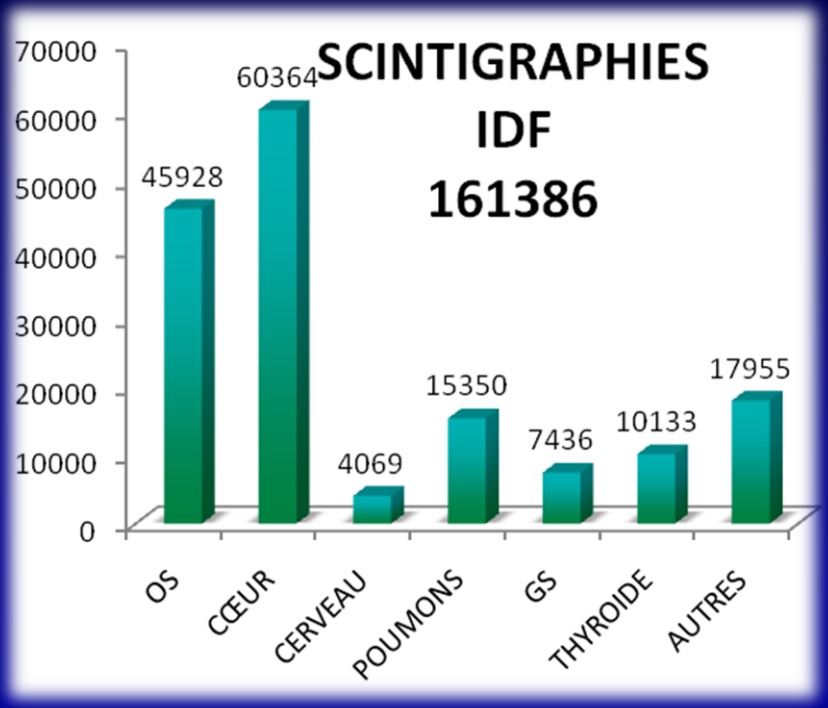
Yes ! No radionuclide emitting gamma “single” photons suited for imaging was a radioisotope of the atoms constituting

- natural organic molecules C, H, O, N, S
- ions of a biologic interest: Na, Cl, F, Ca, P, Fe.

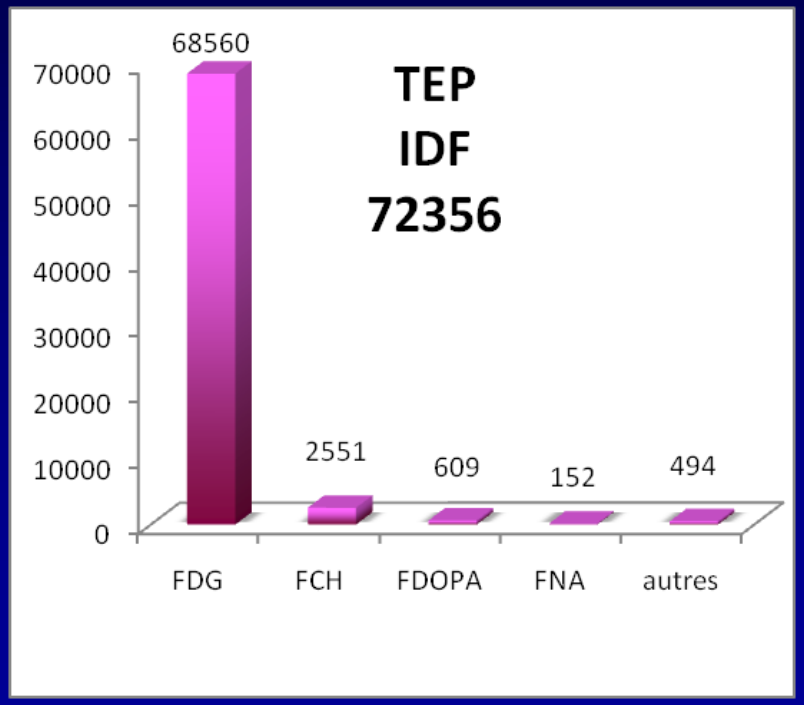
In contrast with radionuclides emitting positrons: 11C, 15O, 13N, 18F.

It was then possible to label small molecules of high biological importance and their analogues for PET: glucose, small lipids, aminoacids, water, ammonium ...

1898 examinations per γ camera



3288 examinations per PET/CT



2013

Oncology

For clinical PET, FDG is not the only registered and reimbursed tracer in France. In EU, 3 other radiopharmaceuticals have been registered: 18F-FDOPA, 18F-fluoride, 18F-fluorocholine (FCH)

And others are used for clinical applications: 18F-fluoroethylthyrosine (FET), 18F-FMISO, 18F-fluoroestradiol (FES), 11C-choline, 11C-acetate, 11C-methionine, 68Ga-somatostatin analogue, 68Ga-PSMA …

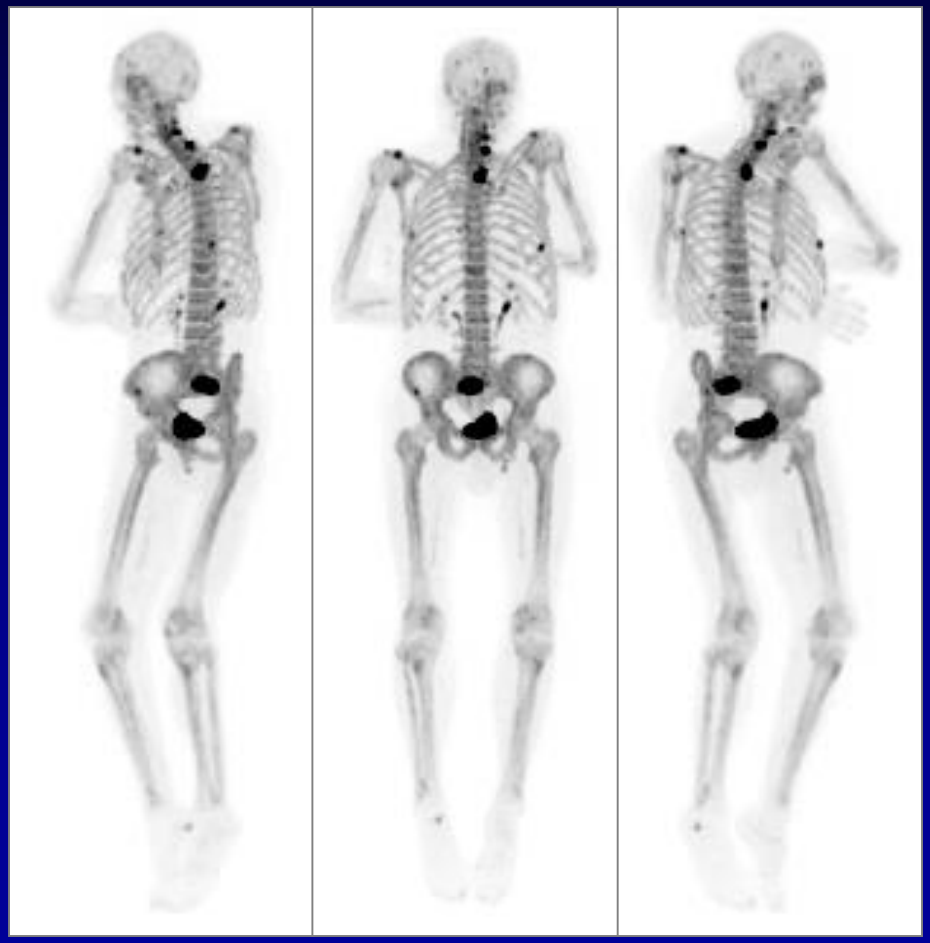
In oncology, PET did open new domains that were not accessible to scintigraphy & SPECT

For the most frequent cancers, NMI was in practice limited to bone scintigraphy in search for bone metastases in advanced or recurrent stages: breast, lung, prostate, colorectal, head & neck …

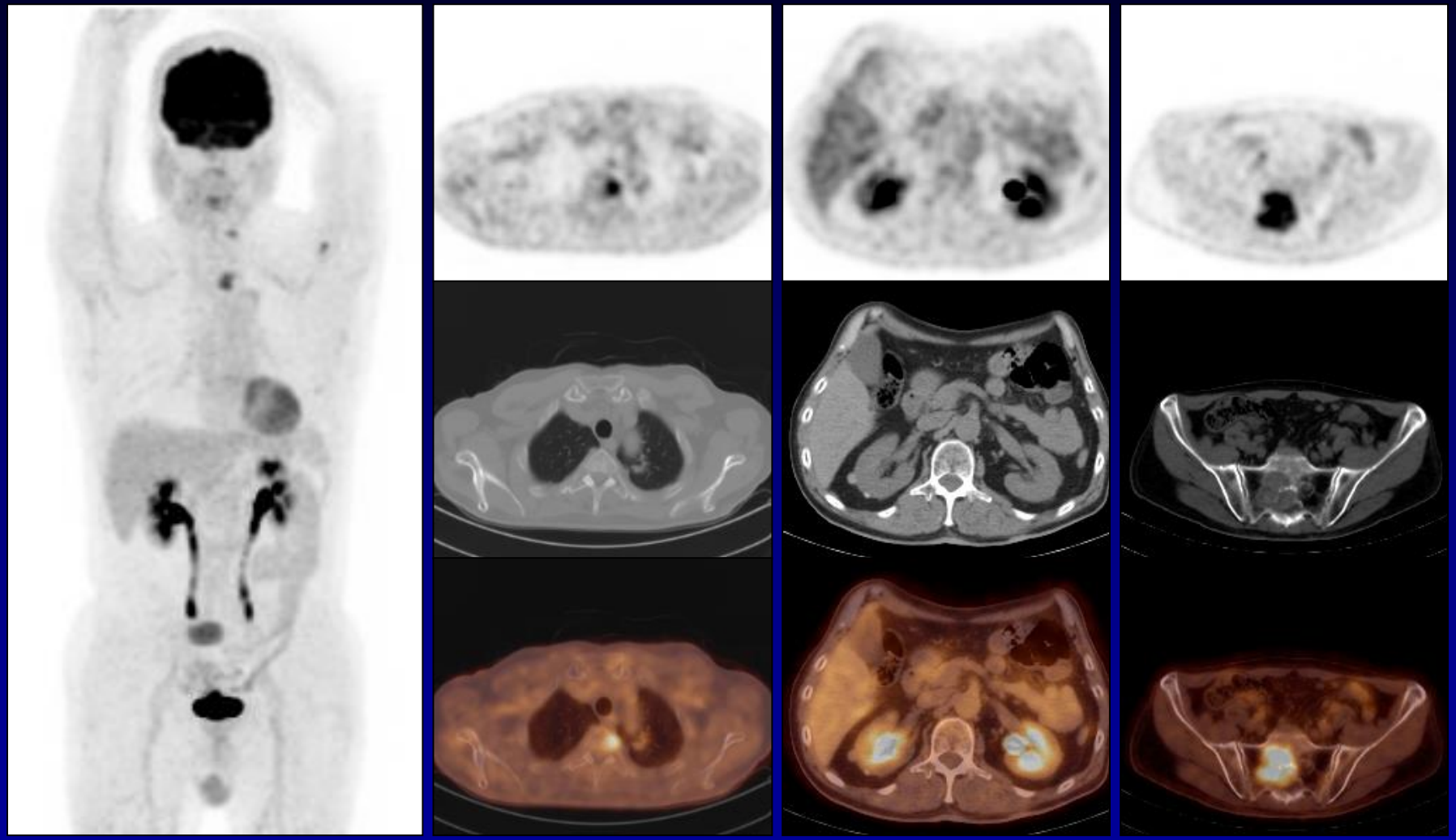
Metabolic PET tracers FDG, FCH or FDOPA enable
- the detection of the primary tumour (cancers of unknown primary, paraneoplastic syndromes)
- the characterisation of a lesion as probably malignant (lung nodule, pancreatic nodule, incidentaloma)
- the evaluation of cancer aggressiveness and prognosis
- the detection of unexpected metastases in lymph nodes, pleura or peritoneum, soft tissue organs and skeleton including bone marrow, and the discovery of second cancers
- the early detection of non responders to therapy.

Non H&N CUP

Clinical context: 79y old man with osteolytic/osteoblastic bone metastases of unknown primary (bone PET 18F-fluoride). Biopsy of sacral lesion: adenocarcinoma. Immunohistochemistry: CK7+, CK20-, TTF1+, PSA-, EGFR+, Kras mutation-



Non H&N CUP (same patient)
FDG PET/CT showed lung primary

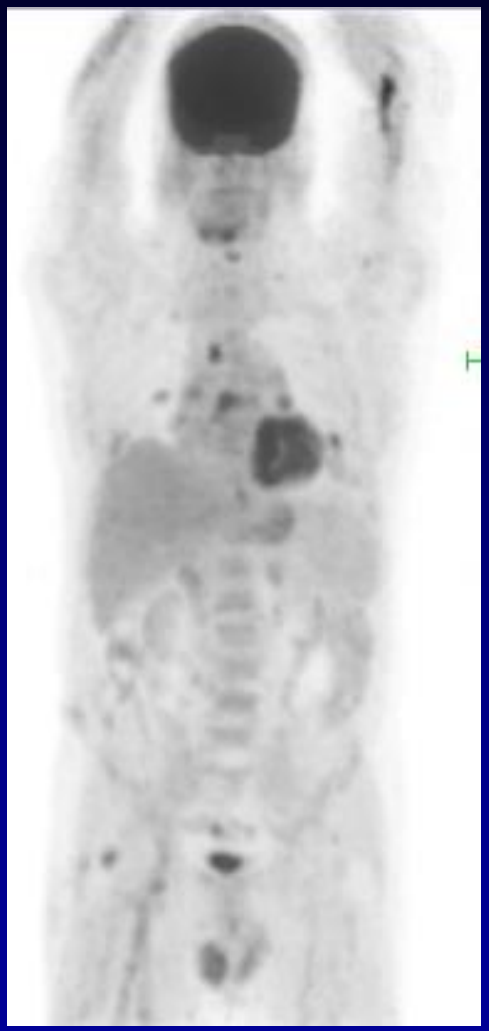


Trousseau's syndrome

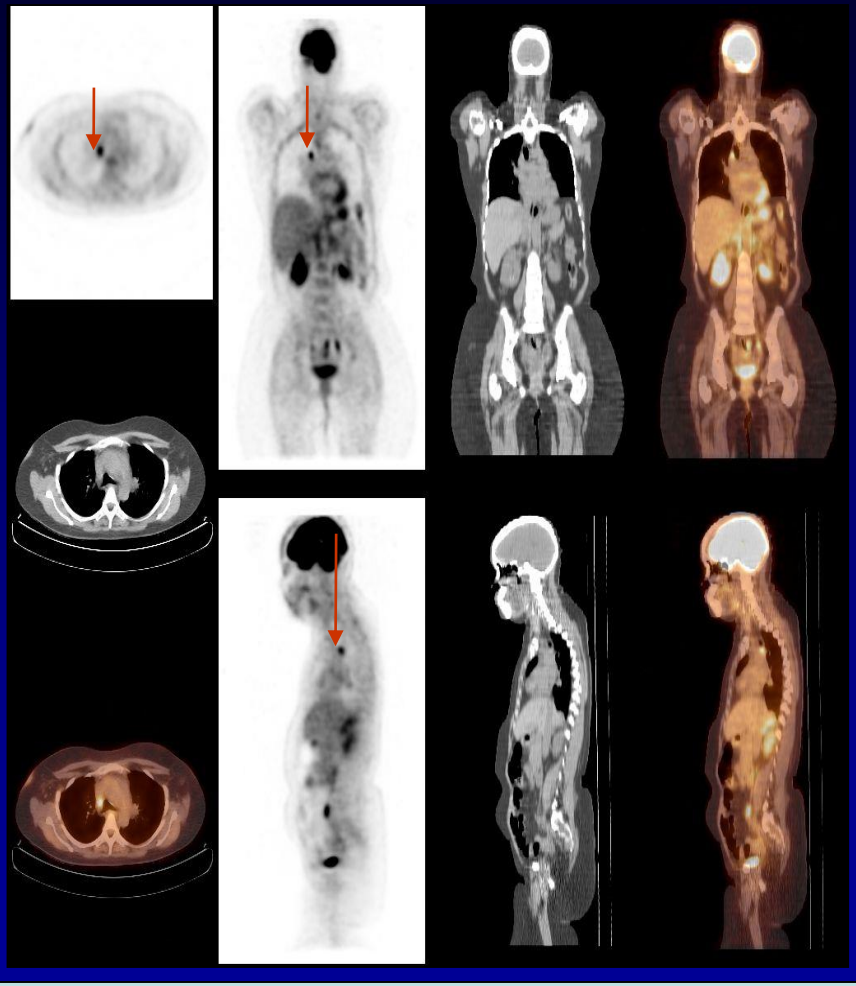
Extensive venous thrombosis of the right arm complicated by a bilateral pulmonary embolism which progressed under anticoagulation treatment, suspicious for Trousseau's syndrome.

