

## **Clinical applications of FDG PET/CT**



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**Nuclear medicine imaging** 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.

They illustrate the **localisation of biological targets** and/or **the extent of functional anomalies**, helping to **select the appropriate therapy** for each patient.

**The intensity of the uptake** is linked to functional characteristics, frequently reflecting **the severity of the disease** and being **a prognostic factor, seeing through time**.

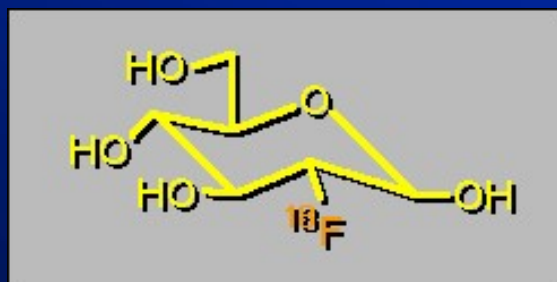
Two different imaging techniques are used according to the radionuclide of the radiotracer

- scintigraphy and tomoscintigraphy (SPECT)
- positron emission tomography (PET), the most recent modality of medical imaging in clinical practice.

In this presentation, it will not be possible to enumerate all the pathologies in which PET using the glucose analogue FDG may influence patient's management, in an adequate way demonstrated on published evidence.

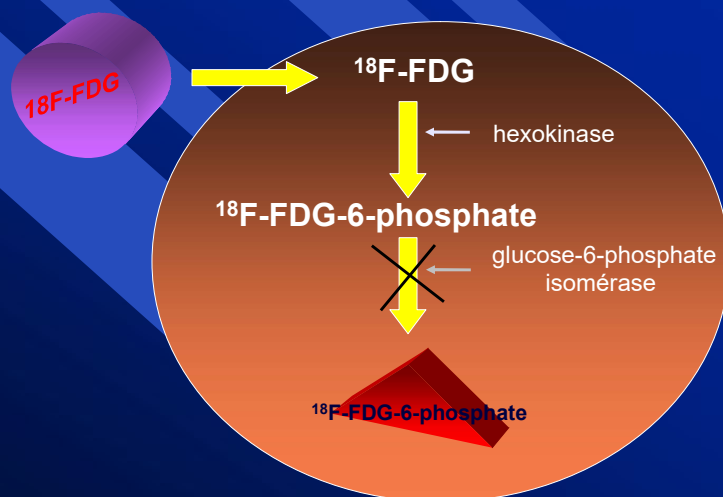
We had to choose examples, favouring frequent life threatening conditions, and ignoring some spectacular case reports.

FDG is the most widely used PET tracer for clinical application



[18-F]-FLUORO-2-DESOXYGLUCOSE,  
metabolic marker :  
- multipurposes  
- but non-specific

## FDG ( $^{18}\text{F}$ ), glucose analogue



## FDG in oncology

In EU, FDG is currently registered in precise settings to detect the increased glucose uptake and metabolism by:

- high grade brain tumours
- head and necks cancers including thyroid cancer
- oesophageal cancer
- lung cancer
- breast cancer
- pancreas cancer
- colorectal cancer
- ovarian cancer
- lymphoma
- melanoma

It can also be useful in aggressive forms of other cancers:

hepatocellular carcinoma, biliary cancer, cancer of testis, of uterus, bladder cancer and renal cell carcinoma, ...

In oncology, FDG 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 ...

As a metabolic non specific tracer, FDG enables

- 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.

## ■ Detection of the primary cancer

- ◆ CUP

- ◆ Paraneoplastic syndromes



## Epidemiology of cancer of unknown primary (CUP)

### Cancer of unknown primary

- accounts for approximately 3-5% of cancer
- is more frequent in men than in women
- peak of incidence at 55-65 year
- 7th to 8th most frequent cancer in the world
- 4th commonest cause of cancer-related death in both men and women

### Common features of CUP

- early presence of metastases
- 30% of patients: 3 or more organs involved vs. 15% of patients with known primary
- unusual metastatic pattern involving kidneys, adrenal, skin and heart

### Median survival of approximately 6-12 months despite therapy

- Certain subgroups are potentially curable
- Factors relating to overall survival: age, sex, lymph node / bone vs. visceral metastases

*Pavlidis N, Carcinoma of unknown primary (CUP). Crit Rev Oncol Hematol 2009;69:271–8.*

## CUP revealed by isolated cervical lymphadenopathy

Biopsy of the revealing adenopathy:

- non-SCC histology → not associated with specific localisation of the primary
- SCC histology
  - group I-III of cervical lymph nodes : H&N origin (CUP ~ 2-9% of all HNSCC)
  - group IV-VI of cervical lymph nodes : favours isubclavicular origin

Similarly as in case of known primary head & neck squamous cell carcinoma:

If primary lesion can be identified, treatment may be targeted and less aggressive

FDG PET/CT detection rate of primary:

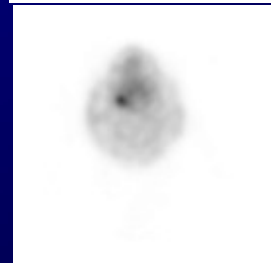
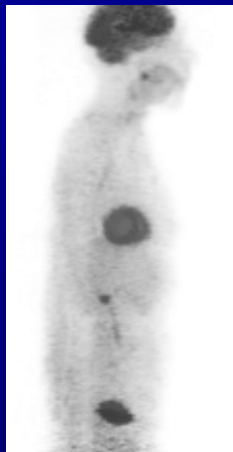
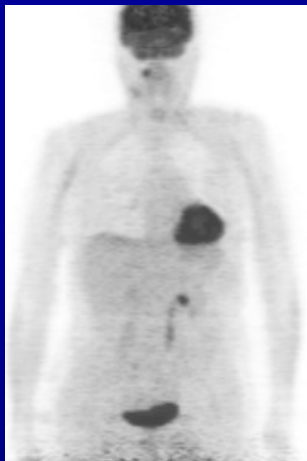
~ 44-55% prior to panendoscopy\*

~ 25% after panendoscopy\*\*

- The most frequent site of FN results of FDG PET/CT: base of the tongue & tonsils

•ESMO guideline 2011: FDG PET can contribute to the management of patients with CUP and especially those with cervical adenopathies and single metastasis\*

\*Johansen et al. Q J Nucl Med Mol Imaging 2011;55:500-8 \*\*Rusthoven et al. Cancer 2004 ;101(11): 2641-9 + ESMO Guidelines Working Group Fizazi et al. Ann Oncol 2011 ; 22 (S6): vi64-8.



