ONCOLOGY 2

Nuclear Medicine Scans: Analysis of uptake mechanism and imaging protocols

ONCOLOGY

Imaging

- "positive uptake"
- non-specific
- specific
- functional imaging

Y emitting RF (SPECT)

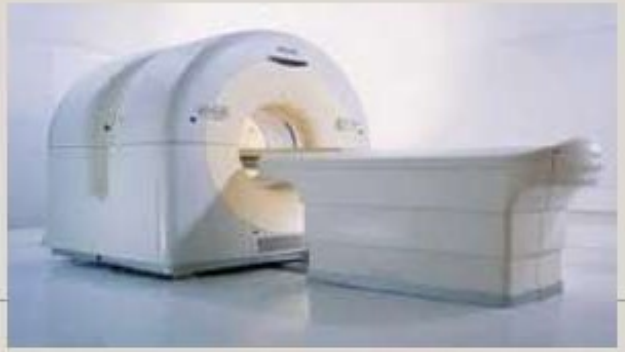
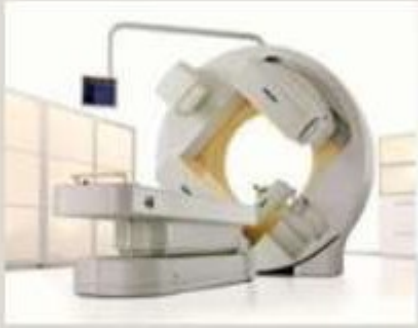
B+ emitting RF (PET)

Therapy

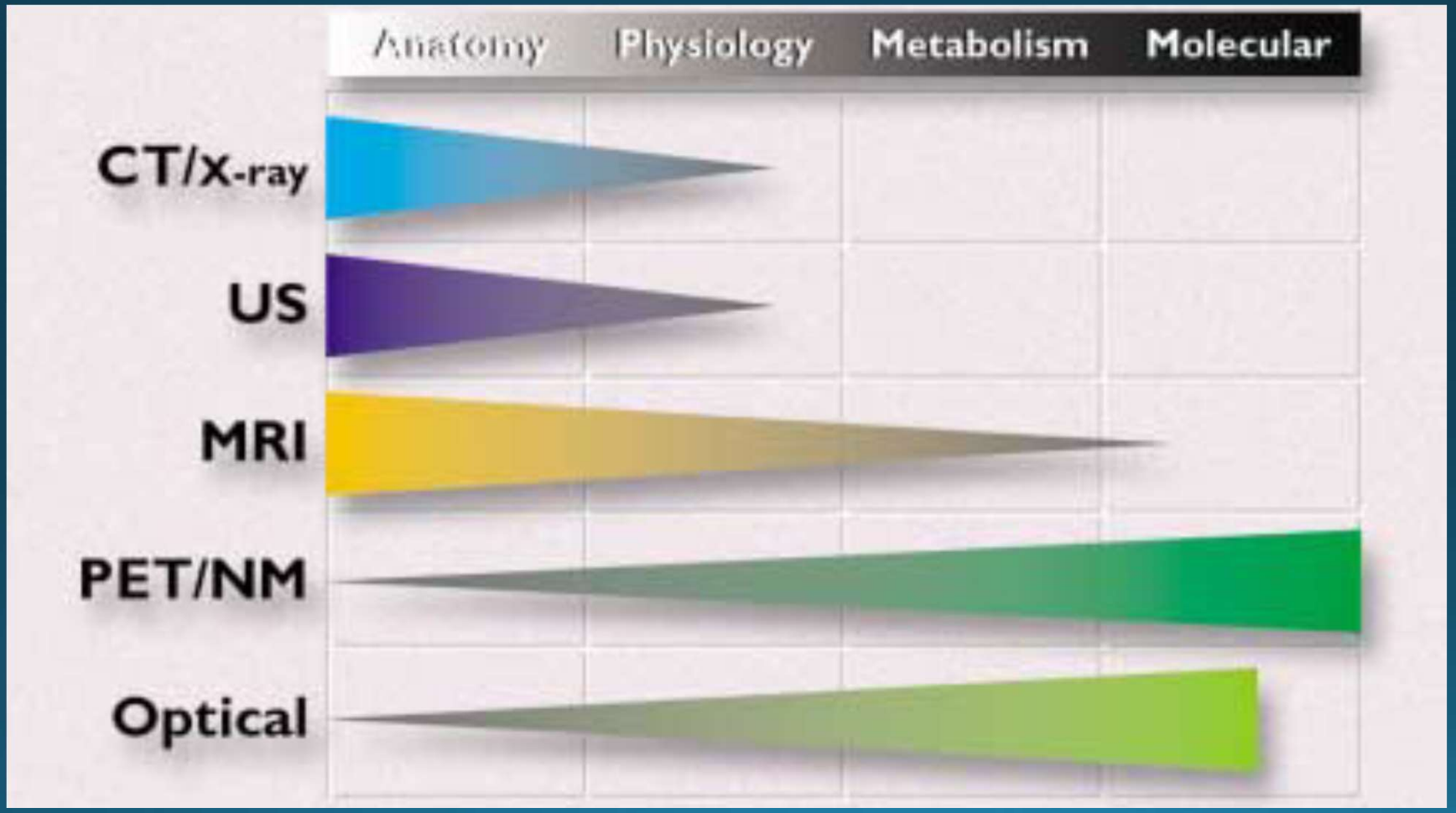
Specific only

B+ emitting RF
α emitting RF

What are the nuclear medicine imaging methods?

Onco PET	PET : 3D PET –CT : 3D (Function and anatomy). PET: Positron emission tomography (2 photons)	
Conventional tumor imaging	Planar: 2D. SPECT: 3D. SPECT-CT : 3D (Function and anatomy). SPECT: Single photon emission computed tomography.	 