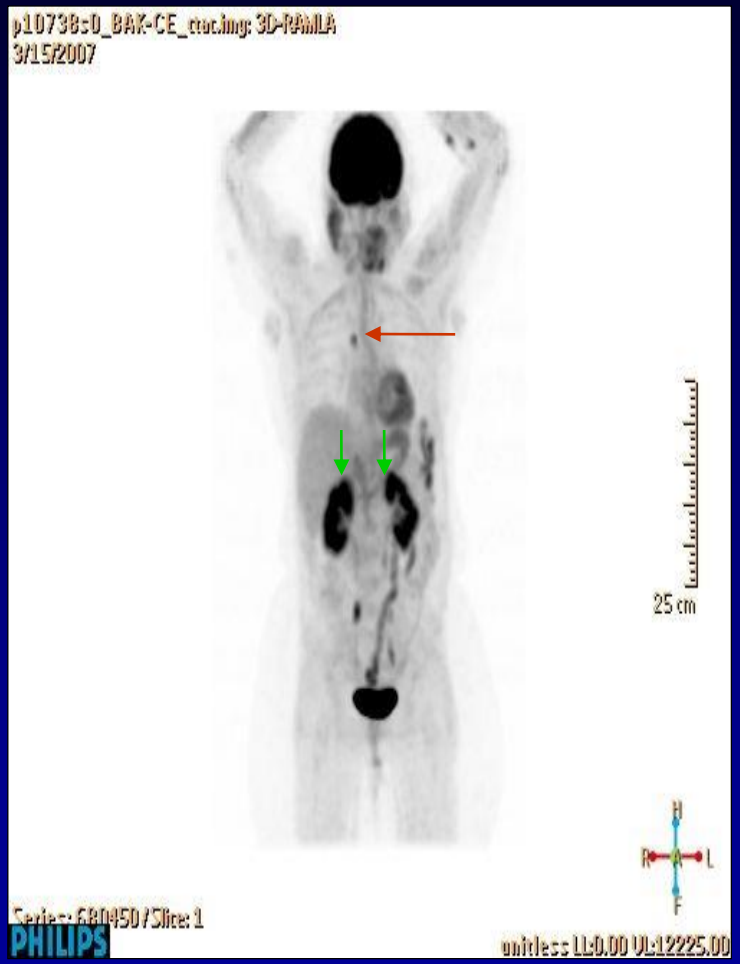
► FDG PET showed foci in the right lung and the mediastinum

Mediastinoscopy and histology confirmed a non-small cell lung cancer



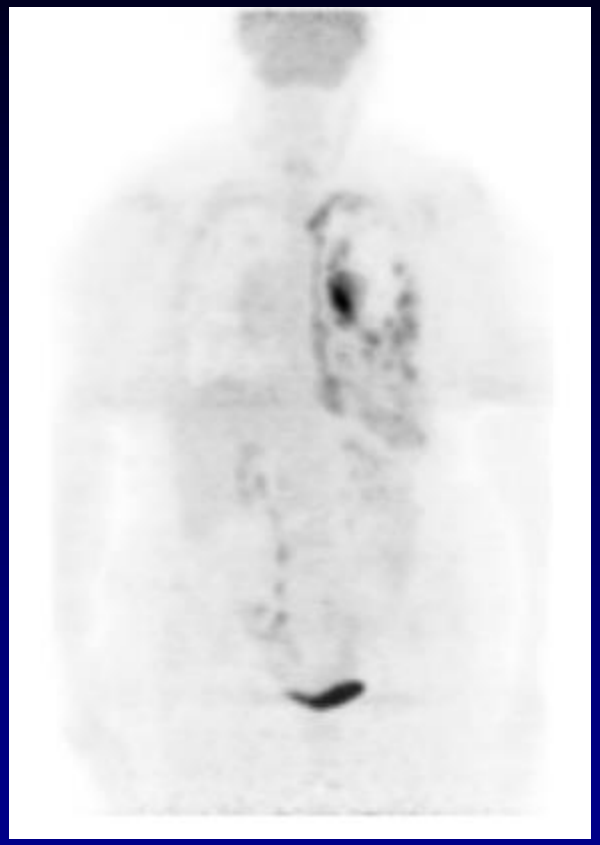
Cushing's syndrome, MRI + petrous sinus sampling: no pituitary adenoma
High ACTH serum level. FDG PET/CT in search for neuroendocrine tumour (NET).



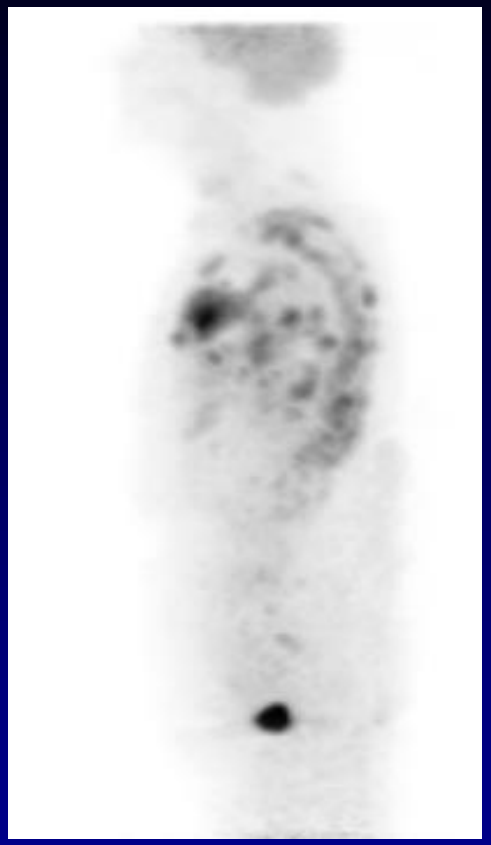


Bilateral adrenal uptake of FDG reflecting overstimulation by ACTH
Bronchial NET confirmed on post surgical histology

Anterior MIP

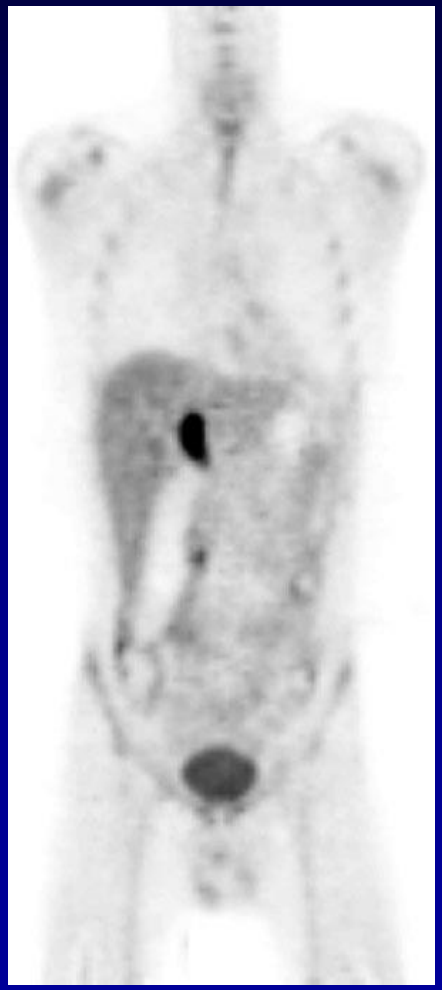


Left profile



Preoperative staging of a left lung adenocarcinoma that was considered resectable after the conventional work-up (CWU).
FDG PET showed the primary tumour, a widespread extension to the left pleura and to the posterior part of a left rib. Management was changed to chemotherapy.

A liver transplant candidate with a type IV Klatskin tumour revealing increased FDG tumour uptake in the hepatic hilum.



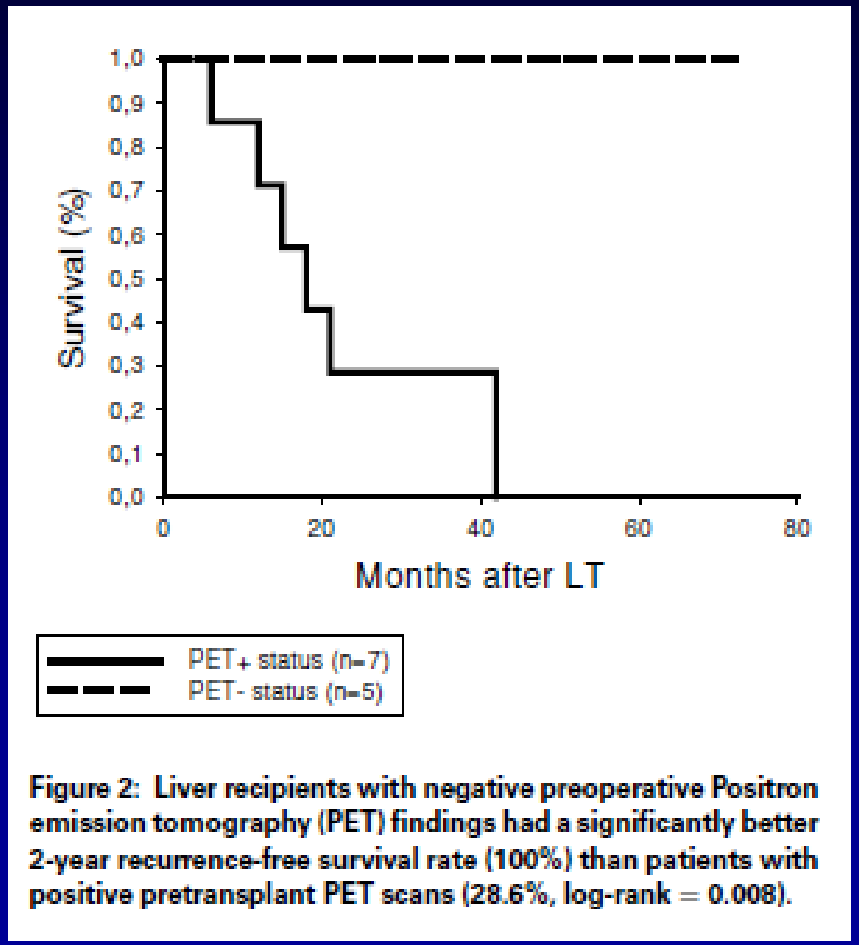
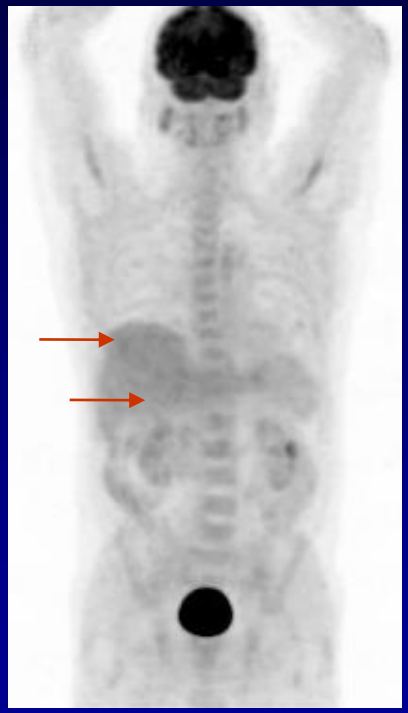


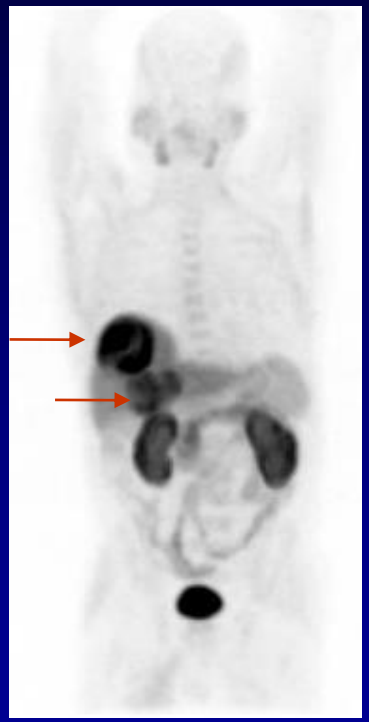
Figure 2: Liver recipients with negative preoperative Positron emission tomography (PET) findings had a significantly better 2-year recurrence-free survival rate (100%) than patients with positive pretransplant PET scans (28.6%, log-rank = 0.008).