CUP

FDG PET : primary in the right tonsil. Resection : SCC.

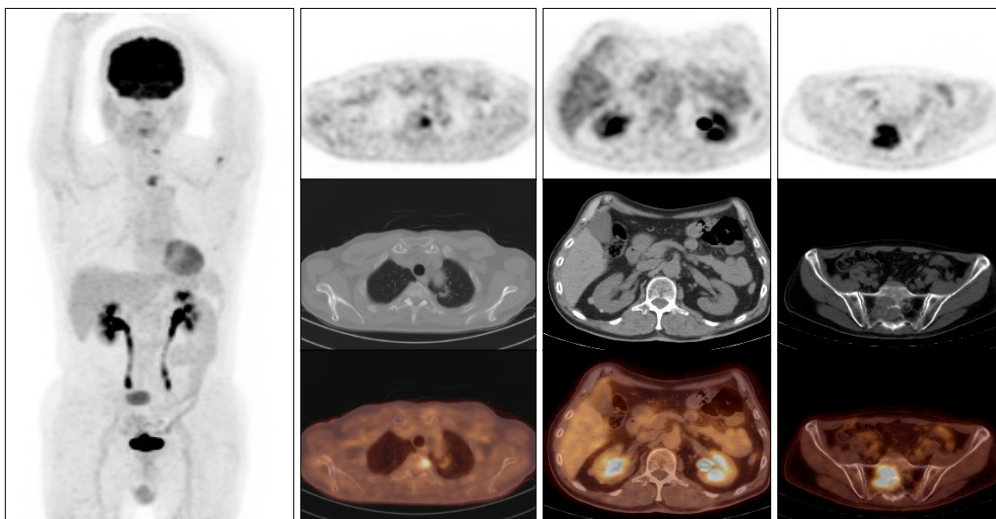
### Non H&N CUP

Clinical context: 79y old man with osteolytic/osteoblastic bone metastases of unknown primary. 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**



## Non H&N CUP detection rate of primary with FDG PET/CT

Author	Nb of patients	Detection rate	Detection rate %
Gutzeit A, Radiology. 2005	45	15/45	33%
Nanni C, Eur J Nucl Med Mol Imaging. 2005	21	12/21	57%
Ambrosini V, Med. 2006	38	20/38	53%
Hu M, Zhonghua Zhong Liu Za Zhi. 2008	67	39/67	54%
Kaya AO, Asian Pac J Cancer Prev. 2008.	43	24/43	56%
Lucić SM, Acta Chir Iugosl. 2009	17	10/17	59%
Yapar Z, Nucl Med Commun 2010	49	22/49	45%
Han A , Cancer Epidemiol. 2012	120	54/120	43%
Møller AK, Oncologist. 2012	136	66/136	49%
Han A , Cancer Epidemiol. 2012	120	54/120	43%
Tamam MO, Eur Rev Med Pharmacol Sci. 2012	432	238/432	55%
Talavera-Rubio Mdel P, Med Clin Barc. 2013	74	38/74	51%
<b>OVERALL</b>	<b>1110</b>	<b>562/1110</b>	<b>51% [CI95% 48-54%]</b>

## ■ Detection of the primary cancer

- ◆ CUP

- ◆ Paraneoplastic syndromes

## Paraneoplastic neurologic syndromes

- FDG PET has approximately a 20% impact rate on management by showing the primary cancer.
- It may also show abnormal CNS uptake.
- The proportion of success is higher when PNS specific antibodies are positive
- Patel RR (*Mayo Clin Proc* 2008;917): 10 malignancies, 8 detected by FDG, 5 by FDG alone, 3 by CT
- Schramm N (*EJNMMI* 2013;1014): 25% of FDG PET/CT findings were not detected by contrast-enhanced CT alone.

Schramm 2013 on 66 patients	sensitivity	specificity
FDG PET/CT	100%	90%
Contrast enhanced CT	78%	88%