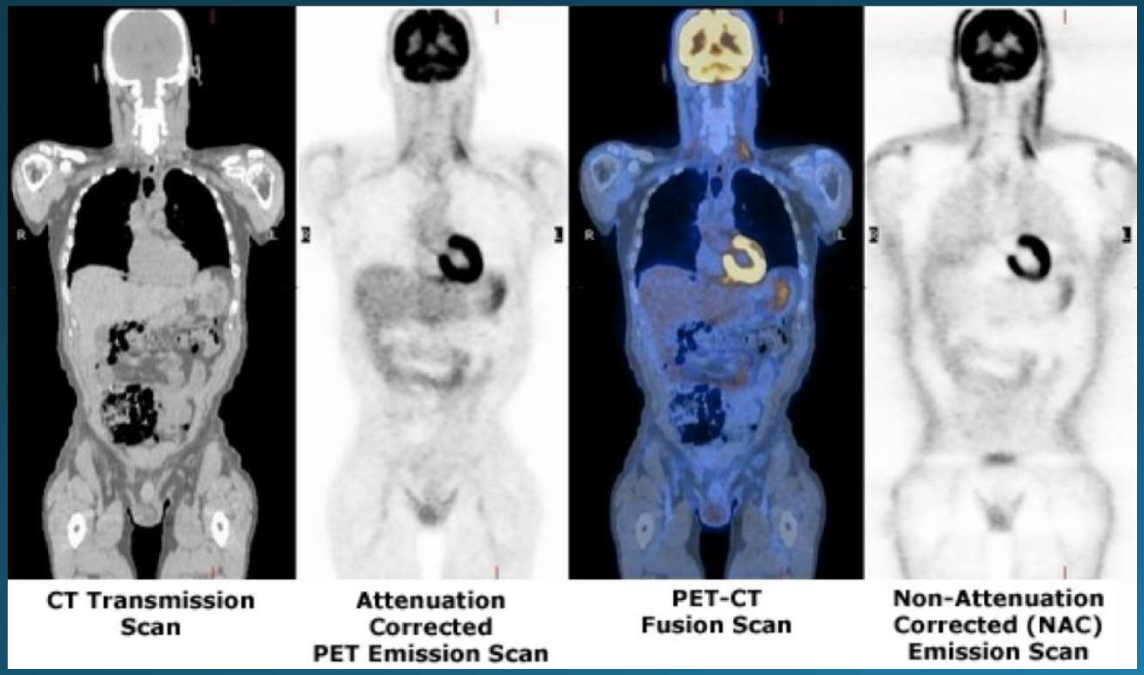
IMAGING clinical practice & research

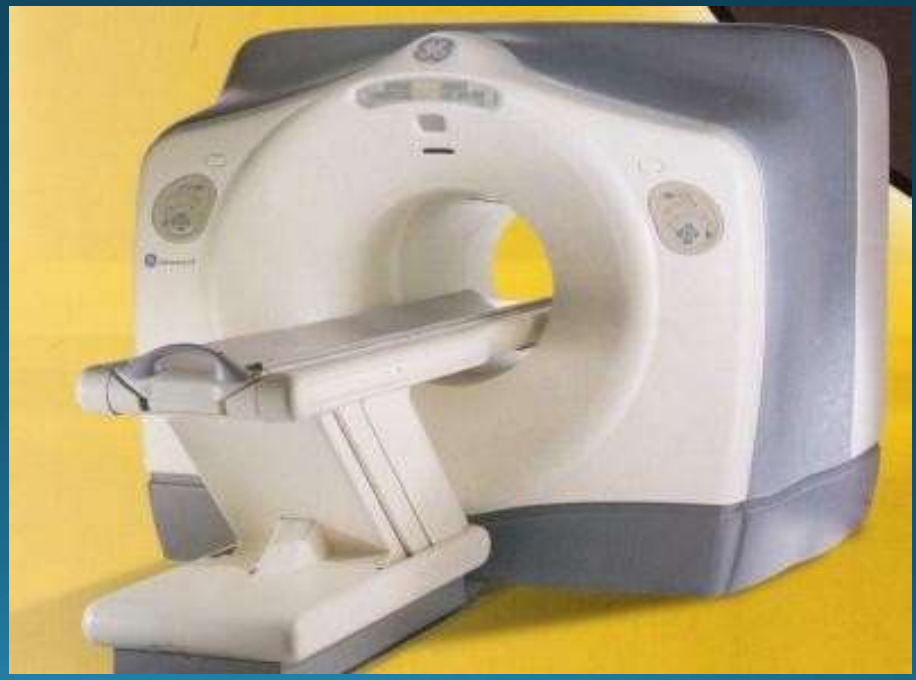


Positron Emission Tomography

PET+CT=PET-CT

the fusion of functional and anatomic information acquired almost simultaneously from which we are able to visualize form and function. an with the CT, which gives us the PET CT





Diagnostic Radiopharmaceuticals

Specific

Binds directly to special tumor antigens or receptors or are accumulated by special metabolic pathway.

PET or PET/CT:

- **Gallium 68** – octreotide analogues (mimics natural somatostatin pharmacologically) (Ga-68 DOTA): For neuroendocrine tumors.
  it's the gold standard and more specific and sensetive. used in KSA
- **Fluorine-18** - fluorodeoxythymidine (F-18- FLT): For tumor proliferation.
  The uptake depends on the degree & rate of proliferation.
- **Fluorine-18**-fluoromisonidazole (F-18-FMISO): For tumor hypoxia.
  Hypoxia is usually located at the tumer's center. You want to know the degree of hypoxia; some centers use oxygen for tumor treatment.

Planar, SPECT or SPECT/CT:

- I-123/131 MIBG for neuroendocrine tumours.
- I-131 for differentiated thyroid carcinomas.
- In-111 or Tc99m octreotide for tumours expressing somatostatin receptors.
  Gallium-68 is more sensitive than Tc99m octreotide.
- Monoclonal antibodies labelled with In111 (Indium-111), I-123/131 or Tc-99m.

Non-Specific

Demonstrate tumor sites but are not specific for malignancy.

What does 'non-specific' mean?
They can tell you if there was a tumor, but they cannot tell you what type of a tumor it is.

PET or PET-CT

- **Fluorine-18 FDG** – anaerobic metabolism.
  - Most commonly used.
  - Highly sensitive, but not specific. E.g. if there was an abnormal uptake in the hilar area, we will not be able to know if it was a large lymph node, or a lung tumor.
  - Excreted by urine.

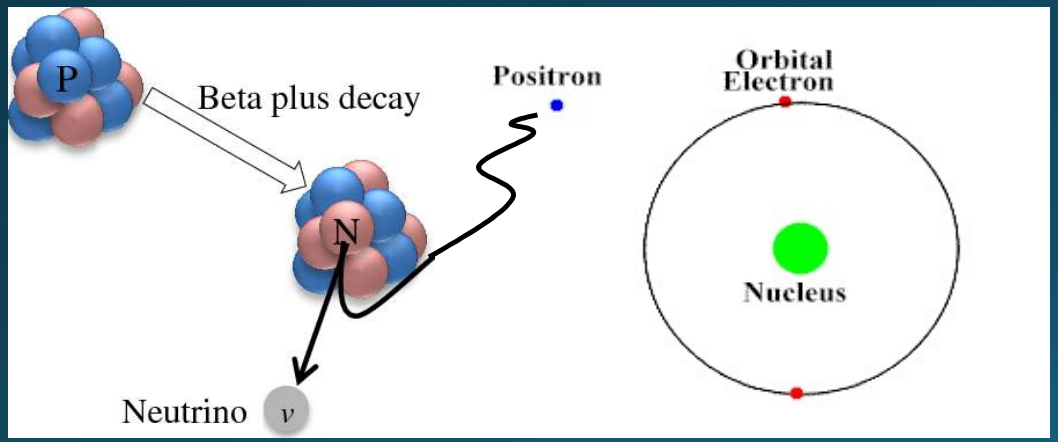
Planar, SPECT or SPECT-CT:

- **Diphosphonates** – bone scan.
  - Most commonly used.
  - Can tell if there was any metastasis, but cannot detect its origin.
- **Ga-67 citrate** – similar to FDG – localising agent.
- **Tc99m Nanocolloid** – bone marrow scan.
- **Tc99m MIBI / Thallium 201** – several tumors.