Kornberg et al. *Am J Transplant 2009; 9: 2631–6*

By detecting aggressive lesions, FDG has a role for patient management. FCH is able to complete metabolic staging by detecting well differentiated primary or metastastatic HCC (similar results have been reported with 11C-acetate)

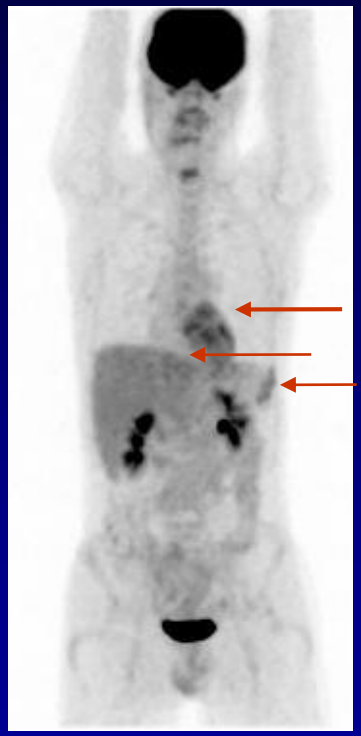


FDG

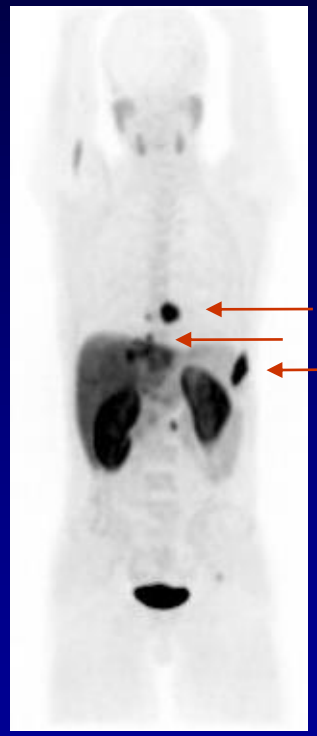


FCH

Primary HCC



FDG



FCH

Primary + metastatic HCC

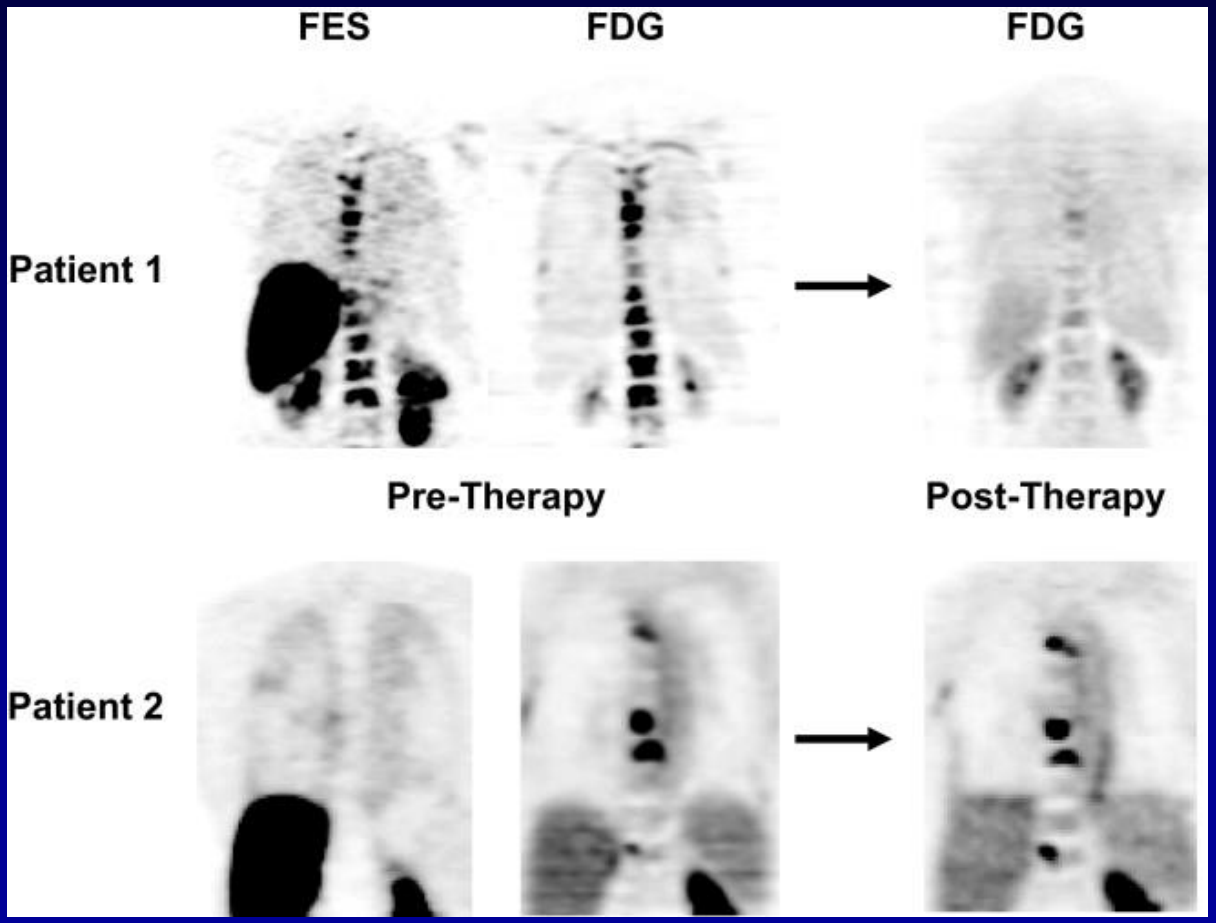
In oncology, PET did open new domains that were not accessible to scintigraphy & SPECT

"Biologic" PET tracers which are more specific such as receptor ligands, antibodies … can be used as "theranostic" agents for a pretherapeutic assessment of the binding and concentration of the corresponding therapeutic agent in cancer targets.

Some current examples : 68Ga-ligands of somatostatin receptors, 18F-fluoroestradiol and hormone therapy, 18F or 68Ga- ligands of integrins and VEGF antogonists ...

18F- fluoroestradiol in breast cancer

Two patients with bone metastases from an ER+ breast cancer



Patient 1: high FES uptake at all sites of active disease, indicating preserved ER expression. This patient subsequently responded to HT.

Patient 2: no FES uptake at active sites of disease seen by FDG-PET, suggesting loss of ER expression, and had no response to hormonal therapy.

Sundarajan et al. Semin Nucl Med. 2007

Can PET replace scintigraphy & SPECT in indications of oncology?

Yes, for most of them.
The most frequent MN imaging in oncology was bone scintigraphy or SPECT (BS); it can be fully replaced by PET.

BS suffers from several drawbacks,
- the major being that BS does not reflect the metastatic tissue itself but the reaction of the cortical bone to its presence.
- therefore early intramedullary metastases are missed
- bisphosphonate treatment may decrease sensitivity
- the persistent uptake by former benign injuries lasting for years that may induce false positive results and the slow modification of the uptake pattern in case of response to therapy
- the flare up reaction is impeding the early evaluation of response to therapy.

Cook GJ, Eur J Nucl Med Mol Imaging. 2011; 38: 7

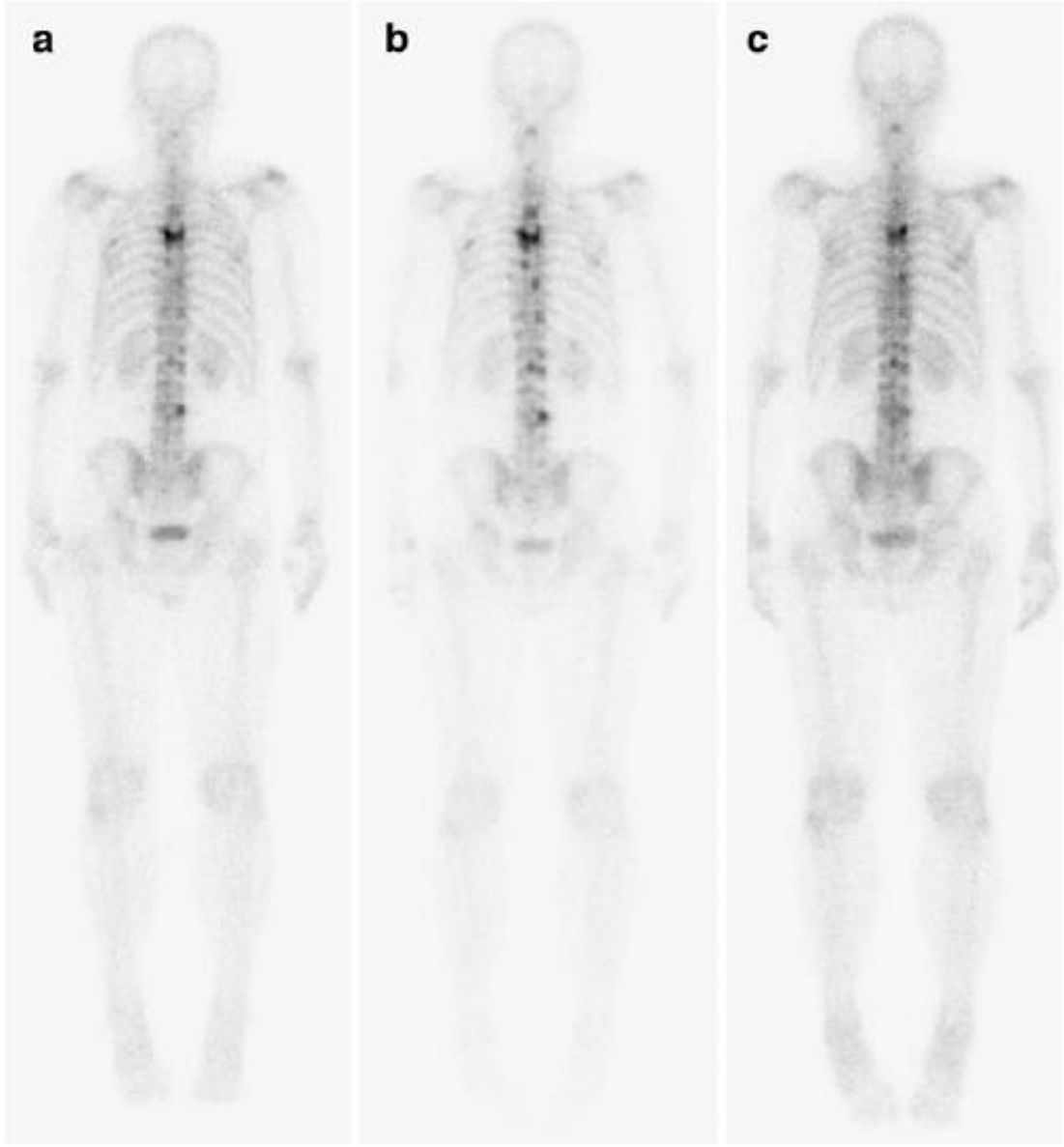
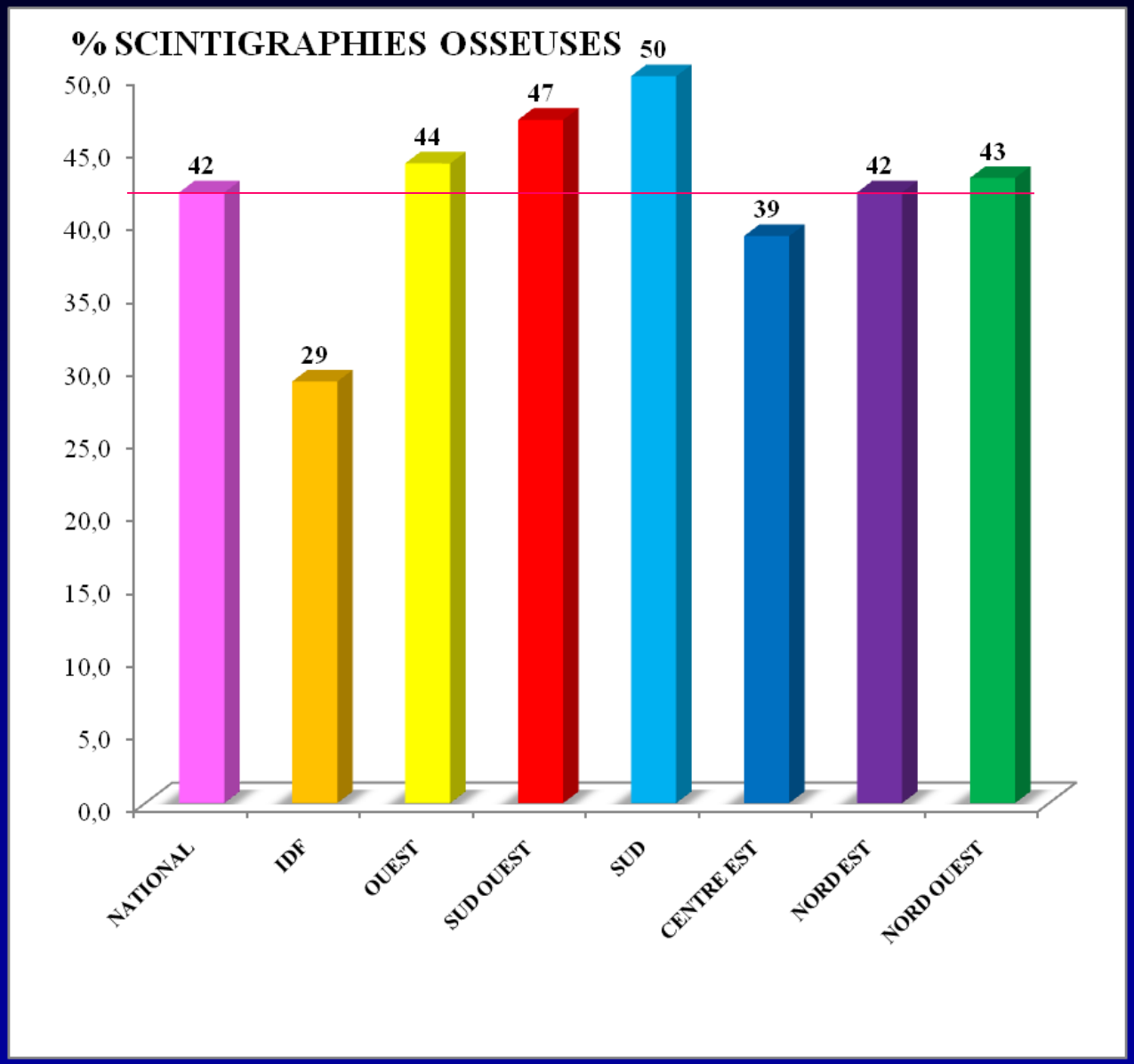


Fig. 1 ^{99m}Tc-MDP bone scans at baseline (a), 6 weeks (b) and 6 months (c) after commencing first-line hormone therapy. There is clear evidence of skeletal metastases on the baseline scan. The metastases show an increase in intensity at 6 weeks which subsequently reduces, typical of the flare phenomenon

Bone SG&SPECT: ca. 46 800 in 2013 in IdF



Which PET tracer(s) to replace bone SG & SPECT in oncology?

18F-fluoride (F Na) could be considered to be the good candidate as it is taken-up due to accretion of cortical bone.