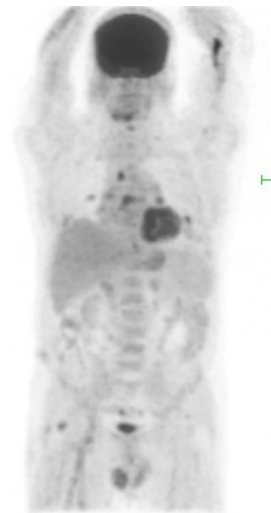


## Trousseau's syndrome

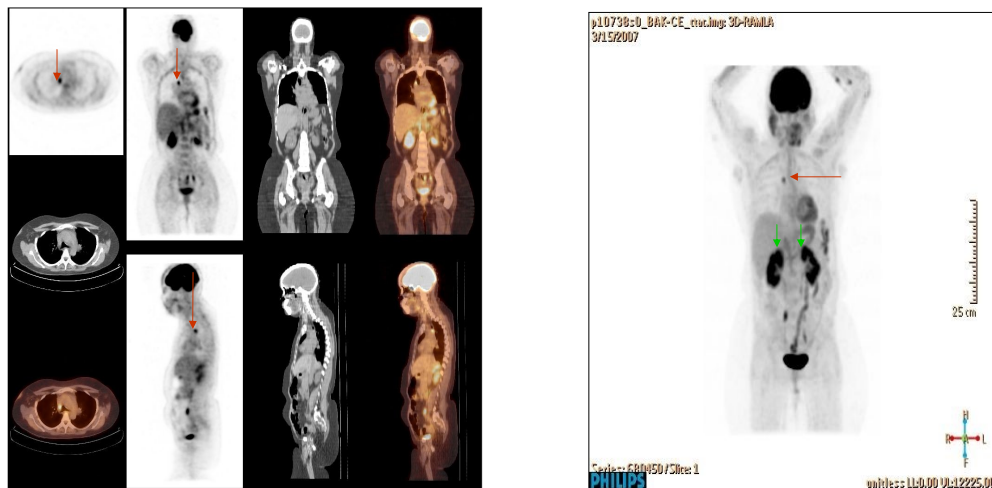
Extensive venous thrombosis of the right arm complicated by a bilateral pulmonary embolism which progressed under anticoagulation treatment, suspicious for Trousseau's syndrome.

► 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

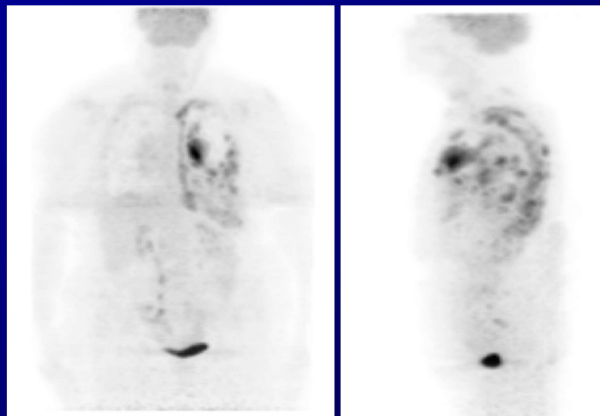
## ■ Staging and management decision

- ◆ Resectability of cancer
- ◆ Selection of HCC patients for liver grafting
- ◆ Radiotherapy

Rotating MIP

Anterior MIP

Left profile



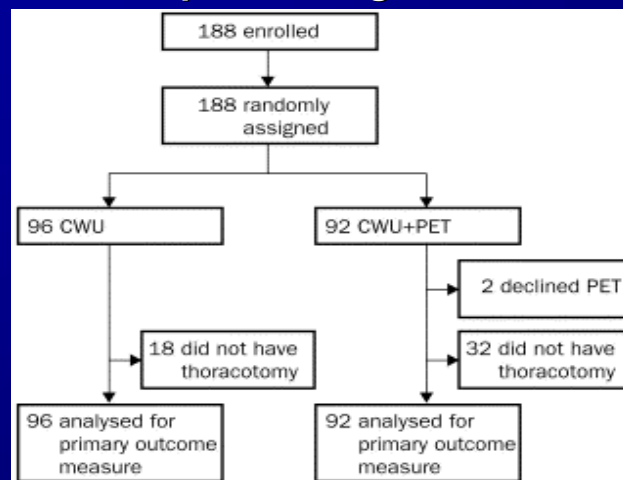
Preoperative staging of a left lung adenocarcinoma that was considered resectable after the conventional work-up (CWU).

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



Hôpital TENON

## Preoperative assessment of patients with suspected lung cancer



Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. Van Tinteren H et al. *Lancet* 2002;359:1388-93.

### Preoperative assessment of patients with suspected lung cancer

(n=92)	CWU (n=96)	CWU+FDG PET
<b>No thoracotomy</b>	18 (19%)	32 (35%)
Confirmed N2/3	10	18
Confirmed Metastases	1	7
Benign primary lesions	2	3
Other tumour	2	1
Intercurrent morbidity or refusal	3	3

Van Tinteren H et al. *Lancet* 2002;359:1388-93.

### Preoperative assessment of patients with suspected lung cancer

	CWU (n=96)	CWU+FDG PET (n=92)
<b>Thoracotomy</b>	78 (81%)	60 (65%)
Indicated	39 (41%)	41 (44%)
Futile	39 (41%)	19 (21%)
Benign	7	2
Explorative	1	1
IIIA-N2	6	4
IIIB	6	2
Recurrence or death < 1 year	19	10

Van Tinteren H et al. *Lancet* 2002;359:1388-93.

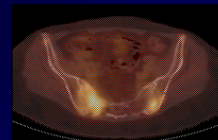
## PET/CT staging of an invasive breast cancer



Bone scintigraphy (TC-HDP)  
23/07/04



FDG PET/CT  
02/08/04



Multiple bone metastases

One subcutaneous focus corresponded to a palpable axillary nodule





## ■ Staging and management decision

- ◆ Resectability of cancer
- ◆ Selection of HCC patients for liver grafting
- ◆ Radiotherapy

Nowadays, liver transplantation is regarded as the ultimate solution for patients with hepatocellular carcinoma (HCC) and cirrhosis. The selection criteria for candidates greatly affect the outcomes of liver transplantation.

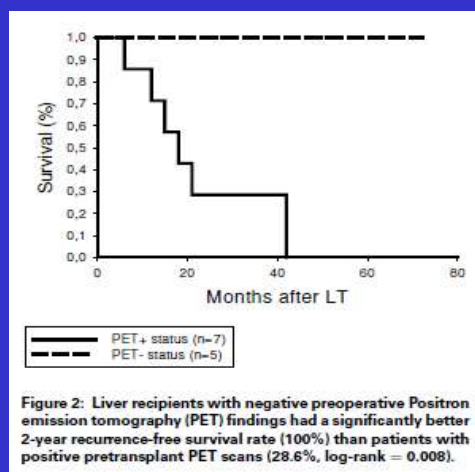
FDG PET can guide the selection of HCC patients eligible for liver transplantation, in addition to Milan criteria (a solitary HCC tumour up to 5 cm in diameter or as many as 3 HCC nodules with a maximum diameter of 3 cm without macrovascular infiltration).