Radiopharmaceuticals - Positron Emitting Isotopes

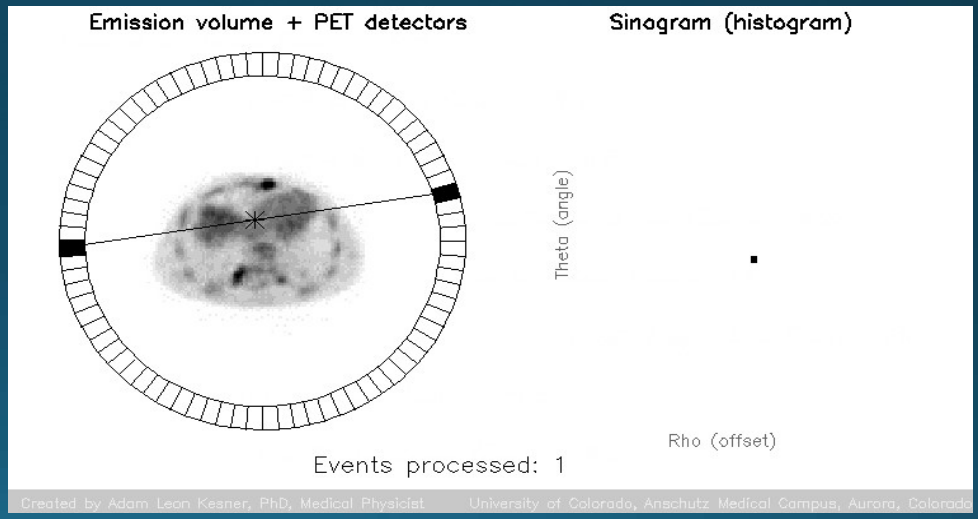
β^+ Decay

Neutron-deficient isotopes can decay by emitting positrons



- Positron travels ~1mm
  - Decelerates
- Annihilates with e^-
- Gamma photons

Positron Emission Tomography (PET)



Scanner is just a photon counter!

Counts gamma-ray *pairs* vs. single gamma

Positron Emitting Isotopes

Cyclotron produced isotopes		Generator produces isotopes			
Isotope	**T/2**	**Isotope**	**T/2**	**Daughter**	**T/2**
Oxygen-15	2 min	Strontium-82	25 days	Rubidium-82	75 sec
Nitrogen-13	10 min	Zinc-62	9.3 hrs	Copper-62	10 min
Carbon-11	20 min	Germanium-68	288 days	Gallium-68	68 min
Fluorine-18	110 min				

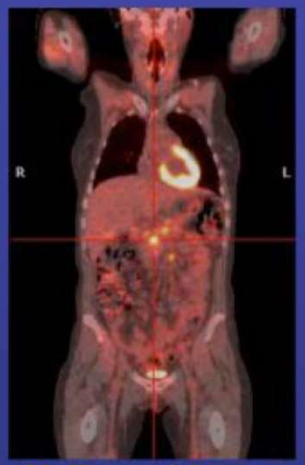
Radiopharmaceuticals - Positron Emitting Isotopes
Uptake mechanism

- Glucose metabolism
  - F-18-fluorodeoxyglucose (FDG)
- Amino acid metabolism
  - C-11-methionine, F-18-tyrosine
- Nucleic acids metabolism
  - F-18-thymidine
- Blood flow
  - N-13-ammonia, O-18-water
- Receptor uptake
  - F-18-estradiol, somatostatine

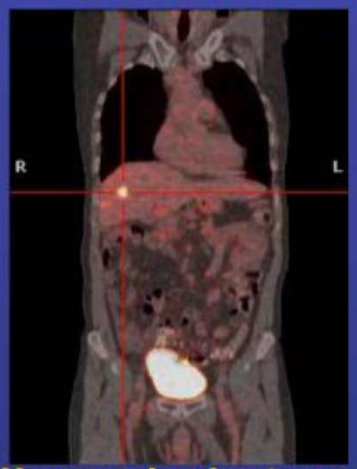
Radiopharmaceuticals - Positron Emitting Isotopes most commonly used

Radiopharmaceuticals	Uptake mechanism
^{18}F FDG	Glucose uptake
^{11}C acetate	oxidative metabolism
^{68}Ga-SSA	Somatostatine receptor
^{11}C tirozin	Cell proliferation
^{11}C FET (fluoro etiltirozin)	Cell proliferation
^{11}C metionine	Cell proliferation
^{11}C/^{18}F choline	Acetylcholinesterase activity
^{18}F FLT (fluoro 3-deoxi timidine)	Cell proliferation
^{18}F FMISO (fluoro misonidasol)	Cell hypoxia
^{18}F Na fluoride	Cell osteoblastic activities

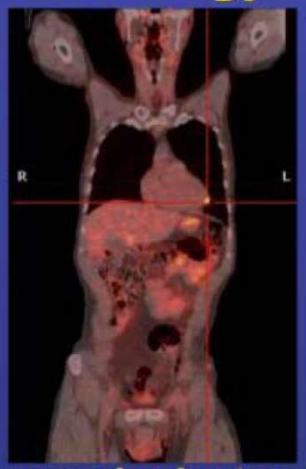
Clinical Research - Oncology



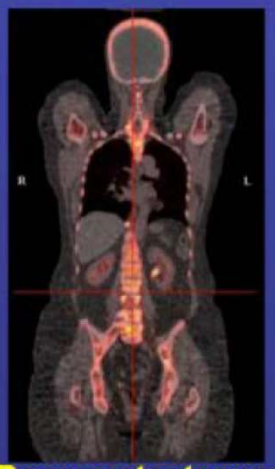
Malignant tumors
^{18}F Fluorodeoxyglucose



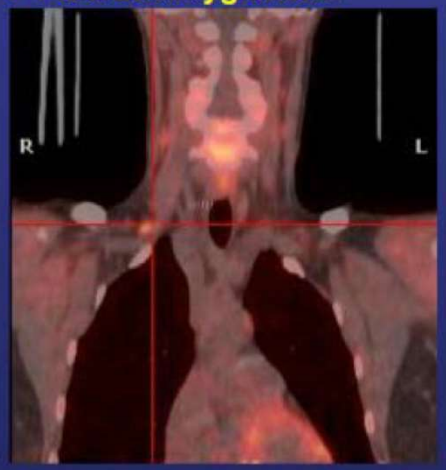
Neuroendocrine tumors
^{68}Ga DOTA-TOC



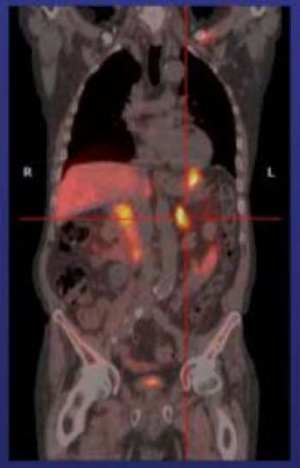
Neuroendocrine tumors
^{11}C 5-Hydroxytryptophan