But F Na actually shares all the main drawbacks of BS:
- It is not taken-up by the metastatic tissue itself but by the normal cortical bone; a focus reflects its reaction to the presence of metastatic tissue.
- early intramedullary metastases are missed
- benign degenerative lesions, even very small, are positive
- the persistent uptake by former benign injuries lasting for years that may induce false positive results and the slow modification of the uptake pattern in case of response to therapy
- the flare up reaction is impeding the early evaluation of response to therapy.

Which PET tracer(s) to replace bone SG & SPECT in case of suspected bone metastases?

The metabolic or specific PET tracers yield a better diagnostic performance for detecting bone metastases, including in bone marrow, and are also able to detect local recurrence, lymph node and soft organs metastases.

Breast cancer: FDG should be 1st line.

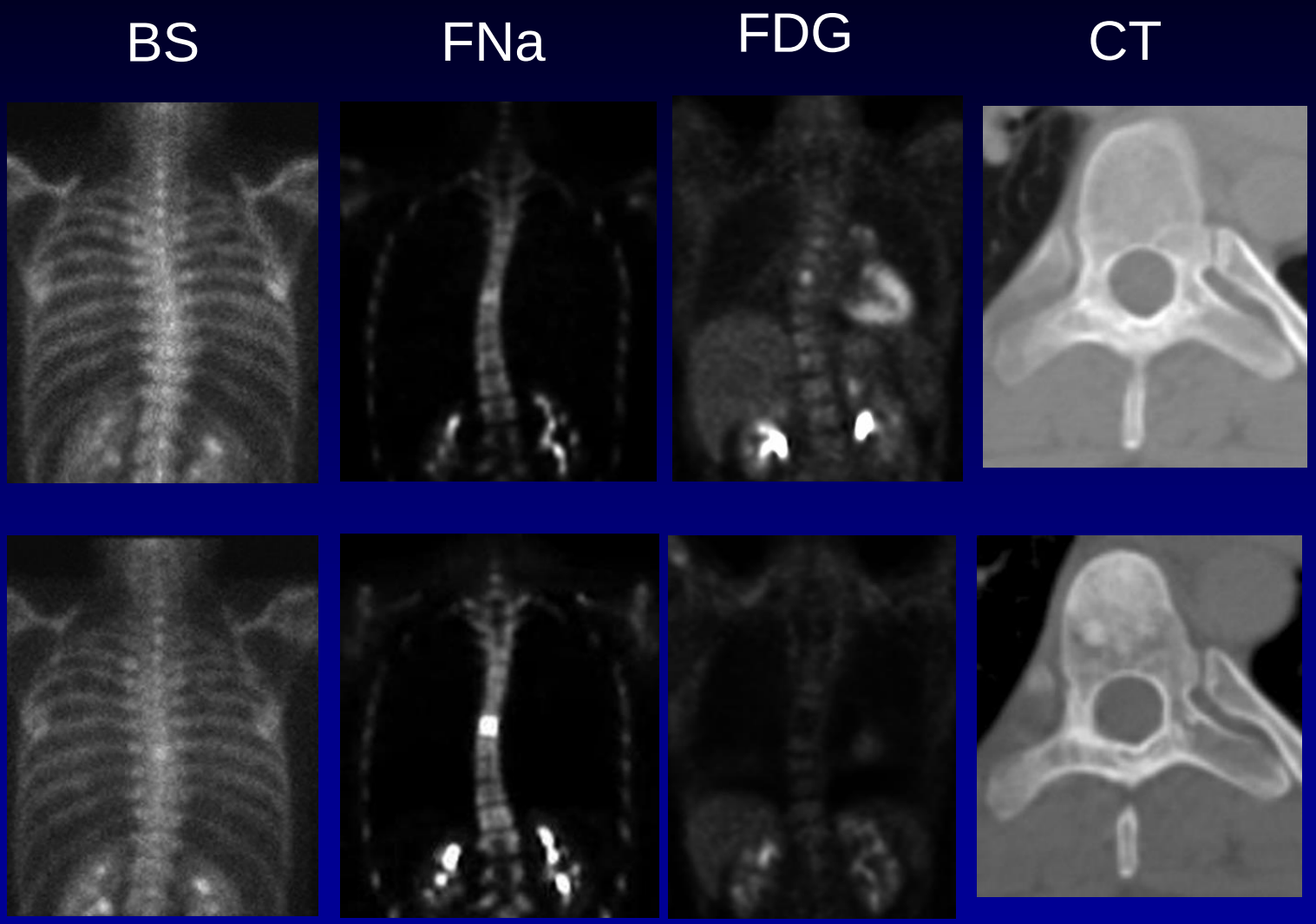
It can lead to false negative results in case of:

- purely osteoblastic metastases, but they are visible on CT,
- or well of differentiated forms of low aggressiveness. In our experience the biologic tracer 18F-fluoestradiol (FES)

Cancer of the lung, head and neck, digestive: FDG as 1st line.

Renal cell cancer: FDG or F Na in indolent forms

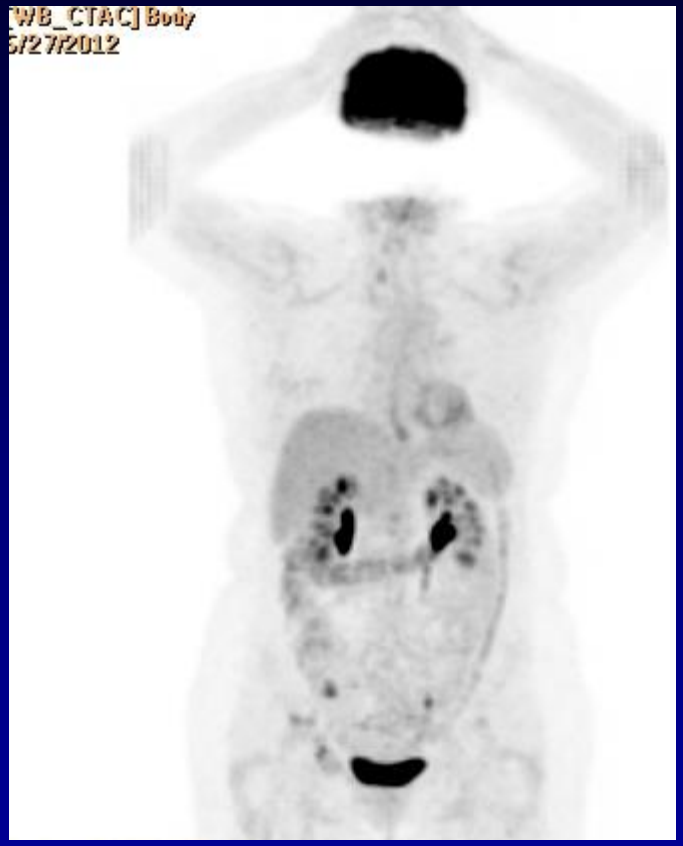
As with BS, the flare reaction has been described with F Na bone PET *Wade AJR 2006:1783 (case report)*



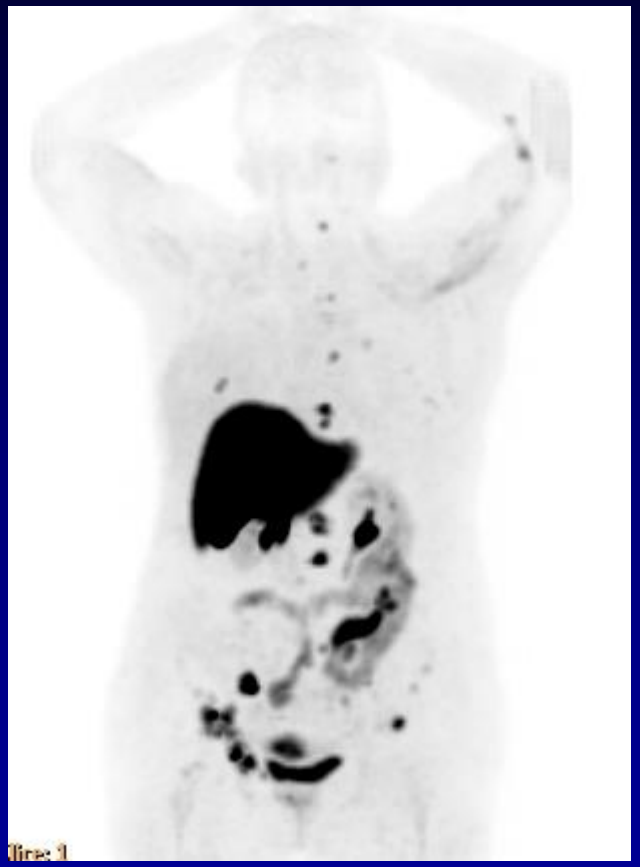
Better sensitivity of FDG or F Na PET vs BS or CT to detect T7 bone met
With chemo, bone flare on BS & F Na but not FDG, osteoblastic reaction on CT

18F-fluoroestradiol in breast cancer

FDG

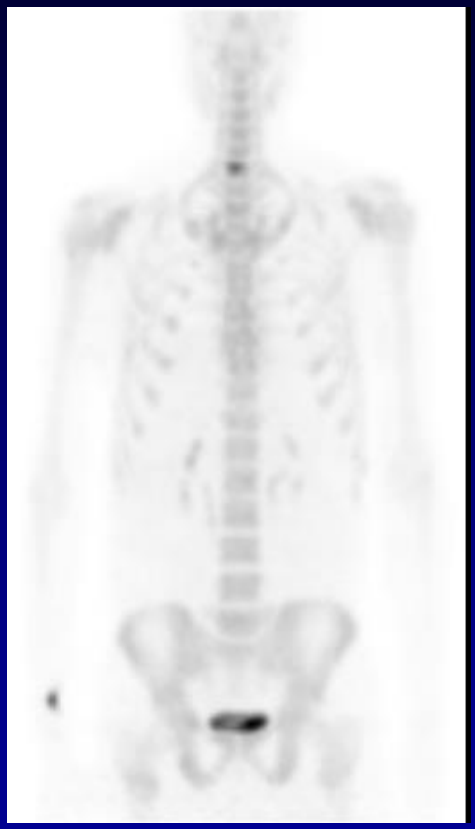


FES

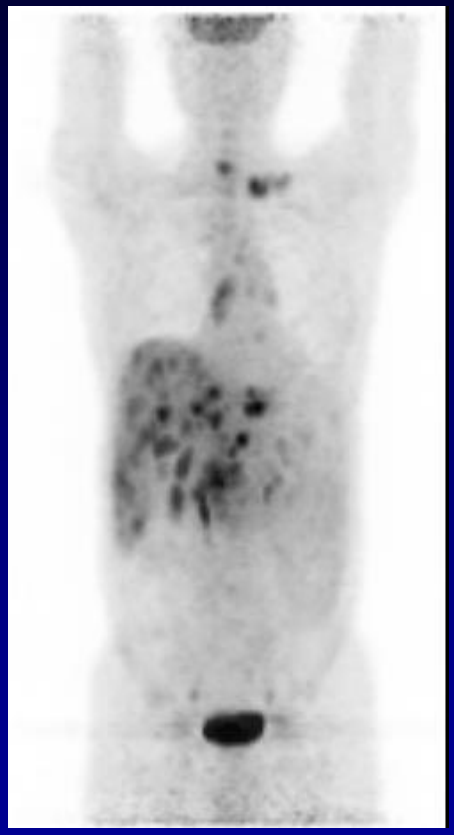


Bone mets FES + FDG -

Staging of pancreas cancer



sodium fluoride (18F)



FDG (18F)

(same patient)

Which PET tracer(s) to replace bone SG & SPECT in case of suspected bone malignancies?

Prostate cancer: 18F-fluorocholine (FCH) or 11C- choline should be 1st line.

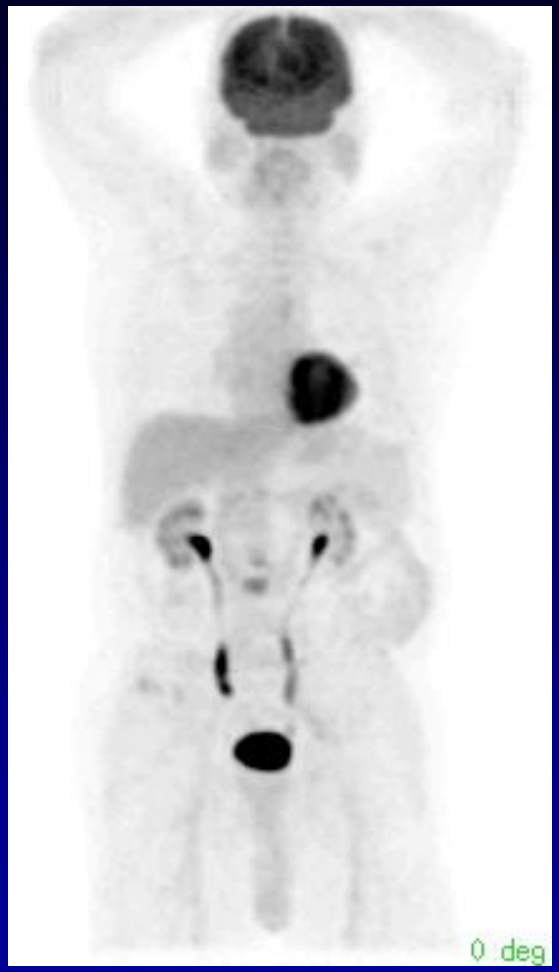
It can lead to false negative results in case of:

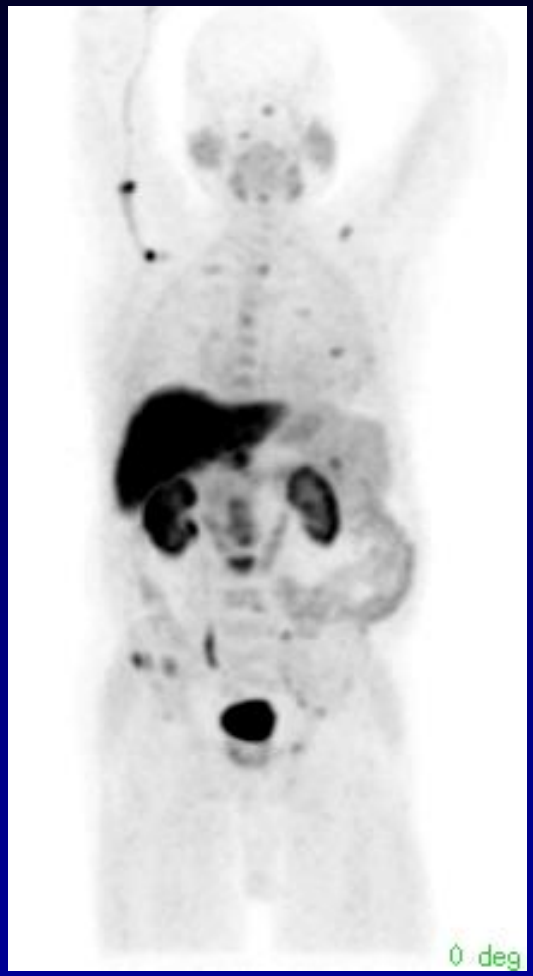
- purely osteoblastic metastases, but they are visible on CT,
- Patients treated with hormone therapy and low serum PSA levels or slow doubling time for serum PSA levels.