**Yang (2006):** 38 HCC patients who received liver transplantation, 2-year recurrence-free survival rate: 46% if pre-grafting FDG positive vs. 85% if FDG negative ( $p < 0.001$ ). Of patients who met the Milan criteria, 4/6 FDG positive had recurrence vs. 0/20 FDG negative.

**Kornberg (2009):** 42 HCC patients, recurrence-free rate after liver transplantation: 50% if pre-grafting FDG positive vs. 96% if FDG negative ( $p < 0.001$ ).

**Kornberg (2012):** Patients with non-FDG-avid HCC beyond the Milan criteria achieved excellent 5-year recurrence-free survival after liver transplantation: 81% vs. 86% for patients with tumours meeting the Milan criteria.

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



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

## ■ Staging and management decision

- ◆ Resectability of cancer
- ◆ Selection of HCC patients for liver grafting
- ◆ radiotherapy

## ■ Selection for radiotherapy and determination of the target volume

- ◆ Indication of further radiotherapy in children with HL
- ◆ Radiotherapy in case of lung cancer

- FDG PET has been shown to be the best **non-invasive** imaging technique to assess therapeutic response in adult patients with lymphoma, including Hodgkin's lymphoma (HL).
- The feasibility and accuracy of FDG PET in childhood lymphoma was reported more than a decade ago (*Montravers et al. EJNM 2002*), including in the prediction of response to treatment.

Prognostic value of interim FDG PET (after 2 cycles) in children with HL or non-Hodgkin lymphoma (NHL)

*Miller E. et al. J Comput Assist Tomogr 2006;30:689-94*

“Interim FDG PET is an excellent prognostic tool in children with HL (n= 24) or NHL (n = 7)”.

28 patients FDG -




27 disease free after an average period of 14 months

3 patients FDG +



Progression of lymphoma

PPV of PET = 100%  
NPV of PET = 96%  
PPV of CT = 14%

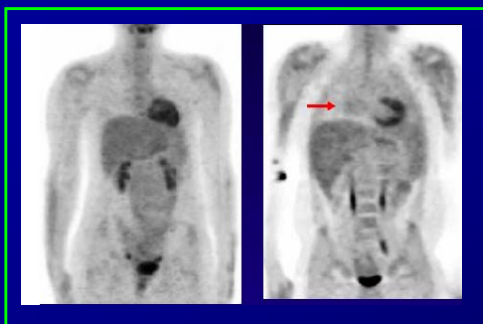
- After chemotherapy, radiotherapy is classically scheduled
- The aim of implementing FDG PET monitoring is to
  - **MINIMIZE** toxicity of the therapeutic regimen
  - **MAXIMIZE** efficacy
- Especially important in children due to specific issues
  - Compromised fertility
  - compromised cardiac function
  - Long term second cancer risk

complications related with the intensity of treatment during primary disease.

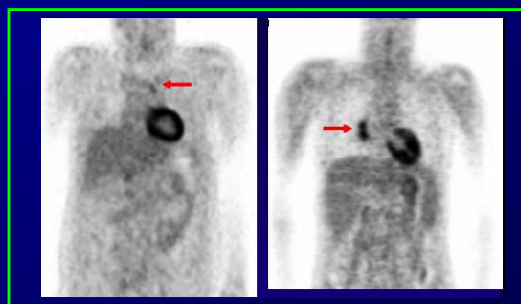
- In a multicentre trial in EU (Euronet), radiotherapy is canceled when metabolic response on FDG PET/CT is obtained with chemotherapy



## Interpretation of response on interim FDG PET



Responders



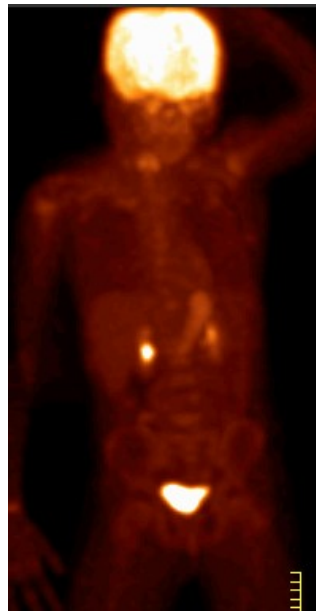
Non responders

*EuroNet PET manual*

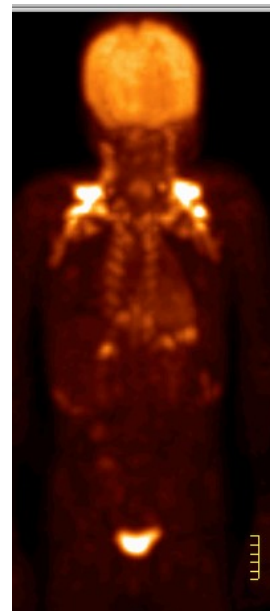
### Interference of brown fat activation