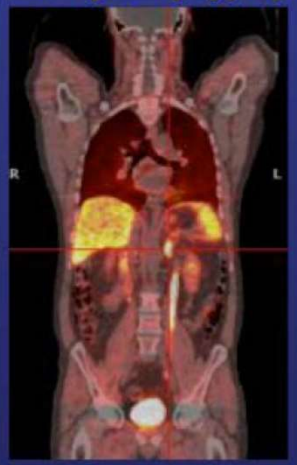
Bone metastases
^{18}F-Fluoride



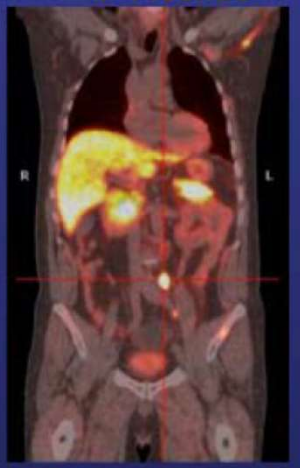
Parathyroid cancer
^{11}C Methionin



Adrenocortical tumors
^{11}C Metomidate

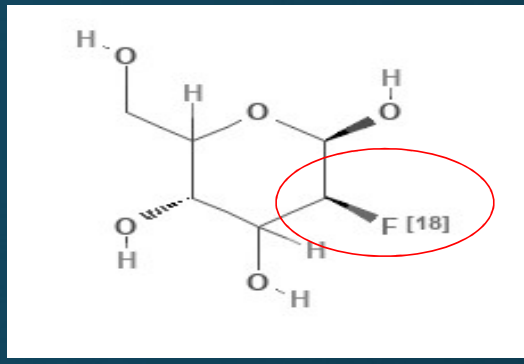


Pheochromocytomas
^{11}C Hydroxyephedrine



Prostate cancer
^{11}C Acetate

FDG: Fluoro-2-deoxy-D-Glucose
Uptake Mechanism

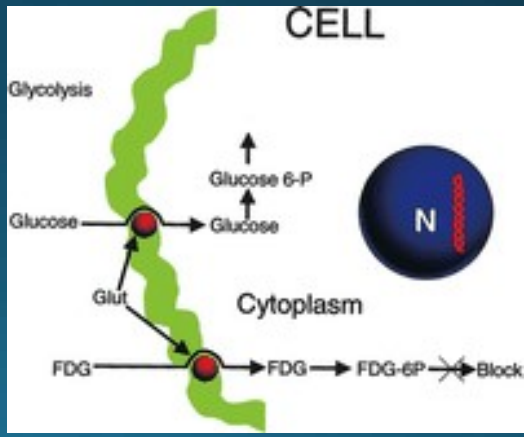


FDG is a glucose analogue (similar to it) used to assess glucose metabolism.

- The only difference between them is kidney excretion.
- FDG transported from intravascular space to the cells by the same mechanism as the glucose.
- In the cell, a substance called "hexoKinase" acts on both FDG and glucose to form:

- FDG-6-phosphatase (FDG-6-PO_4-).
- Glucose-6-phosphatase.

- FDG-6-PO_4- can't progress further into glucose metabolism and remains trapped intracellularly in proportion to glycolytic rate of the cell.

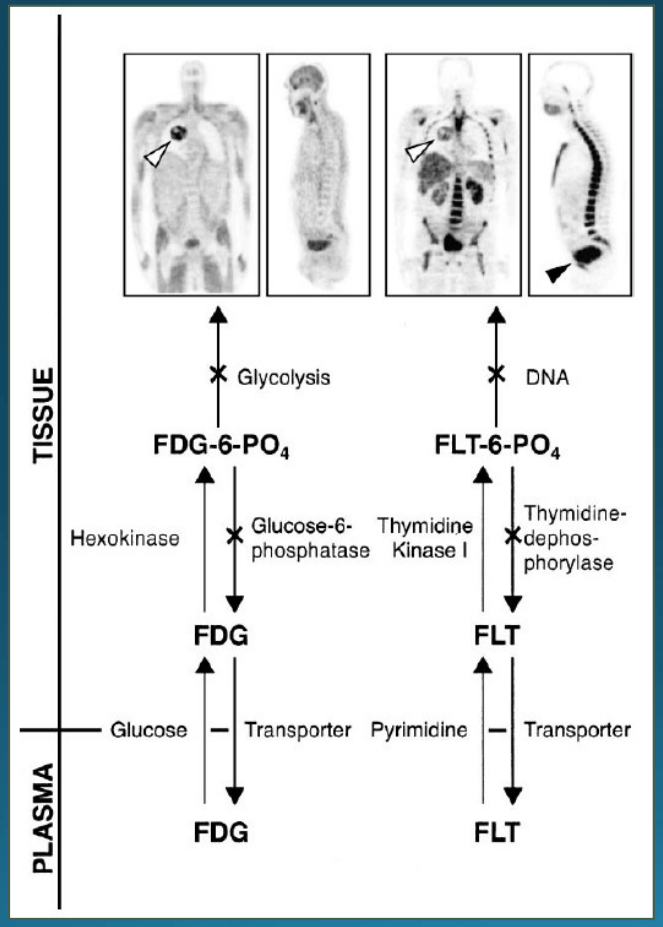


*In tumors, there is high rate of glycolysis (High compounds concentration) compared to normal cells and higher level of hexoKinase.

RADIOPHARMACEUTICALS

- Cellular functional Specificity -

Fluorodeoxyglucose (FDG) is phosphorylated to FDG-6-PO4 by hexokinase. Since the activity of glucose-6-phosphatase is negligible, FDG-6-phosphate is essentially trapped in tumor cells.