Possibly, ligands of prostate membrane specific antigen PSMA labelled with 18F or better 68Ga will replace FCH in future.

Primary bone neoplasia (osteosarcoma or Ewing sarcoma), myeloma and plasmacytoma: FDG PET, since it has superior diagnostic performance compared to bone SG&SPECT or bone PET with F Na.

Initial staging of advanced prostate cancer (Gleason 8)





FDG

FCH

(same patient)

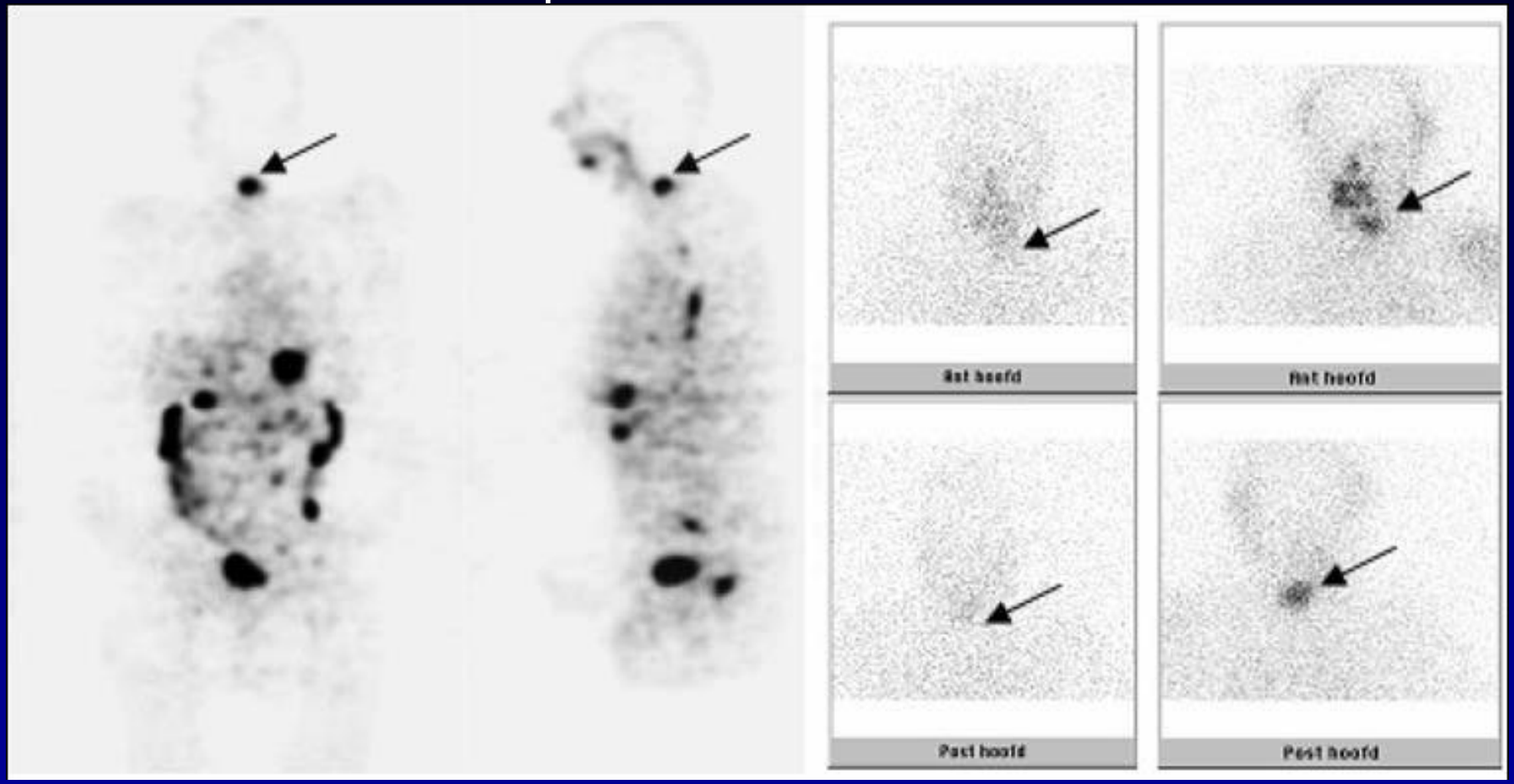
Can PET replace other scintigraphy & SPECT examinations in indications of oncology?

In the management of lymphomas, FDG PET has already replaced 67Ga.

For grading and viability of brain tumours, 201Tl or 99mTc-sestamibi SPECT is being replaced by PET with aminoacids (11C-methionine, FDOPA, FET) or FDG in glioblastomas.

To explore metastatic thyroid cancer, FDG PET is complementary to radioactive iodine. FDG-positive iodine-negative lesions are of bad prognosis and require a specific management.
Furthermore, 124I PET is much more effective than whole-body 131I or 123I SG & SPECT in search for recurrent thyroid cancer. It bears no risk of lesion stunning for the subsequent treatment with 131I.

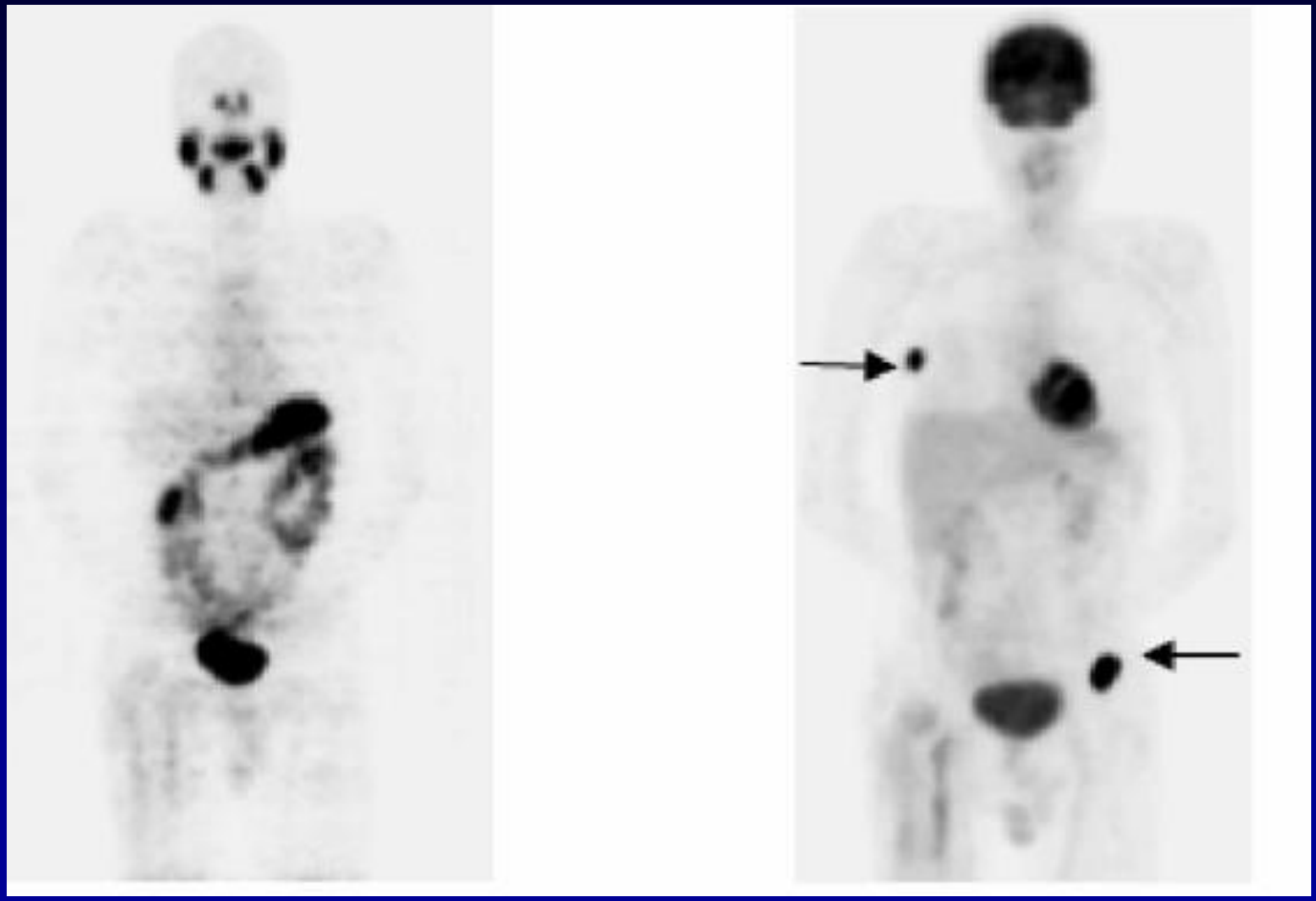
A vertebral metastasis of thyroid cancer visible on the pre-treatment 124I PET but not on « diagnostic » 131I, confirmed on post-treatment 131I



Pre-treatment 124I Diagnostic 131I Post-treatment 131I

Pham et al. EJNM 2008: 958

Differentiated thyroid cancer « Flip-Flop » 124I & FDG



Pham et al. EJNM 2008: 958

Can PET replace other scintigraphy & SPECT examinations in rarer indications of oncology?

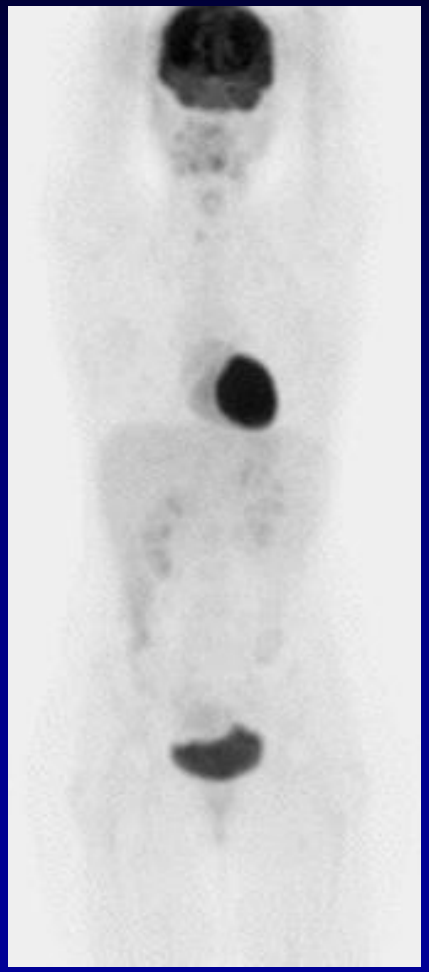
In the management of phaeochromocytoma, paraganglioma or neuroblastoma, FDOPA is replacing 123I-MIBG; in aggressive forms, FDG should (also) be performed.

For medullary thyroid carcinoma, FDOPA is also the 1st line examination, replacing 201Tl or 99mTc sestamibi or DMSA V.

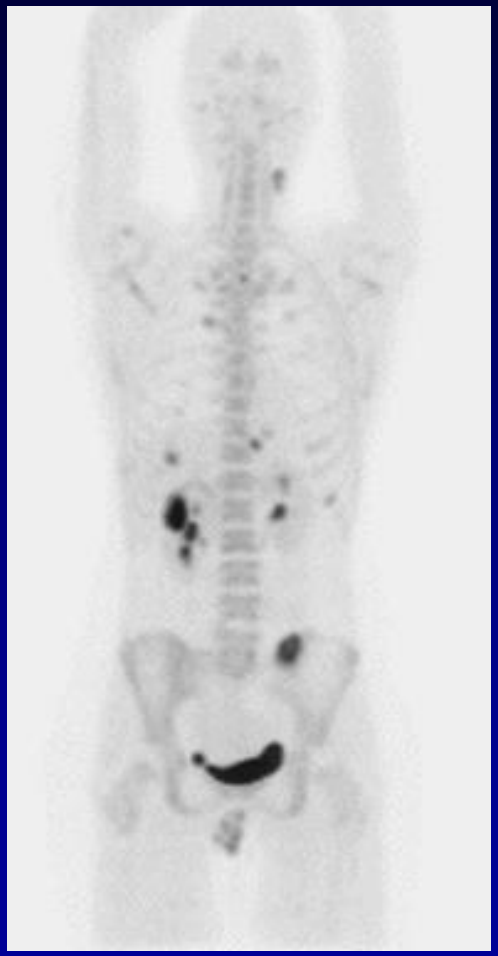
In digestive neuroendocrine tumours, somatostatin receptor SG&SPECT with 111In-pentetreotide ou 99mTc somatostatin analogues is being replaced

- by somatostatin receptor PET with 68Ga DOTATOC or DOTATE,
- or by FDOPA for midgut tumours.