Baseline



After 2 cycles



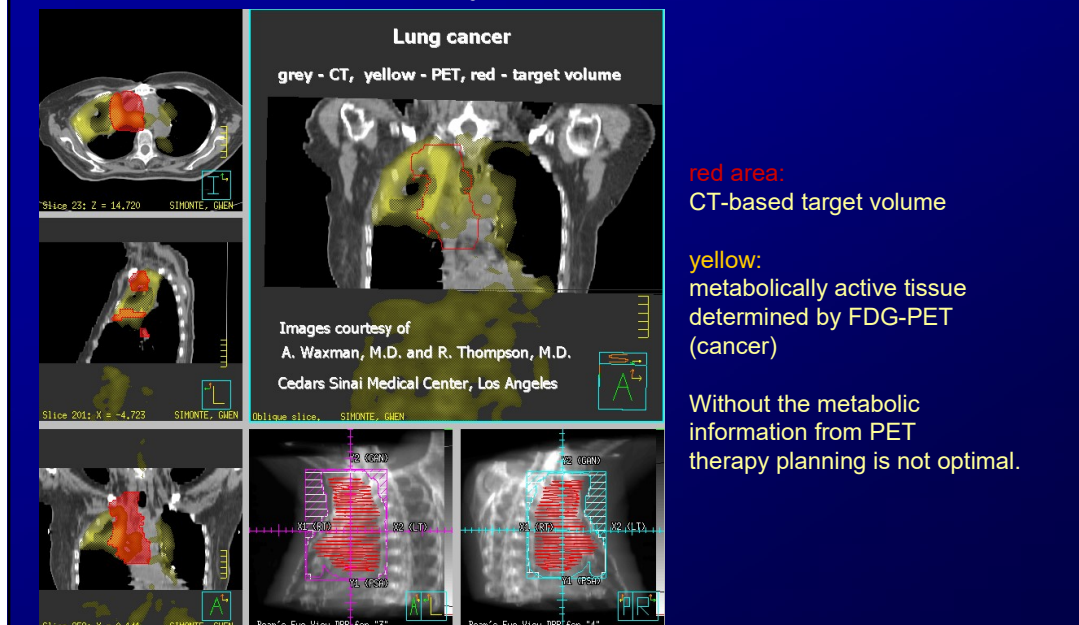
After 4 cycles



## ■ Selection for radiotherapy and determination of the target volume

- ◆ Indication of further radiotherapy in children with HL
- ◆ Radiotherapy in case of lung cancer

## Determination of radiotherapy target volume of lung cancer by FDG PET



Deniaud-Alexandre et al. *Int J Radiat Oncol Biol Phys.* 2005;63(5):1432-41 delineated the Gross Tumour Volume (GTV) in 92 NSCLC patients by FDG PET/CT and found that the GTV on PET/CT was reduced in 23% of the patients and increased in 26% of cases compared to GTV on CT, and 21 patients had a GTV change of  $\geq 25\%$ .

Several studies confirmed these results; e.g. recently ...

The Radiation Therapy Oncology Group (RTOG) 0515 designed a phase II prospective trial to quantify the impact of FDG PET/CT compared with CT alone on radiation treatment plans in NSCLC (Bradley et al. *Int. J. Radiat. Oncol. Biol. Phys.* 2012; 82, 435–41).

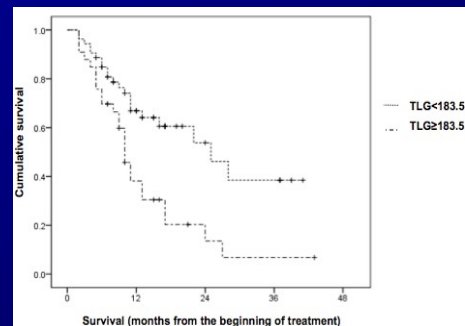
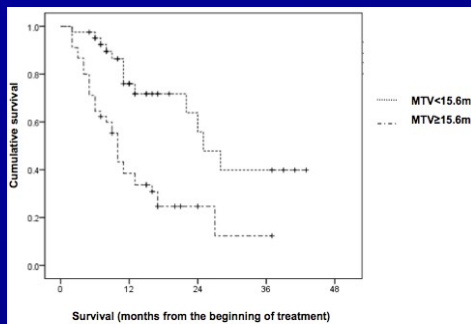
47 patients underwent FDG PET/CT followed by definite RT (>60 Gy) based on PET/CT- generated radiation plan. Mean follow-up was for 12.9 months.

- GTVs derived from PET/CT were significantly smaller than that from CT only (mean GTV volume 86 vs. 99 mL).
- FDG PET/CT changed nodal GTV contours in 51% of the patients.
- The elective nodal failure rate for GTVs derived by FDG PET/CT was very low (1/50=2%).

## ■ Prognosis

- Quantification of uptake has a limited accuracy for characterising lesions since FDG uptake by some inflammatory, infectious or benign lesions overlaps with that of malignant lesions.
- However, the intensity of FDG uptake by a malignant tumour has a prognostic value: more intense uptake, worse prognosis.
- The techniques for quantification of uptake will be addressed in the next session. In clinical practice, the SUV was initially used but has been replaced by the SUVmax which is more reproducible between readers. More recently a volumetric approach has been proposed « peak » SUL, metabolic tumour volume (MTV) and total lesion glycolysis (TLG), which are gradually becoming used routinely.

## Prognostic evaluation in oesophageal cancer



Significant difference in overall survival according to the tumour MTV and TLG (but not to SUVmax) on FDG PET/CT performed prior to initial treatment

*Li, Asian Pac J Cancer Prev, 2014 : 1369*

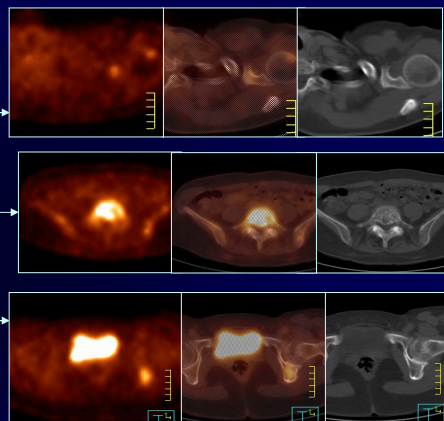
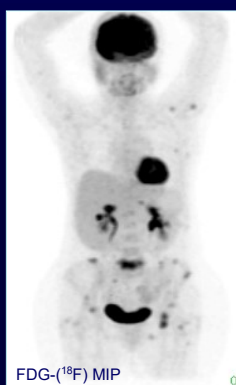
- Restaging and optimisation of management in case of occult recurrence

- ◆ Breast cancer

- ◆ Others



### Distant recurrence of a breast cancer



Restaging of a breast cancer recurrence

Bone scintigraphy : pathologic uptake by the 5th lumbar vertebra (L5).