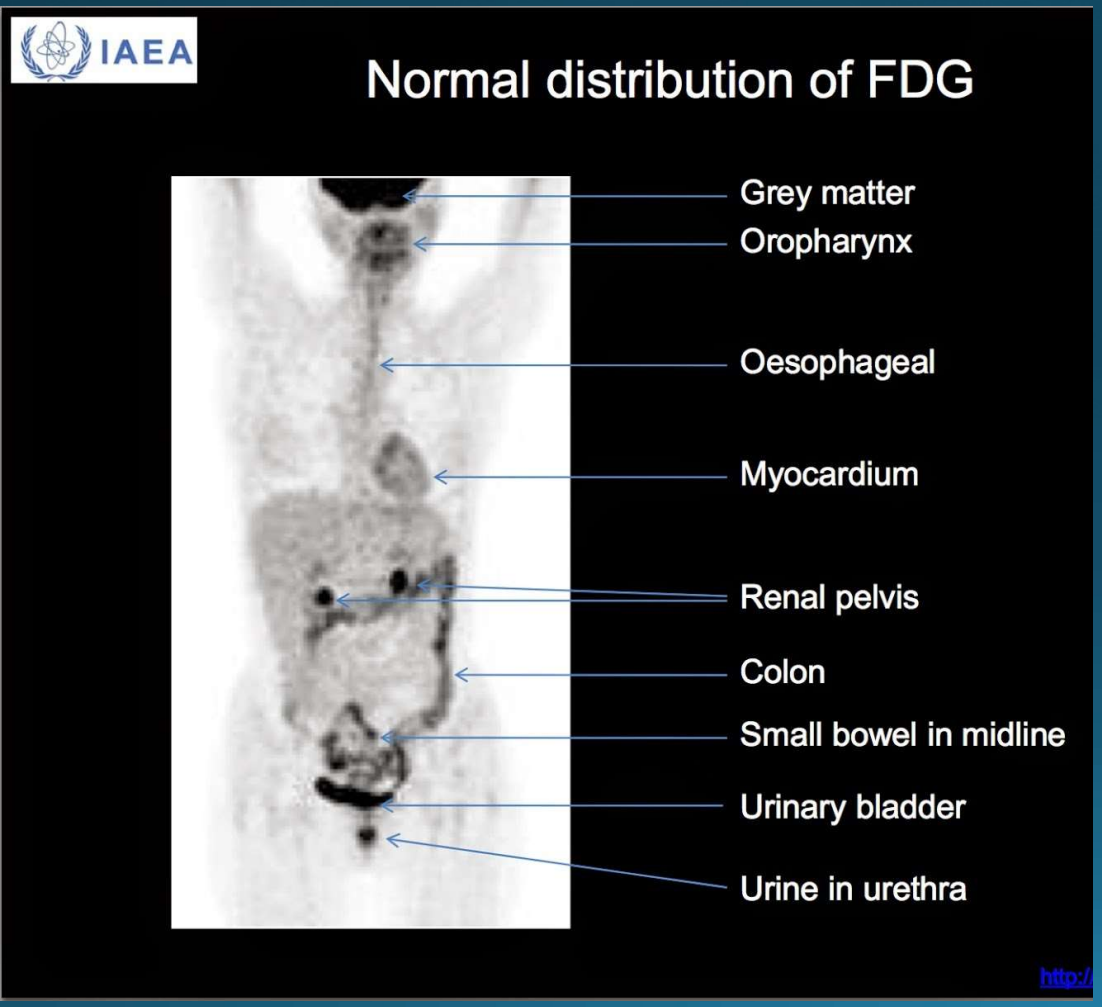


Fluorothymidine (FLT) is phosphorylated by thymidine kinase to FLT-6-PO4 and accumulates in tumor cells.

It is described as a marker of cell proliferation.

Czernin J and Phelps ME.. *Annu Rev Med*, 2002; 53: 89-112.

FDG: Normal distribution



- **Brain**: High uptake (brain's main energy source is glucose).
- **Heart**: Should **NOT** be seen in the fasting image.
- **Liver**: less uptake.
- **Kidneys**: unlike glucose, FDG is excreted in urine.
- **GI**: Mild clearance, faintly seen.
- **Muscles**: Low, increase with exercise.

Quantification in PET

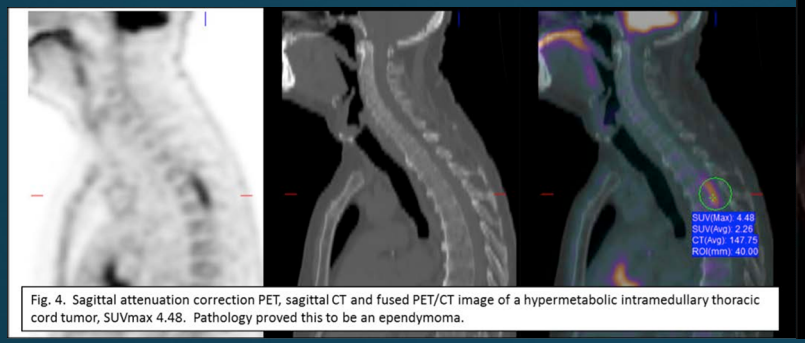
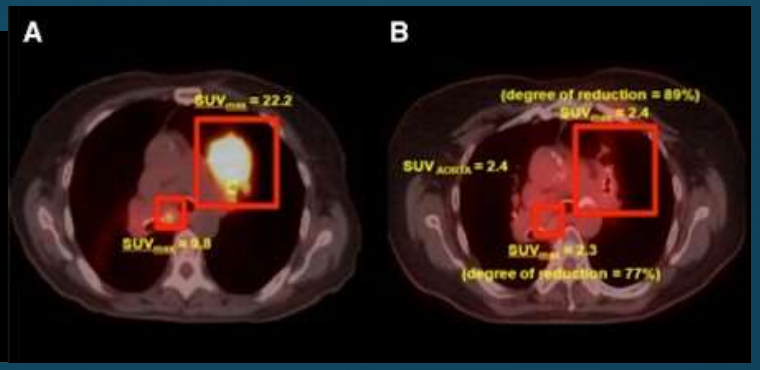


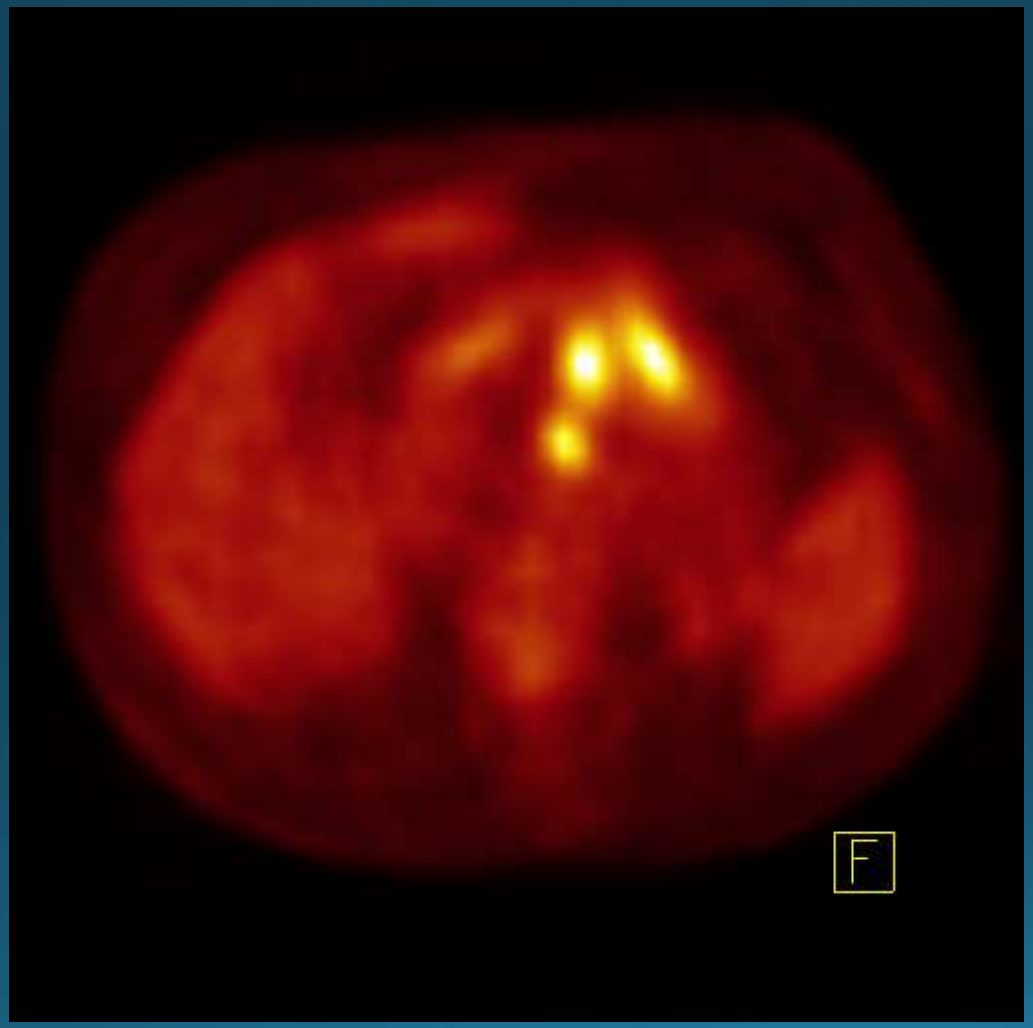
Fig. 4. Sagittal attenuation correction PET, sagittal CT and fused PET/CT image of a hypermetabolic intramedullary thoracic cord tumor, SUVmax 4.48. Pathology proved this to be an ependymoma.