Restaging of **medullary thyroid cancer** (MTC) with known secondary bone lesions. Patient referred for FDG and FDOPA PET/CT to characterise hepatic lesions



False negative FDG PET



True positive FDOPA PET

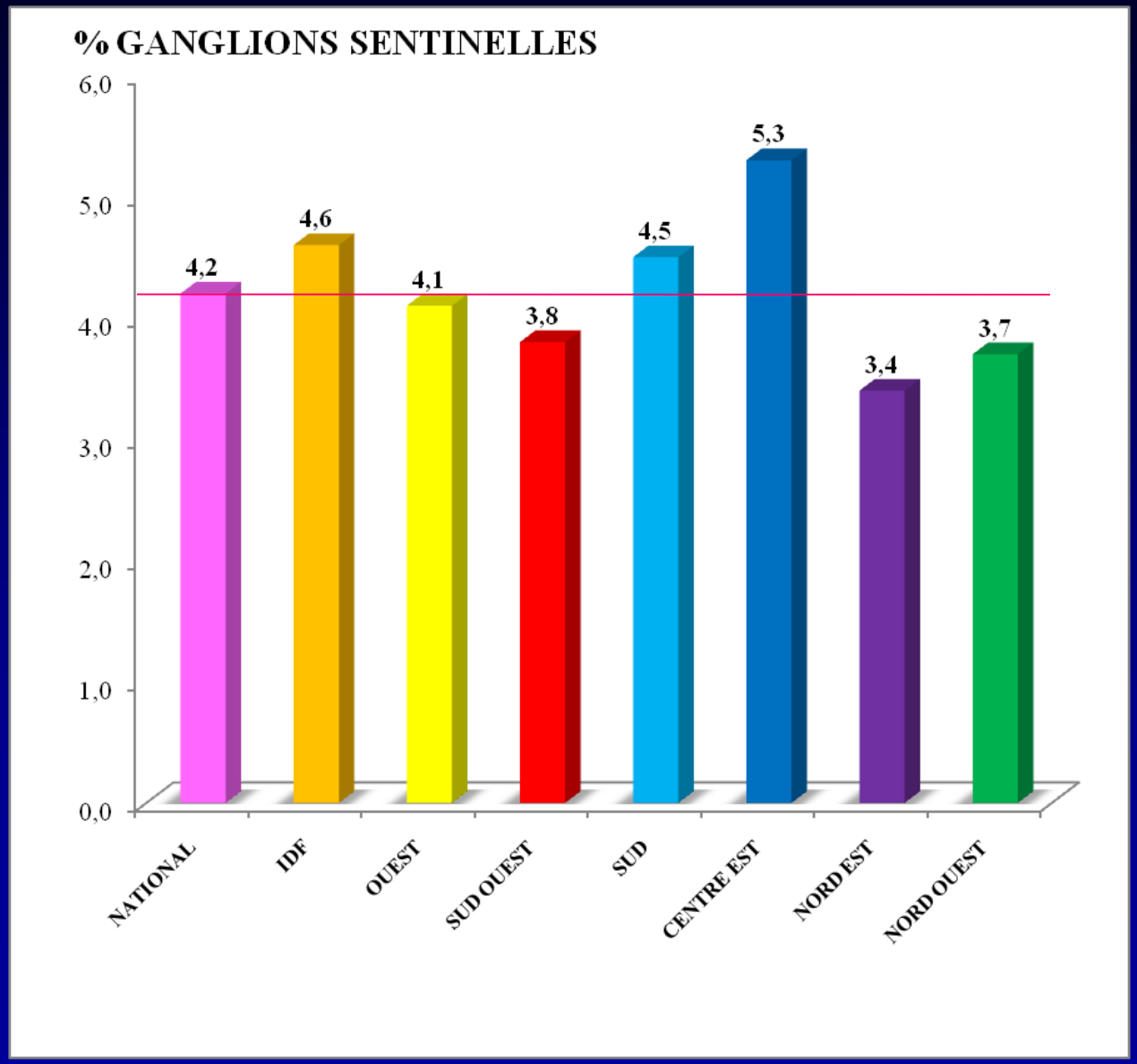
If PET would be widely available and reimbursed, what would be left for scintigraphy & SPECT in oncology?

In my opinion,

- sentinel lymph node detection

- and a few pretherapeutic functional examinations such as V/Q SPECT prior to surgery of the lung, search for vascular shunts before radioembolisation of liver lesions … even though the labelling of macroagregates with 68Ga and 68Ga-galligas for ventilation has been proposed.

Sentinel lymph node: ca. 7 400 in 2013 for IdF



Inflammation and infection

In EU, FDG is currently registered in several indications.

F Na is also registered to elucidate long lasting back pain after non-contributive MRI.

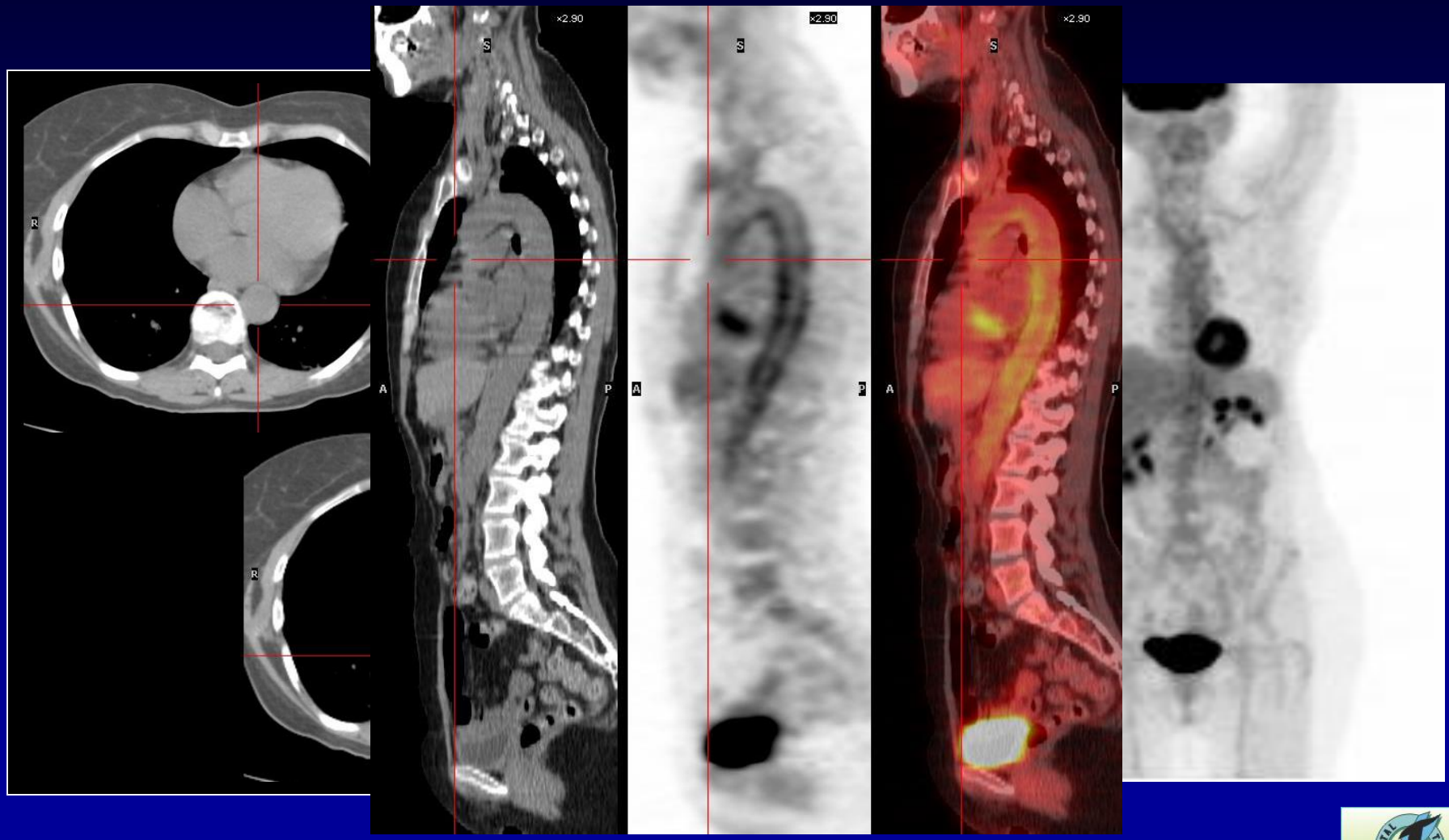
PET did open new domains that were not accessible to scintigraphy & SPECT in inflammation and in fever of unknown origin

In France, SG&SPECT was in practice limited to gallium-67 for sarcoidosis

FDG has now replaced 67Ga in France in this indication and in many others inflammatory conditions which needed superior resolution, in particular vasculitis

Fever of unknown origin is elucidated with FDG in a rather large proportion of cases

FDG PET in a case of aortitis



Can PET replace scintigraphy & SPECT for the management of inflammation or infection?

Yes, for most of them.

FDG PET can replace 67Ga SG or SPECT in all its indications, including detection of infection in the axial skeleton and extension of tuberculosis.

FDG PET can partially replace SG & SPECT with 111In- or 99mTc- radiolabeled leucocytes, to detect infection of the appendicular skeleton and of biomaterials in particular in a context of fever.

FDG PET is far easier to perform, implies no exposure of the personnel to the potentially infected blood of the patient, yields images of better resolution and results can be obtained in les than 2h.

In contrast radiolabeled leucocytes are more specific to differentiate infection from inflammation.

Radiolabeling of leucocytes with FDG has been proposed, but is not performed routinely.

Cardiology - angiology

In EU, FDG is currently registered to detect myocardial viability.

For myocardial perfusion, rubidium PET is scarcely performed, as the 82Rb generator is not currently registered in EU.

Same for short lived 13N-ammonia or 15O-water which require an on-site cyclotron.

Can PET replace SPECT for exploring the myocardial perfusion?

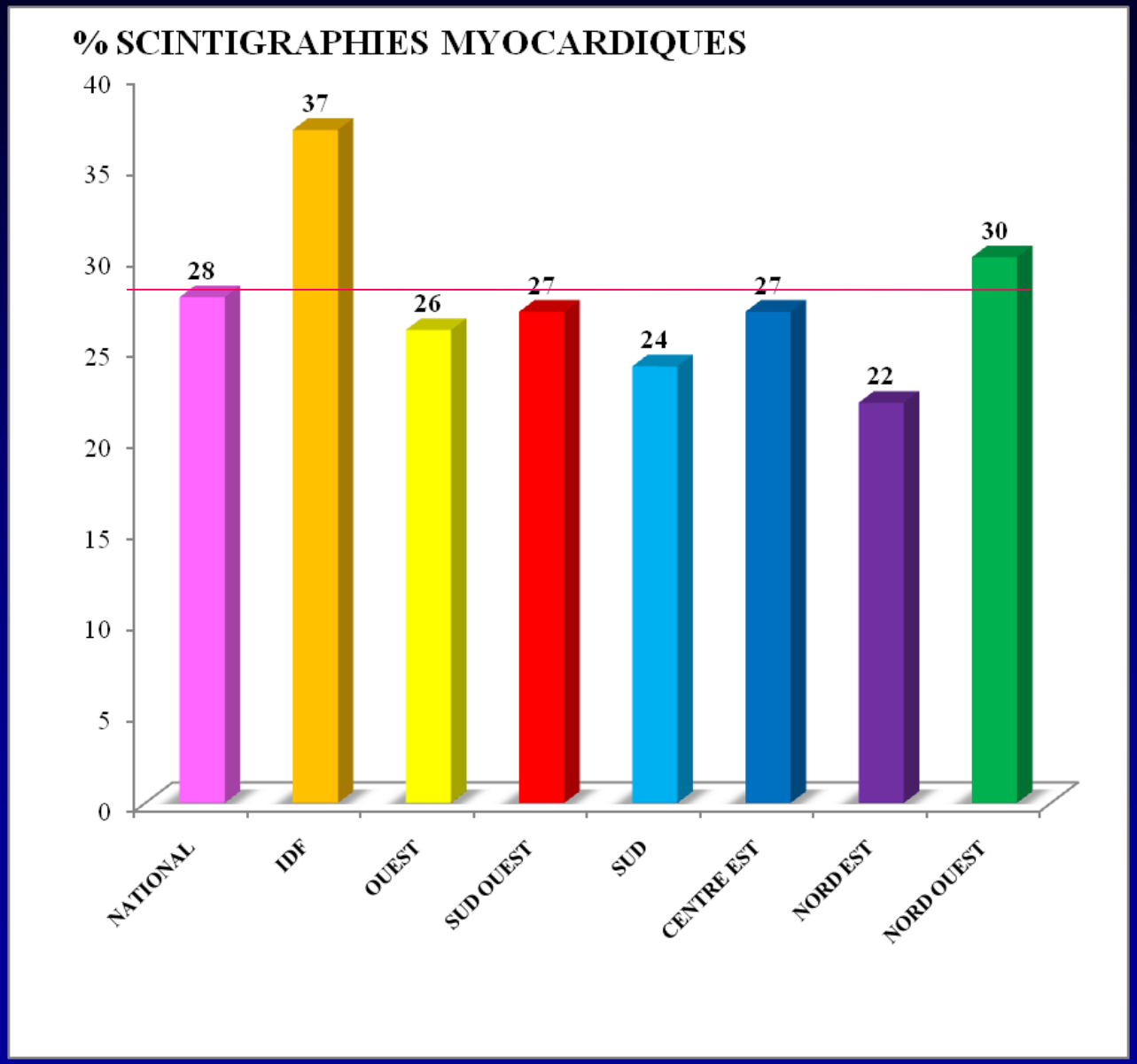
No, at least at the moment.

SPECT with 99mTc-sestamibi or 201Tl in case of suspected viability has now become the 1st indication for γ cameras in IdF.

CZT γ cameras dedicated to heart imaging permit a rapid imaging, with an improved image quality and are suited for nuclear cardiology centres.

As long as a 18F labelled PET tracer of myocardial perfusion is not validated and its superiority over SPECT demonstrated, I foresee no significant shift of nuclear cardiology to PET, at least in IdF.

Myocardium SPECT: ca. 59 700 in 2013 in IdF



In angiology, will PET open new domains that are not accessible to scintigraphy & SPECT?

Yes, and its role will most probably widen.

We already mentioned the established role of FDG PET in imaging the extension of vasculitis to the large vessels.

F Na PET mas have an important role as an adjunct to the calcium score, as its permits to differentiate plaques with an active calcium deposition from inactive plaques with residual calcifications.

Other tracers to detect the vulnerable atherosclerotic plaques are being developed and validated.

-

Neurology

In EU, FDG is currently registered to detect inter-ictal photopenic areas in case of intractable epilepsy.
As an alternative, tracers for brain perfusion SPECT imaging have also been used for intra-ictal injection and subsequent imaging; due to the very demanding logistics very few teams perform this examination.

FDG is also used in practice in difficult cases of suspected dementia or mild cognitive impairment.

Several PET tracers of the amyloid substance have recently been registered in EU.

In EU, FDOPA is currently registered for the exploration of Parkinson disease.

Can PET replace SPECT for functionnal imaging in neurology?