X Rays and CT: confirmation without other lesion

FDG PET/CT : multiple bone metastases

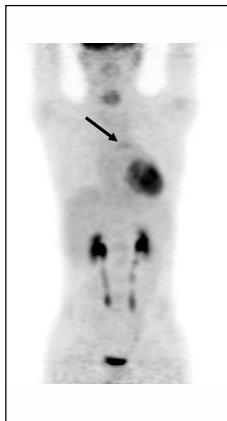


- Optimisation of management in case of occult recurrence

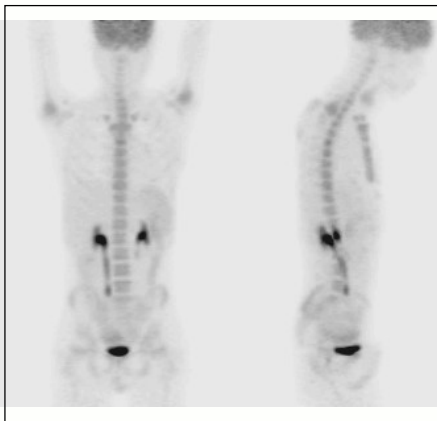
- ◆ Breast cancer

- ◆ Others

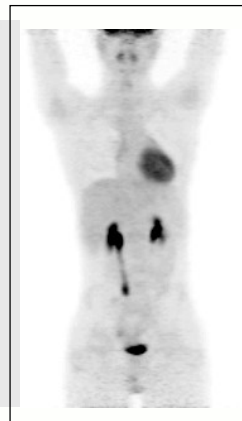
Restaging lymphoma : bone marrow activation after treatment by  
granulocyte colony stimulating factor



Viable tumour  
in a small  
residual mass  
after 4 cycles



After 2 cycles of a 2<sup>nd</sup>  
line chemotherapy



At the end of 2nd line  
therapy



- Monitoring early response to chemotherapy or inhibitor therapy
- ◆ Neoadjuvant chemotherapy
- ◆ Gleevec treatment of GIST

## PET/CT & detection of persistent HNSCC

### Evaluation of neoadjuvant chemotherapy

**Complete responders** to neoadjuvant chemotherapy have a significantly **better survival rate** than patients with residual disease (*Cognetti 1988: 1989*).

Early evaluation of neoadjuvant chemotherapy is desirable in the clinical decision to **discontinue chemotherapy in non-responders**.

RECIST criteria: 2 or more cycles of chemotherapy

→ non-responders may miss the opportunity for surgery.

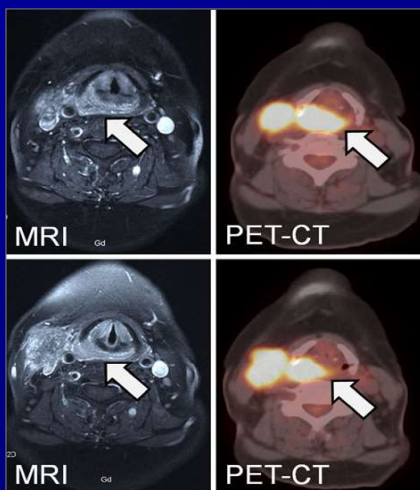
FDG PET/CT can predict histopathologic response to neoadjuvant chemotherapy in HNSCC patients with higher accuracy than MRI and is an independent prognostic factor for the disease specific survival rate.

Non-response in the primary lesion evaluated by FDG PET/CT is significantly linked to a poor local control rate and a short disease specific survival rate.

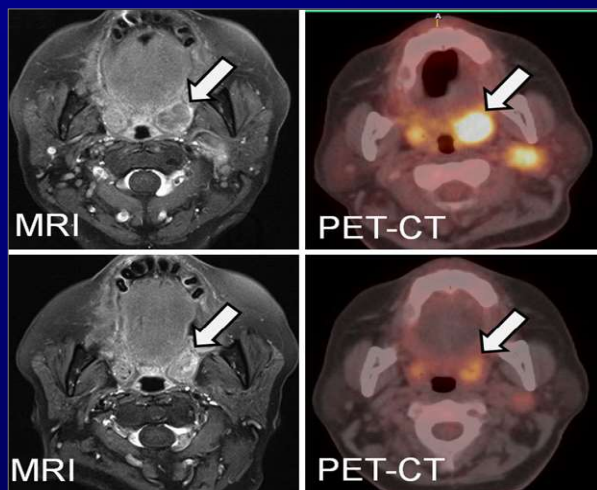
The detection of progression can frequently be done visually when new foci are detected. But differentiating CR, PR and SD requires quantification of FDG uptake. A practical drawback is that follow-up PET/CT should be performed in the same metabolic conditions, in particular same time after FDG injection.

**H&N cancer. Responders (after completion of neoadjuvant chemotherapy):**  
 decrease in SUVmax  $\geq 55.5\%$  or NAC SUVmax  $\leq 3.5$   
 and decrease in size  $\geq 30\%$  (RECIST)

**Non responder**



**Responder**



Kikuchi, Mol Imaging Biol, 2011

## Monitoring induction chemotherapy of breast cancer

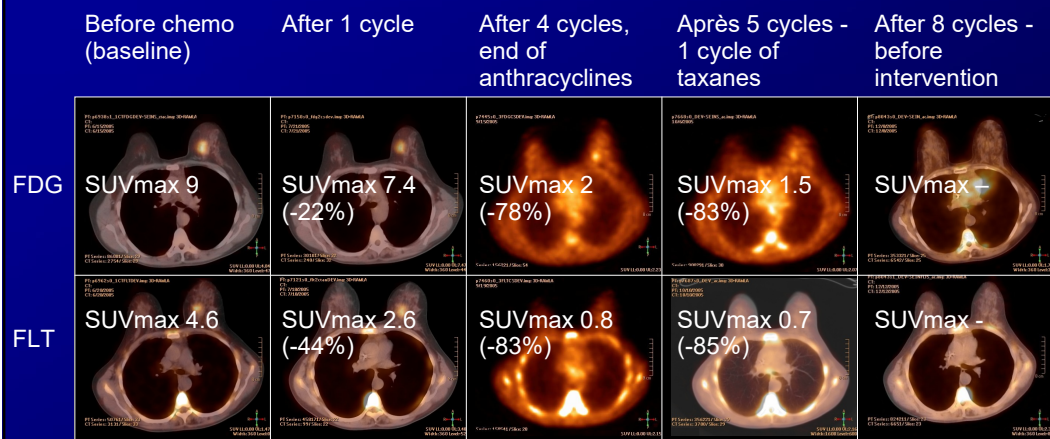


Patient, 49 yo, left upper internal quadrant, 24mm on US. Prone PET images.