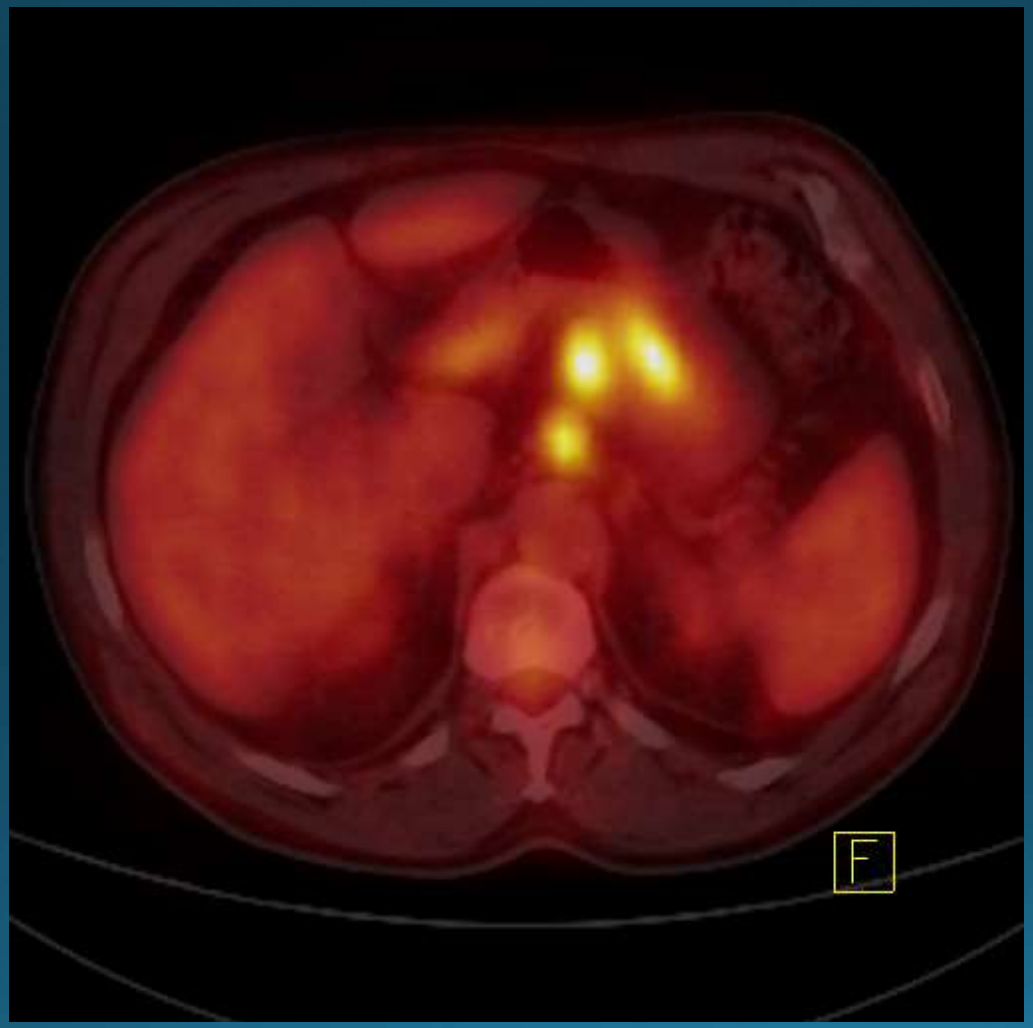
Standardized Uptake Values (SUV)

$$\mathrm{SUV} = \frac{\mathrm{Act_{voi}(kBq/ml)}}{\mathrm{Act_{administered}(MBq)/BW(kg)}}$$

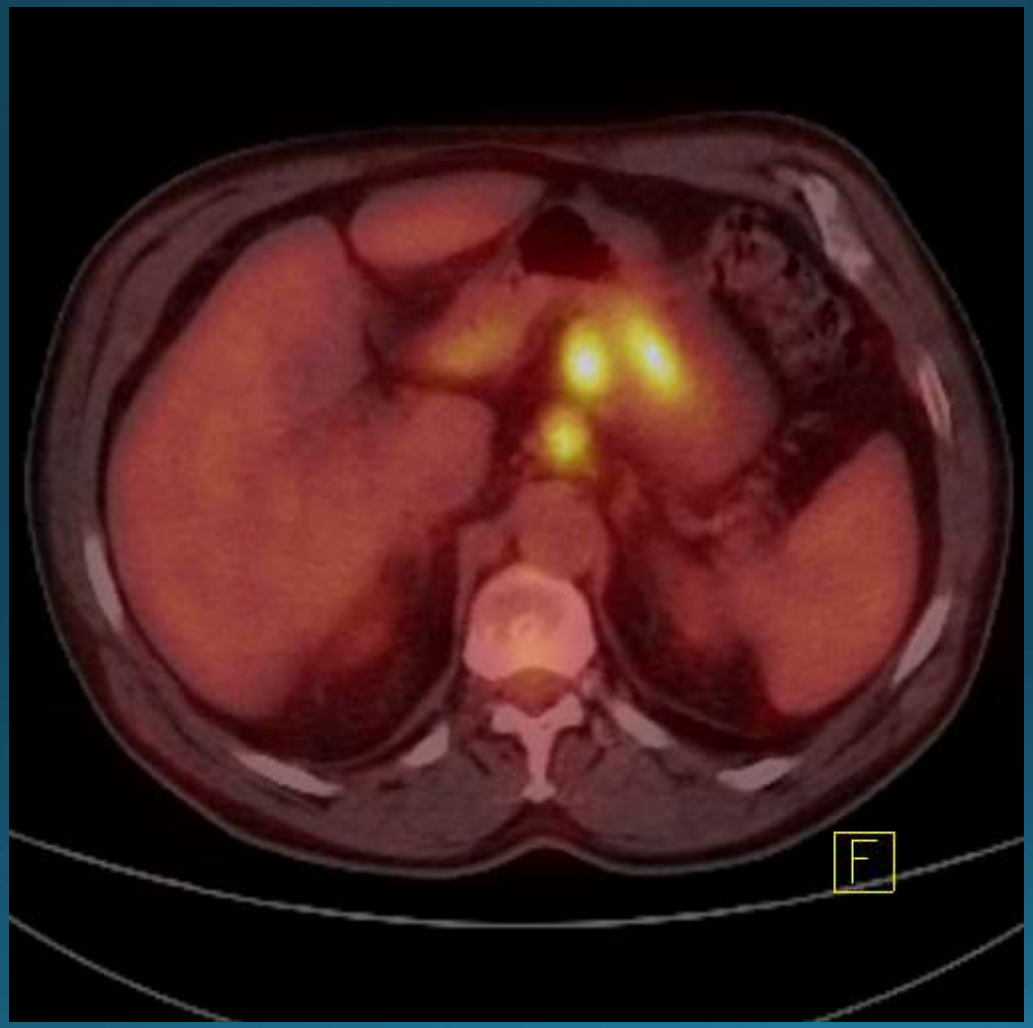
Quantification provides the link between the concentrations of radioactivity measured in tissue and the underlying physiologic processes occurring in the organ. It relates the rate at which radioactivity levels in the body change over time to quantitative parameters such as absolute rate glucose metabolism, regional blood flow, or concentrations of receptors or other binding sites