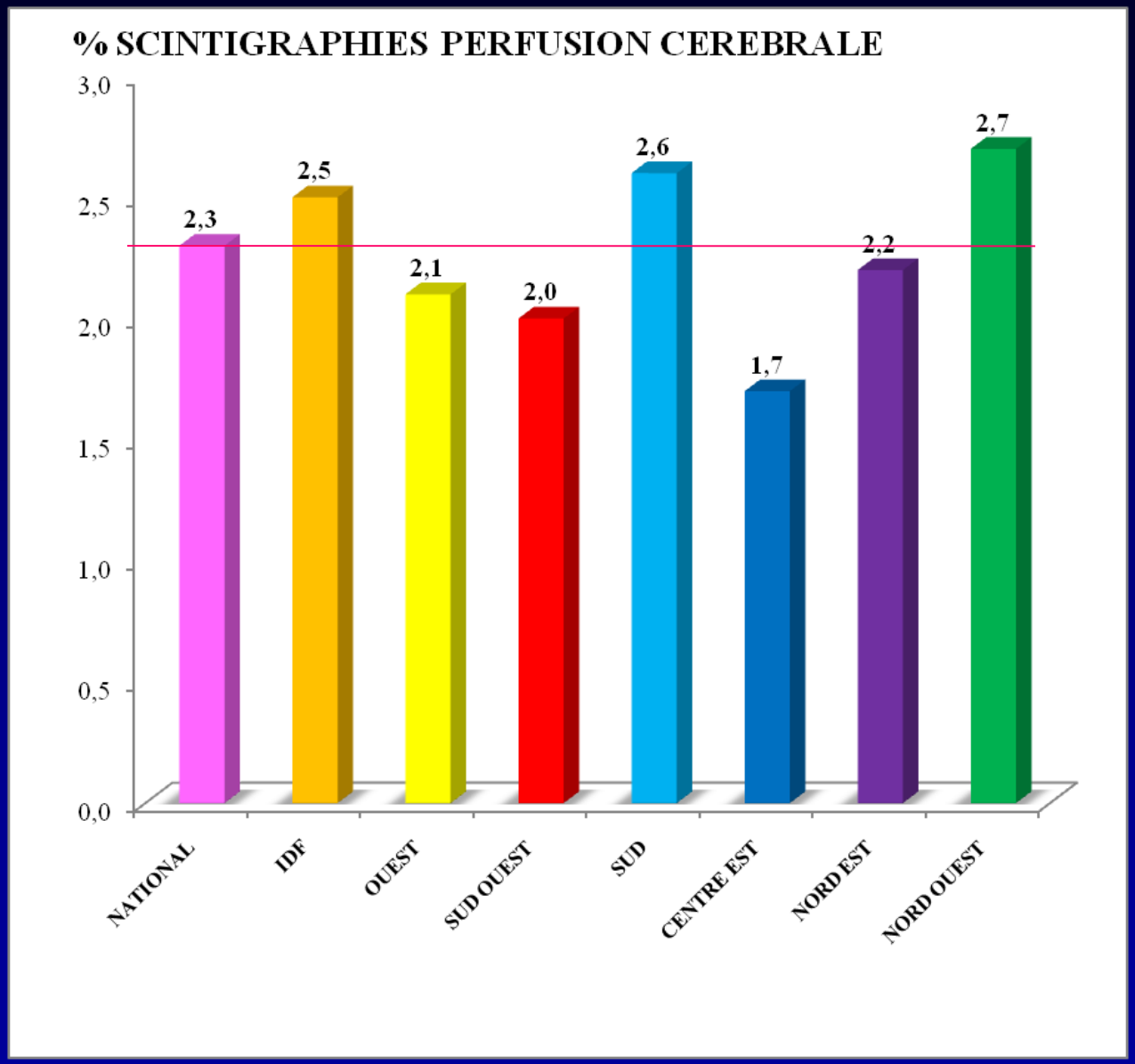
Yes, according to the specialists of the large neurology centres.

PET/CT and PET/MRI are preferred to SPECT/CT due to a better definition of the PET images and to a more accurate and reproducible quantification of uptake, in particular by fine structures.

FDG can replace 99mTc-HMPAO and FDOPA can replace PET 123I ligands of the dopamine transporter that are as expensive, even though the imaging targets are not identical.

No ligand of the amyloid substance or of the tau protein has been developed for SPECT imaging.

Brain perfusion SPECT: ca. 4 000 in 2013 in IdF



Other indications of NM imaging

- - Lung V/Q SG&SPECT: probably no replacement by PET, even though the labelling of macroagregates with 68Ga and 68Ga-galligas for ventilation has been proposed.

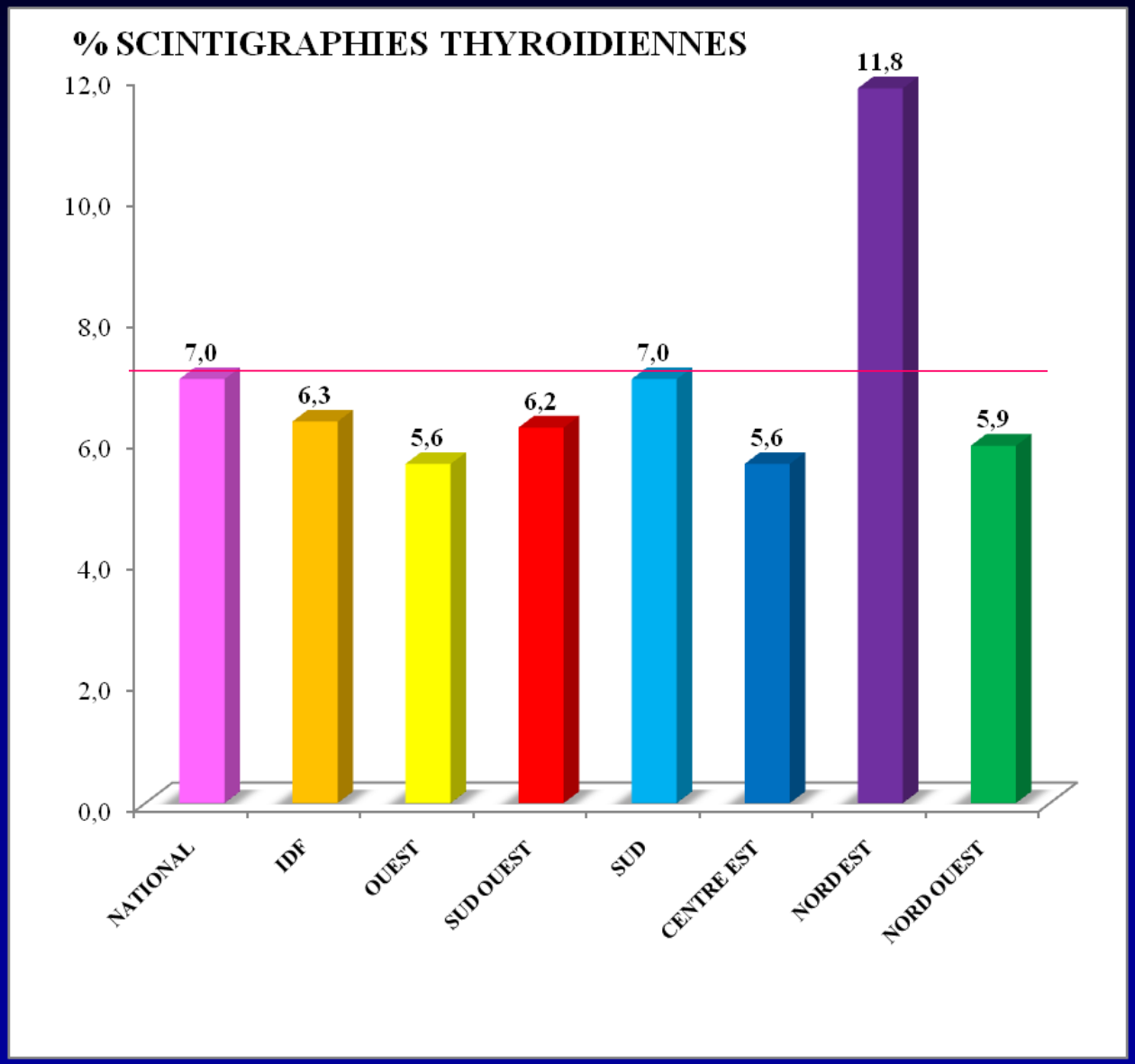
- - Thyroid scintigraphy: no replacement by PET anticipated, even if 124I becomes more available due to its unfavourable dosimetry in benign conditions

- - Renal, salivary, biliary SG: probably no replacement by PET, even though recent PET machines are able to perform rapid dynamic acquisition using list mode

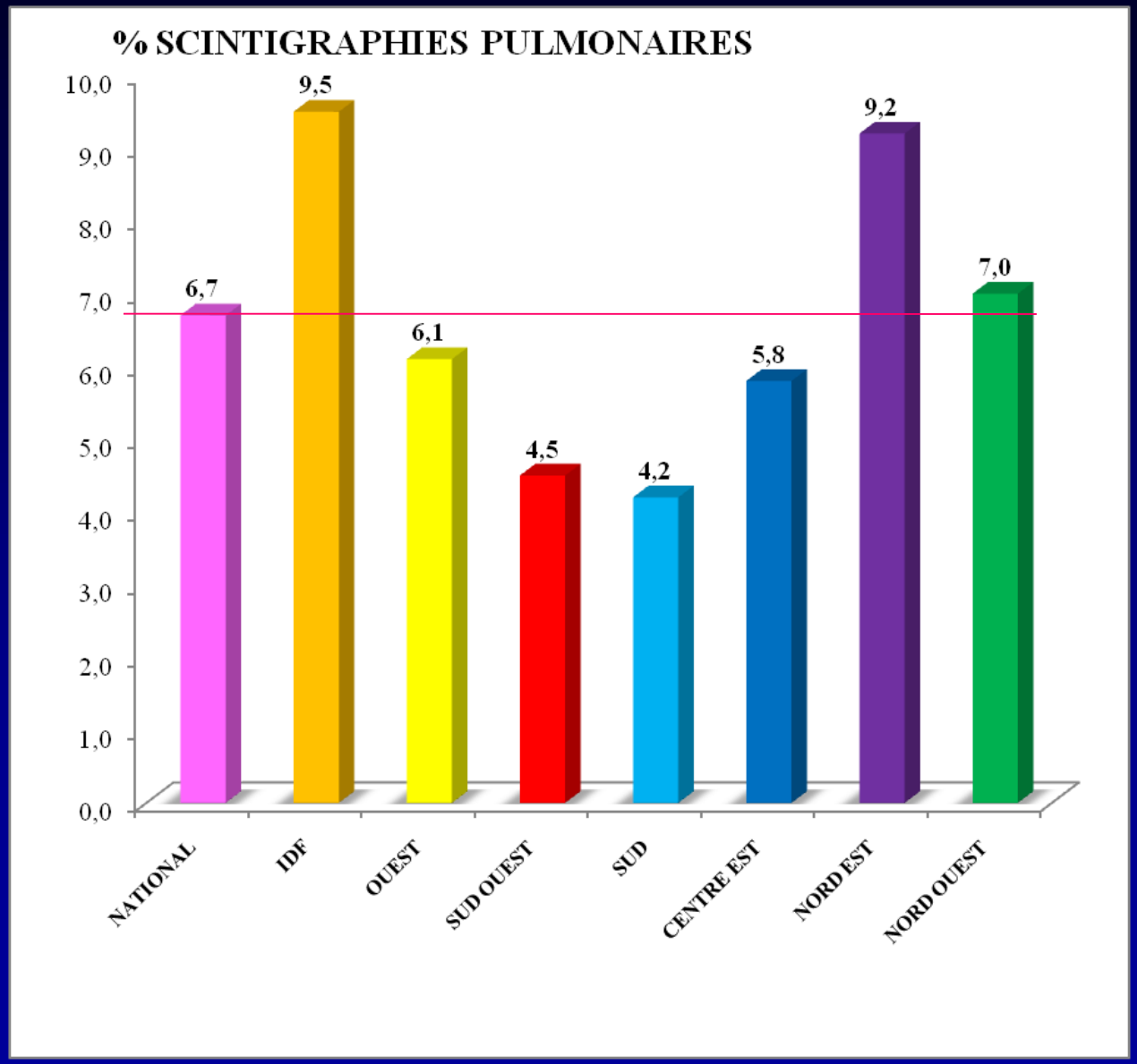
- - Parathyroid scintigraphy: possible replacement by PET, logistics of 11C-methionine are difficult but FCH is available and recent pilot studies showed it is superior to 99mTc-sestaMIBI SG&SPECT

- - Somatostatin receptor scintigraphy: full replacement by somatostatin receptor PET

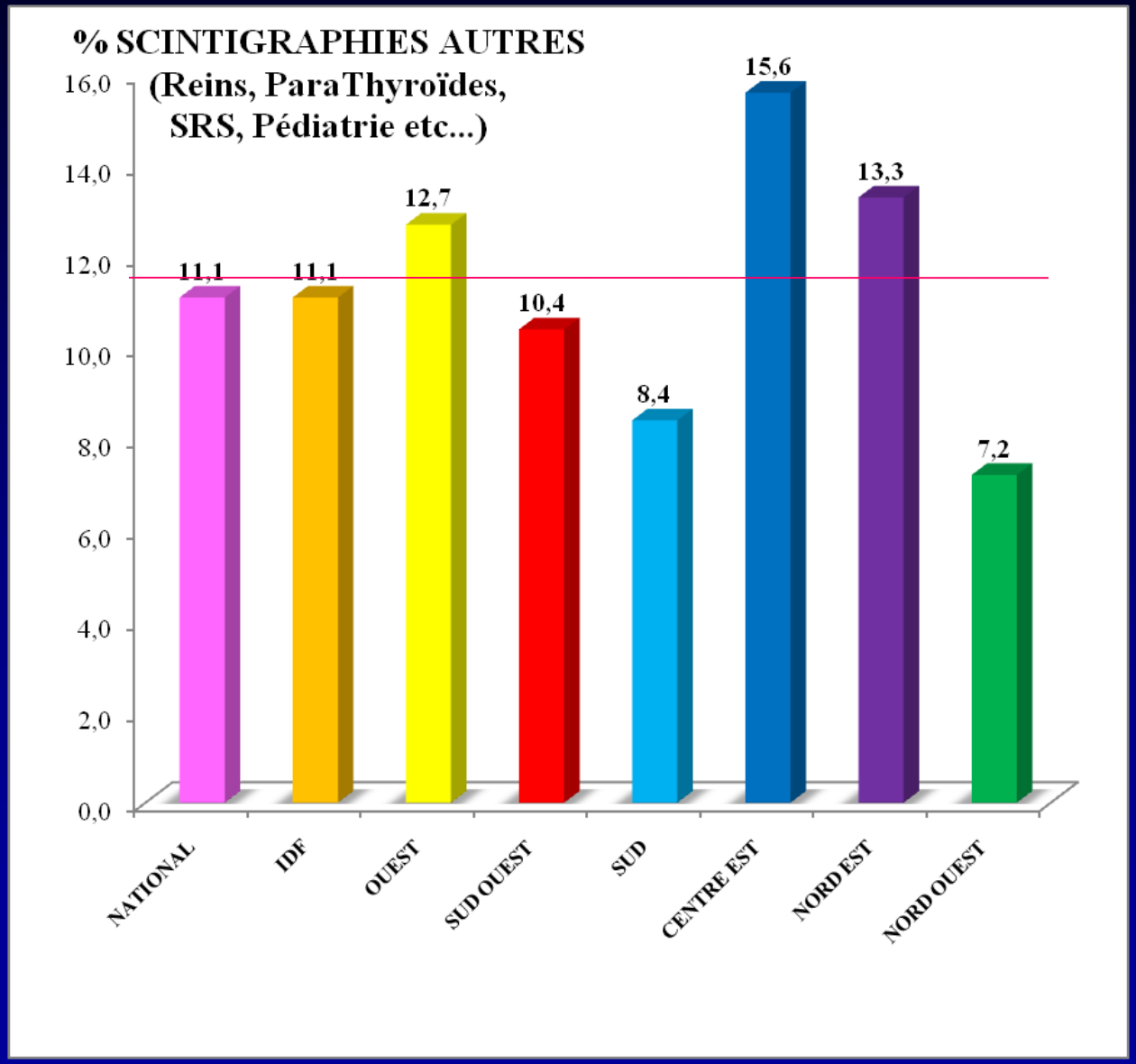
Thyroid scintigraphy: ca. 10 200 in 2013 in IdF