Biopsy: ductal breast cancer SBR 3+2+1, ER 100%, PR 50%, Her2 +, T2N0M0, stage IIB

Post-surgery histology: residual ductal cancer SBR 3+3+1, ER 90%, PR <10%, Ki67 = 5%

Complete remission at 39 months



- Monitoring early response to chemotherapy or inhibitor therapy
- ◆ Neoadjuvant chemotherapy
- ◆ Gleevec treatment of GIST



## **Gastroenteropancreatic stromal tumours (GIST)**

Mesenchymal tumours of the digestive tract located in:

Stomach: 60 - 70%

Gut: 20 - 30%

Colon - rectum: 10%

Oesophagus < 1%

Expression on the surface of tumour cells of a mutated tyrosine kinase receptor (c-kit) with spontaneous activation.

These tumours are resistant to chemotherapy and radiotherapy but their management was profoundly changed by the introduction of tyrosine kinase inhibitor imatinib (Gleevec).

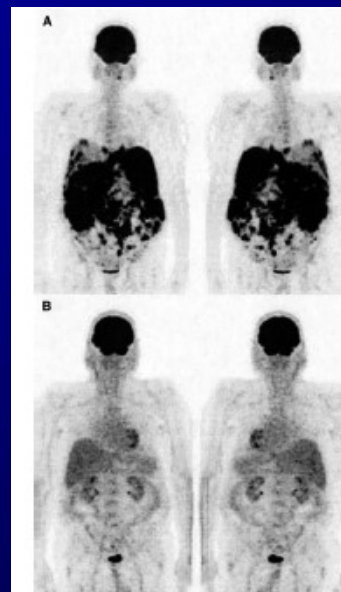
Around 15% of the tumours do not respond to this treatment, and others may become refractory.

FDG PET is able to objectivise metabolic tumour response to imatinib, as early as 48h after beginning of treatment.

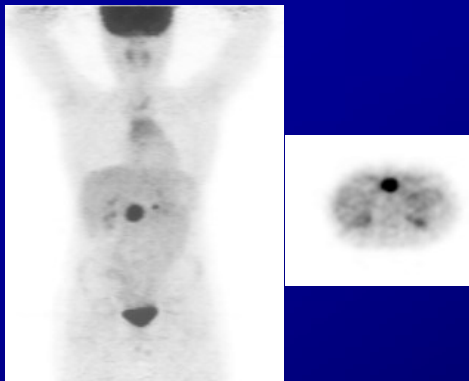
Gastric GIST before treatment

After 10 weeks of imatinib treatment:  
responder

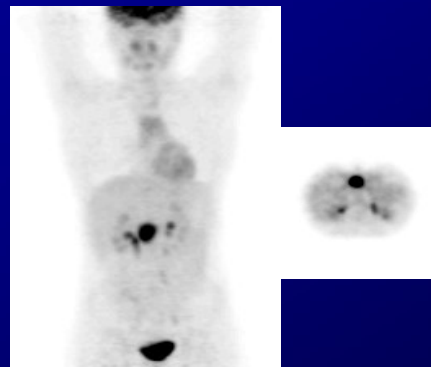
*Zaknun et al. Clin Nucl Med 2005;30: 945-51*



After surgery



During imatinib treatment



A GIST was resected in this 14 yo boy.

A 1st FDG PET was performed to characterise a post-operative residual mass. It showed an intense FDG uptake corresponding to viable GIST tissue. Imatinib treatment was started.

After 4 months of treatment, a 2<sup>nd</sup> FDG PET was performed to monitor efficacy: the FDG focus was unchanged, showing a lack of metabolic response: non-responder.

## FGD for imaging inflammation and infection

In EU, FDG is currently registered in several indications.

Localisation of abnormal foci guiding the aetiological diagnosis in case of fever of unknown origin

Diagnosis of infection

Suspected chronic infection of bone and/or adjacent structures: osteomyelitis, spondylitis, diskitis or osteitis including when metallic implants are present

Diabetic patient with a foot suspicious of Charcot's neuroarthropathy, osteomyelitis and/or soft tissue infection

Painful hip prosthesis

Vascular prosthesis

Fever in an AIDS patient

Detection of the extension of inflammation

Sarcoidosis

Inflammatory bowel disease

Vasculitis involving the great vessels

Therapy follow-up:

Unresectable alveolar echinococcosis, in search for active localisations of the parasite during medical treatment and after treatment discontinuation.