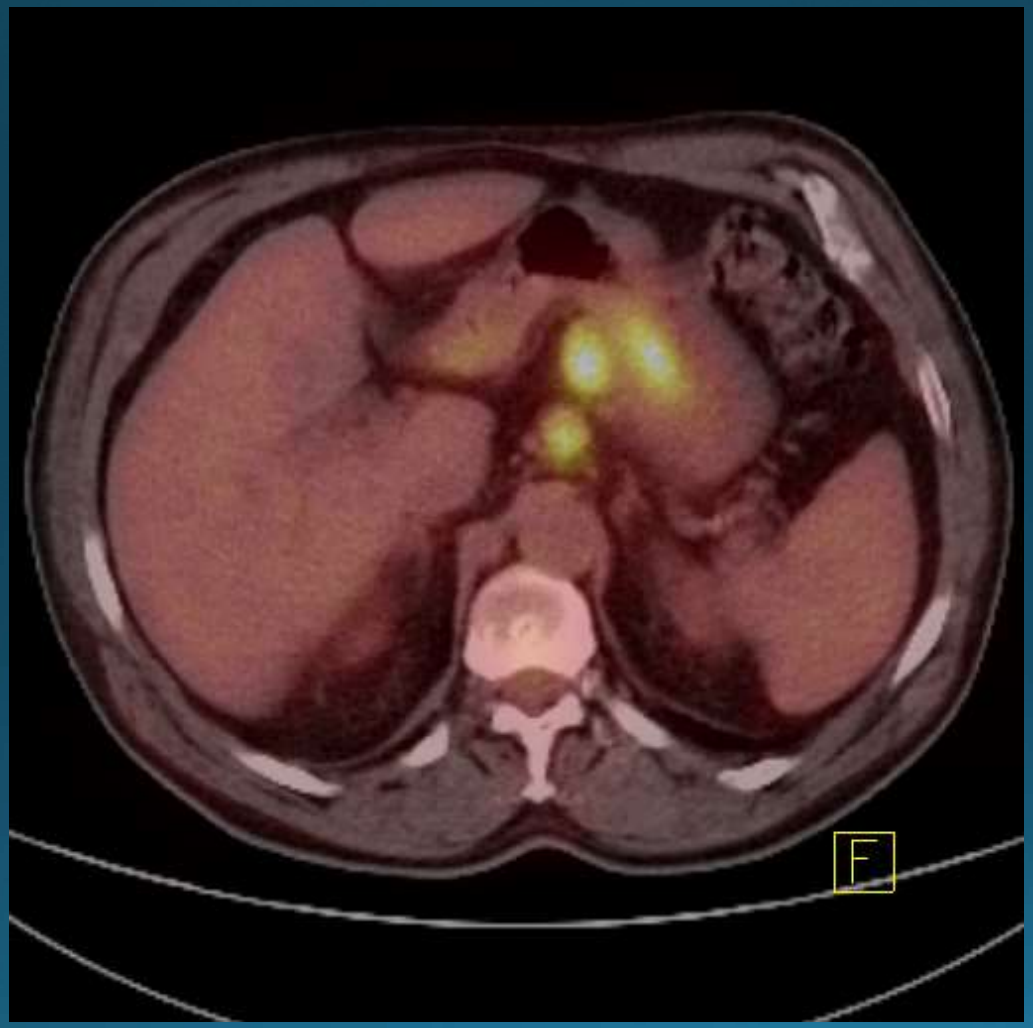
Stomach cancer



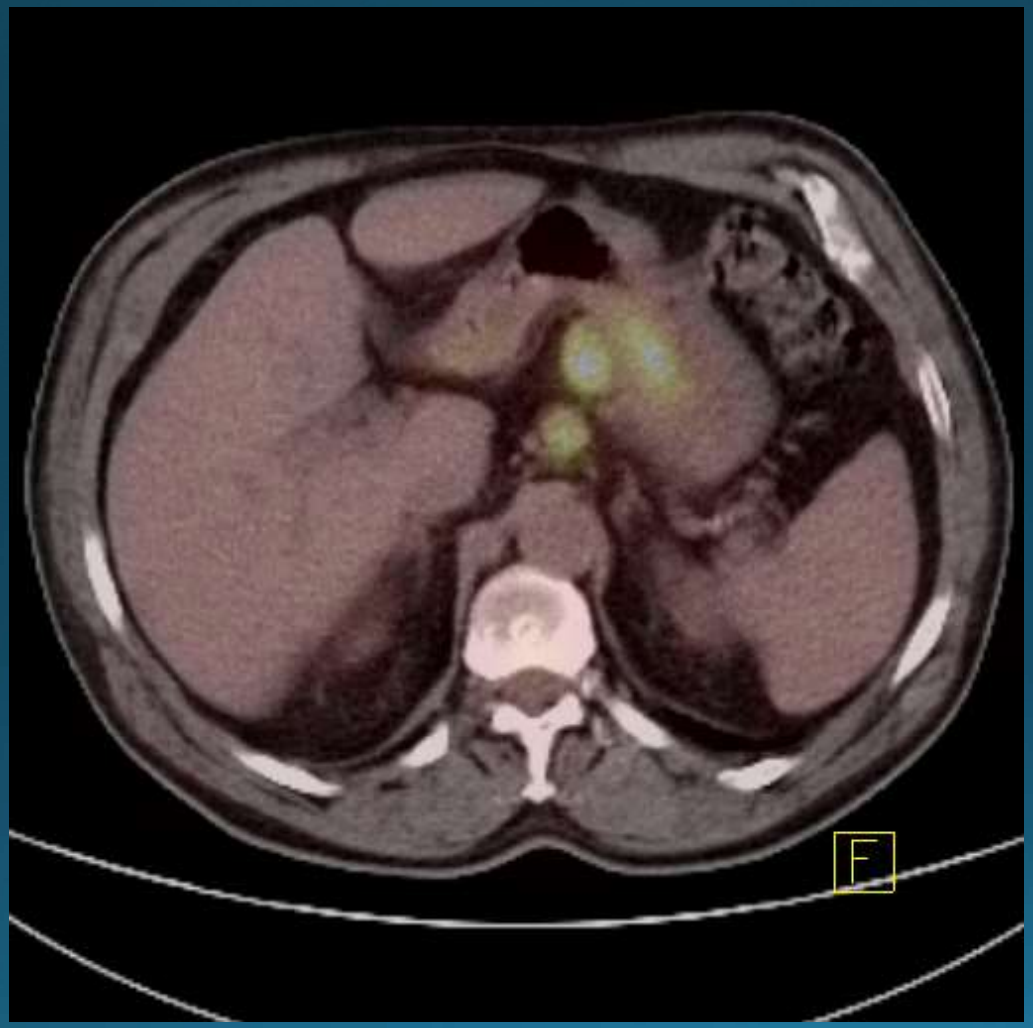
Stomach cancer