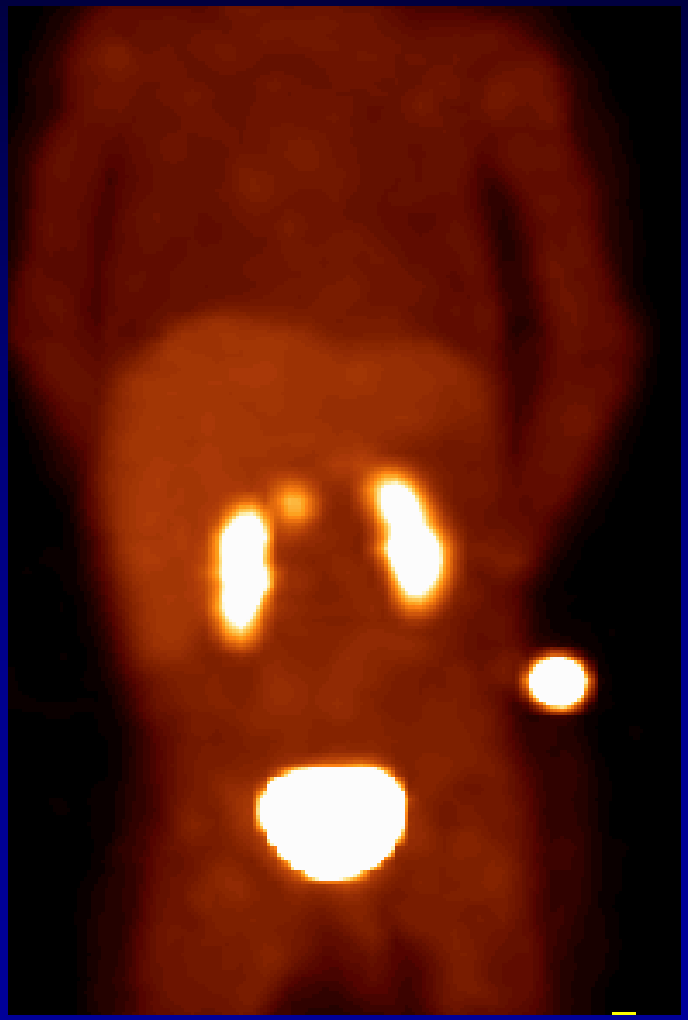
Lung SG&SPECT: ca. 15 300 in 2013 in IdF

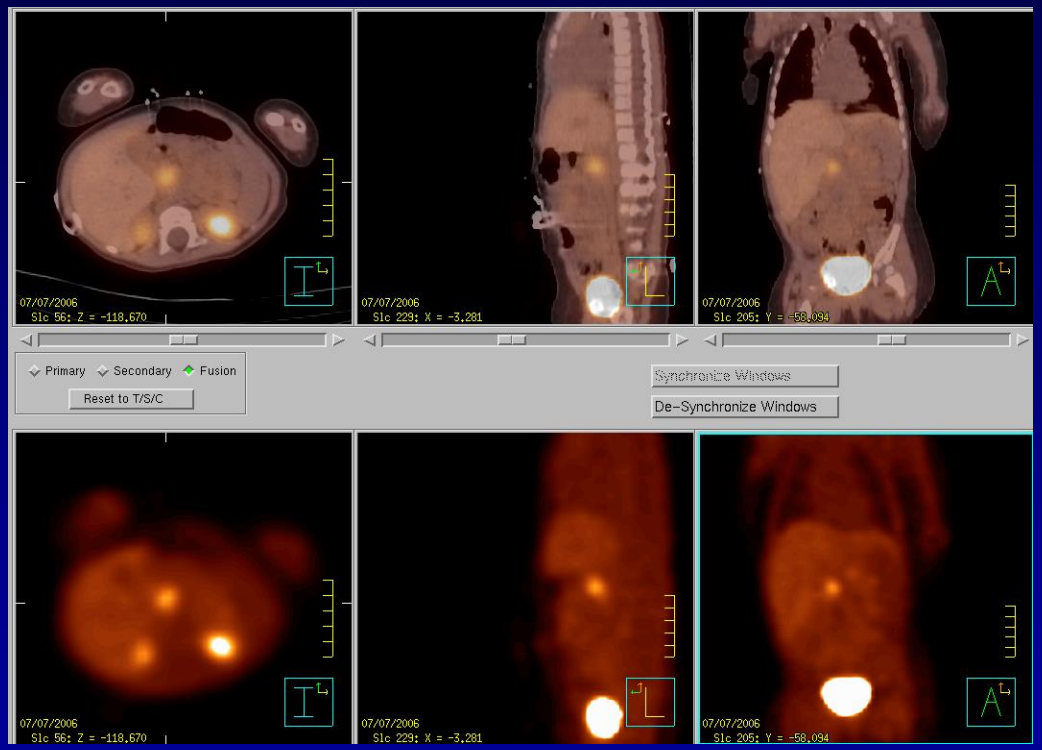


Other SG&SPECT (kidney, parathyroid, somatostatin receptors, paediatrics …): ca. 17 900 in 2013 in IdF

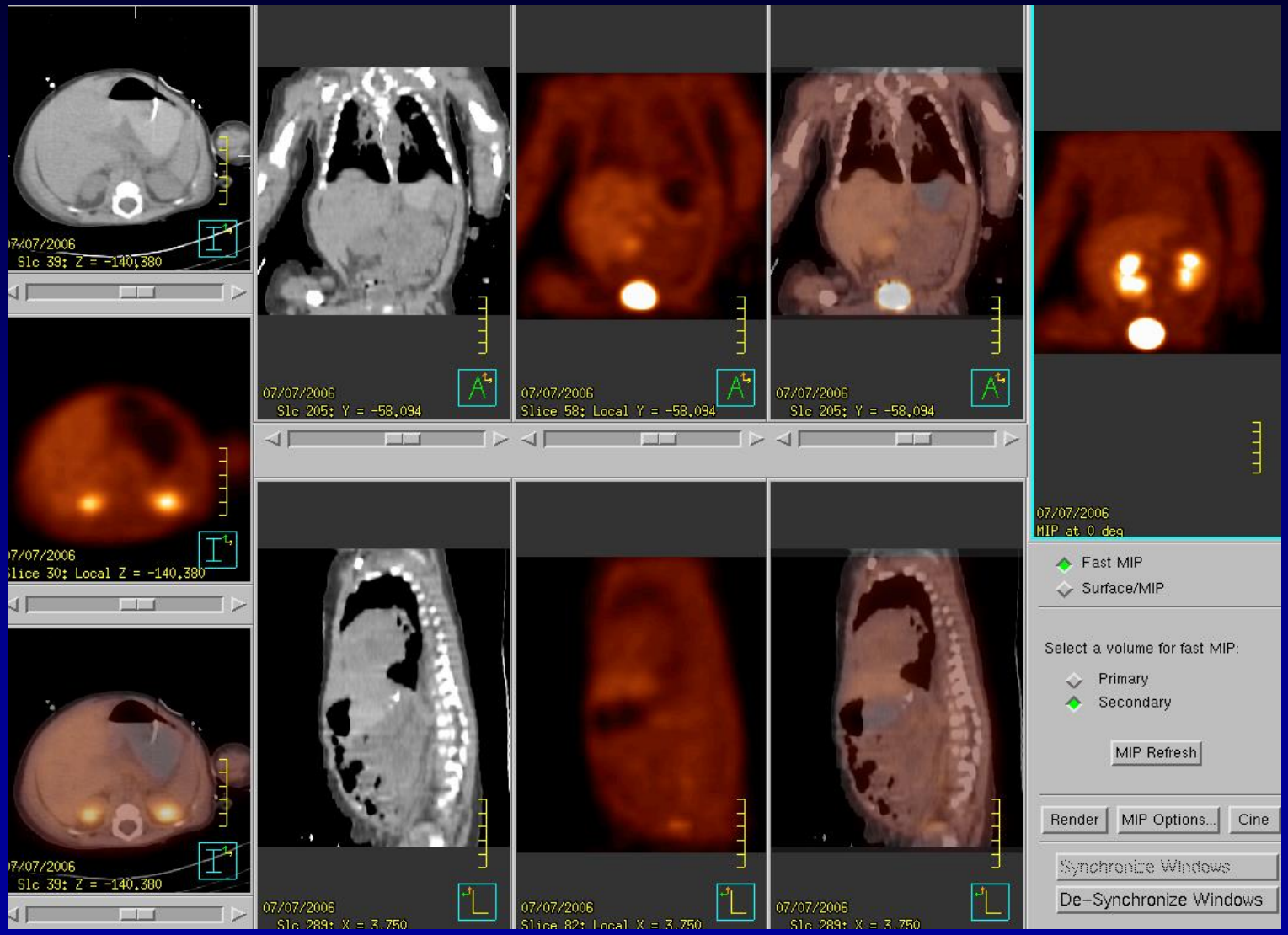


FDOPA PET/CT in an infant with congenital hyperinsulinism
Clear focus of uptake in the head of the pancreas.
The infant was cured after resection.

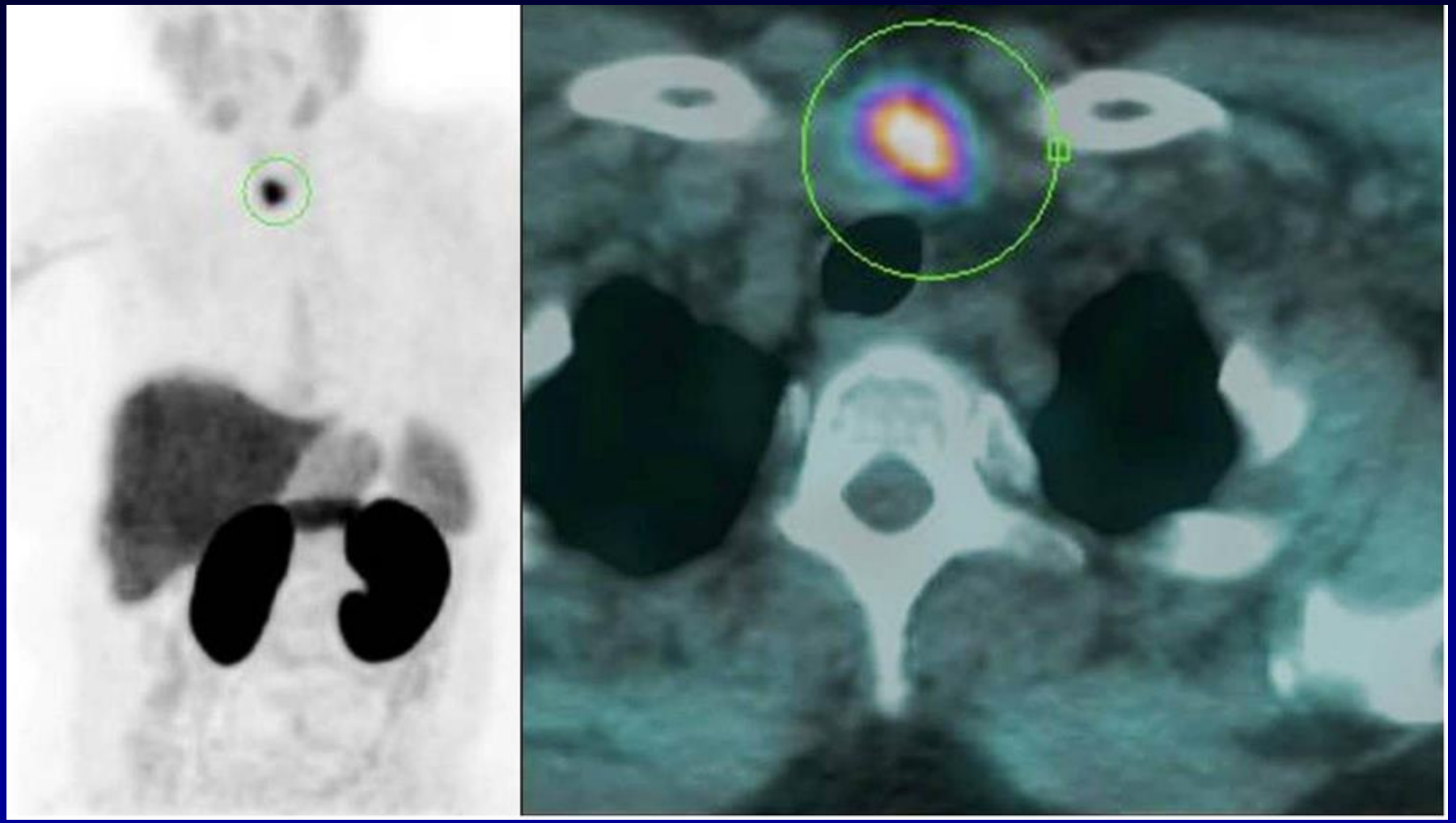




FDOPA PET/CT in another infant with congenital hyperinsulinism
No focus was visible on FDOPA PET.
Nevertheless laparotomy was performed in this infant and histology confirmed a diffuse hypertrophy of the beta cells of the pancreas.



FCH in primary hyperparathyroidism
PTH = 94 pg/L



In conclusion

- - In my opinion, PET is the future of NM
- - For tracers that are frequently used (FDG and a few others), 18F labelling and delivery by an industrial firm will probably dominate the market, requiring no on site cyclotron or radiopharmacy
- - For tracers that are less frequently used or that should be available at short notice, on site labelling from the eluate of a generator (68Ge/68Ga) will develop
- - For ligands that bind slowly to their targets, long lived positron emitting radionuclides are available: 64Cu, 89Zr, 124I …
- - Thus it seems no longer advisable to develop tracers for SG&SPECT, except for intraoperative detection.

Conclusion (continued)

- - From a rapid calculation on the data above in 2013 in IdF,
- - replace all bone SG&SPECT, all brain SPECT, all somatostatin receptor, MIBG and parathyroid SG&SPECT by would need +17 PET machines (at 3300/year/machine) from 22 to 39
- - This shift would make 30 γ cameras redundant (at 1900/year/machine) from 85 to 55.

- - This could be achieved rapidly, assuming γ cameras have to be renewed after 8.5 years, 10 need to be replaced each year. Replacing γ cameras by PET machines in almost all cases would lead to + 17 PET machines after 2 years,
- - resulting in a superior detection of cancer lesions, brain damage, neuroendocrine tumours, … with a proven impact on patient management and better decisions.

- - Actually this rough calculation assumes stability of demand and just internal shift within nuclear medicine, whereas demand for PET is driven by new indications and not just this shift: +17 might not be enough.