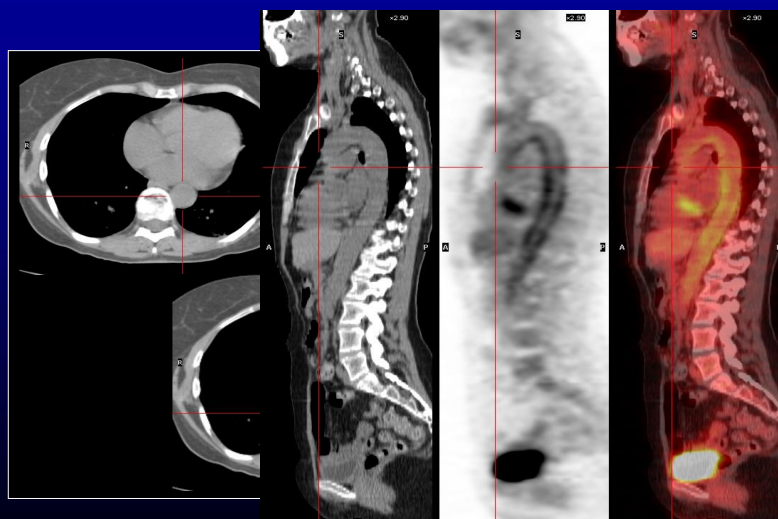
PET did open new domains that were not accessible to scintigraphy & SPECT in inflammation and in fever of unknown origin

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

FDG has now replaced  $^{67}\text{Ga}$  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  $^{67}\text{Ga}$  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  $^{111}\text{In}$ - or  $^{99\text{m}}\text{Tc}$ -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 less than 2h.

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

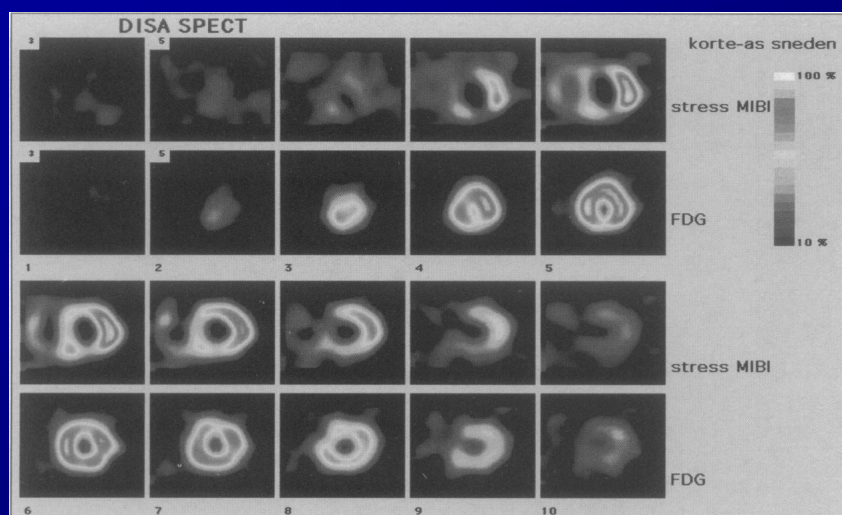
Radiolabeling of leucocytes with FDG has been proposed, but is not performed routinely.

## **FDG in cardiology - angiology**

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

It is a reference imaging in this indication but there are alternative e.g. ultrasonography with dobutamine test.





Myocardium viability assessed by the FDG uptake in a large perfusion defect (on sestamibi stress images) *Slart Neth HeartJ2005;13:408-15.*

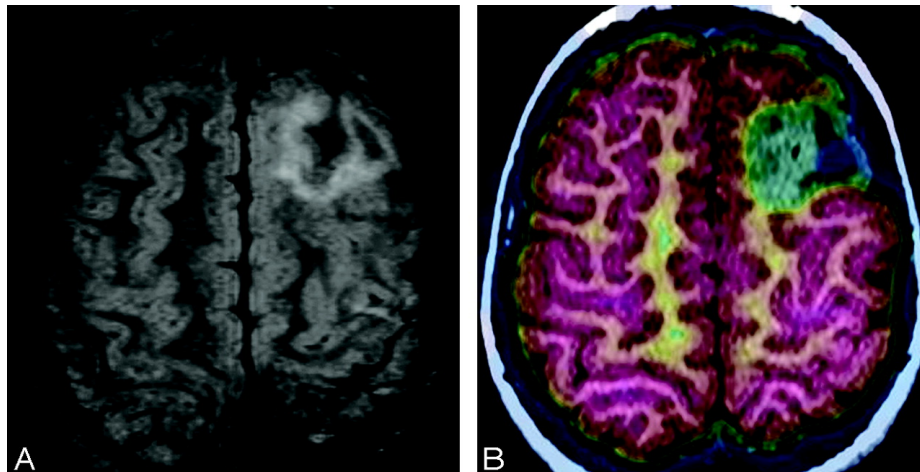
## **FDG in neurology**

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.

## FCD type II in a 5-year-old girl: Frontal cortical dysplasia



K.K. Lee, and N. Salamon AJNR Am J Neuroradiol  
2009;30:1811-1816



## Can FDG replace SPECT for functional imaging in neurology?

At least partly, 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 in suspected dementia, but not the dopaminergic neurons.

No ligand of the amyloid substance or of the tau protein, another approach for the diagnosis of Alzheimer disease, has been developed for SPECT imaging, whereas several PET agents have recently been registered.

## Conclusions

- We have illustrated the diagnostic utility of FDG PET (/CT) with examples, mostly in oncology, and the corresponding published evidence, but the potential of NM imaging, FDG PET in particular, for personalised medicine is much wider than presented in this short summary.
- FDG PET(/CT) is not meant for screening but can be very useful in detecting the primary cancer in difficult cases (CUP, paraneoplastic syndromes with autoantibodies) with a major consequence on the management and the prognosis
- FDG PET(/CT) can help selecting the appropriate therapy for patients, at staging and at restaging: surgery, radiotherapy, anticancer drugs.

- FDG PET/CT is useful to monitor anticancer drug treatment, in particular to detect resistance

- The biologic in vitro approach is complementary to the PET in vivo functional approach: serum biochemical markers, immunohistochemistry of the primary tumour or of a metastasis, circulating cells, DNA or mRNA.

The polyclonal nature of almost all malignancies, with uneven genomic anomalies limits the validity of this approach for treating and monitoring patients with drugs targeting overexpression of receptors or specific mutations.

- Year after year, new PET tracers are being registered, filling the few performance gaps of FDG.