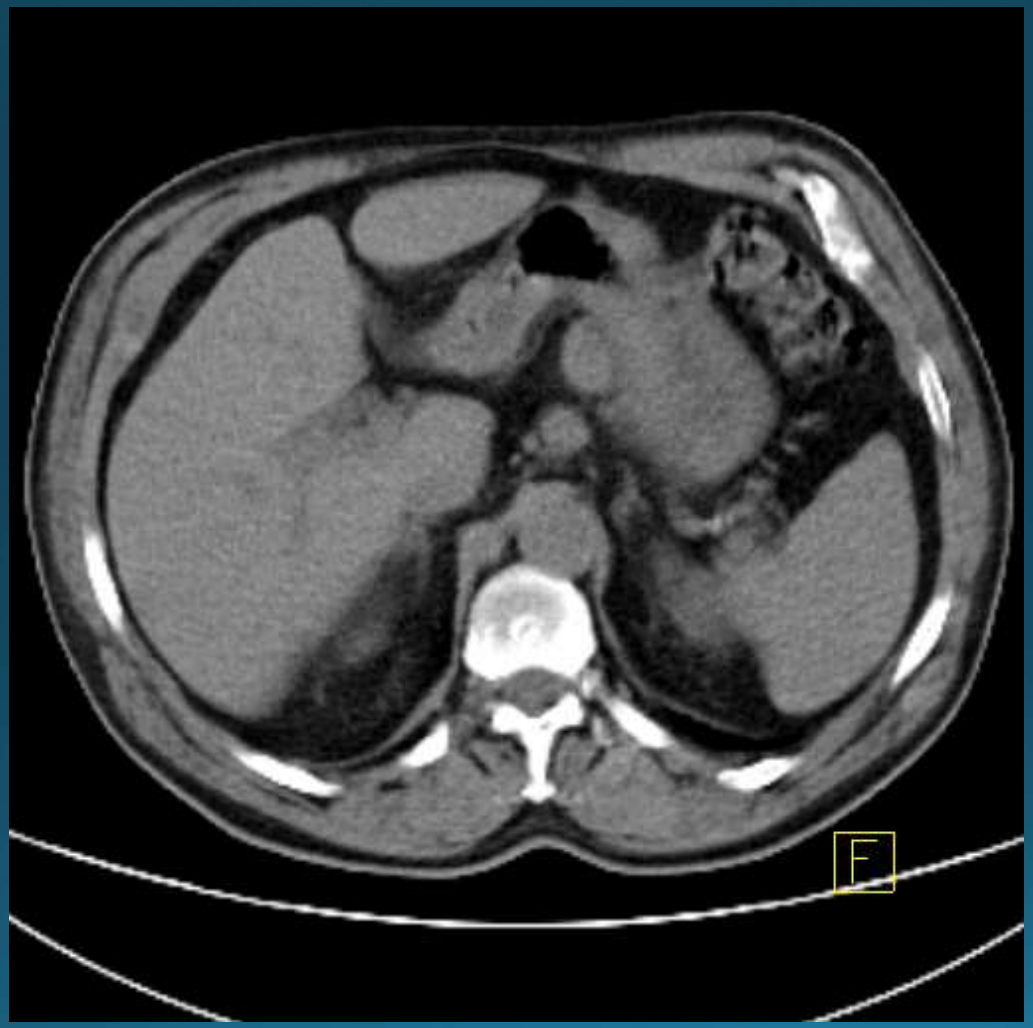
Stomach cancer



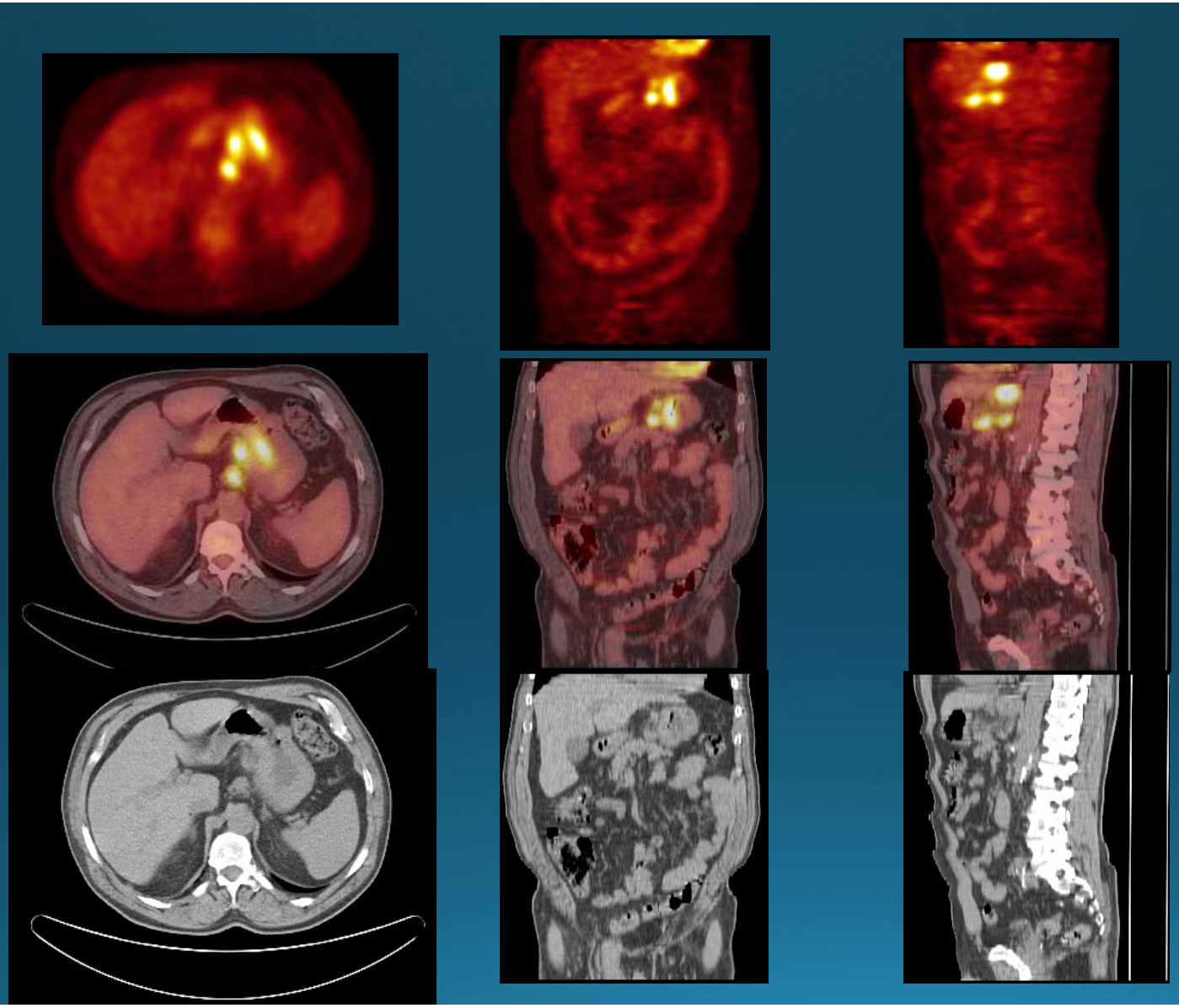
Stomach cancer



Stomach cancer



Stomach cancer



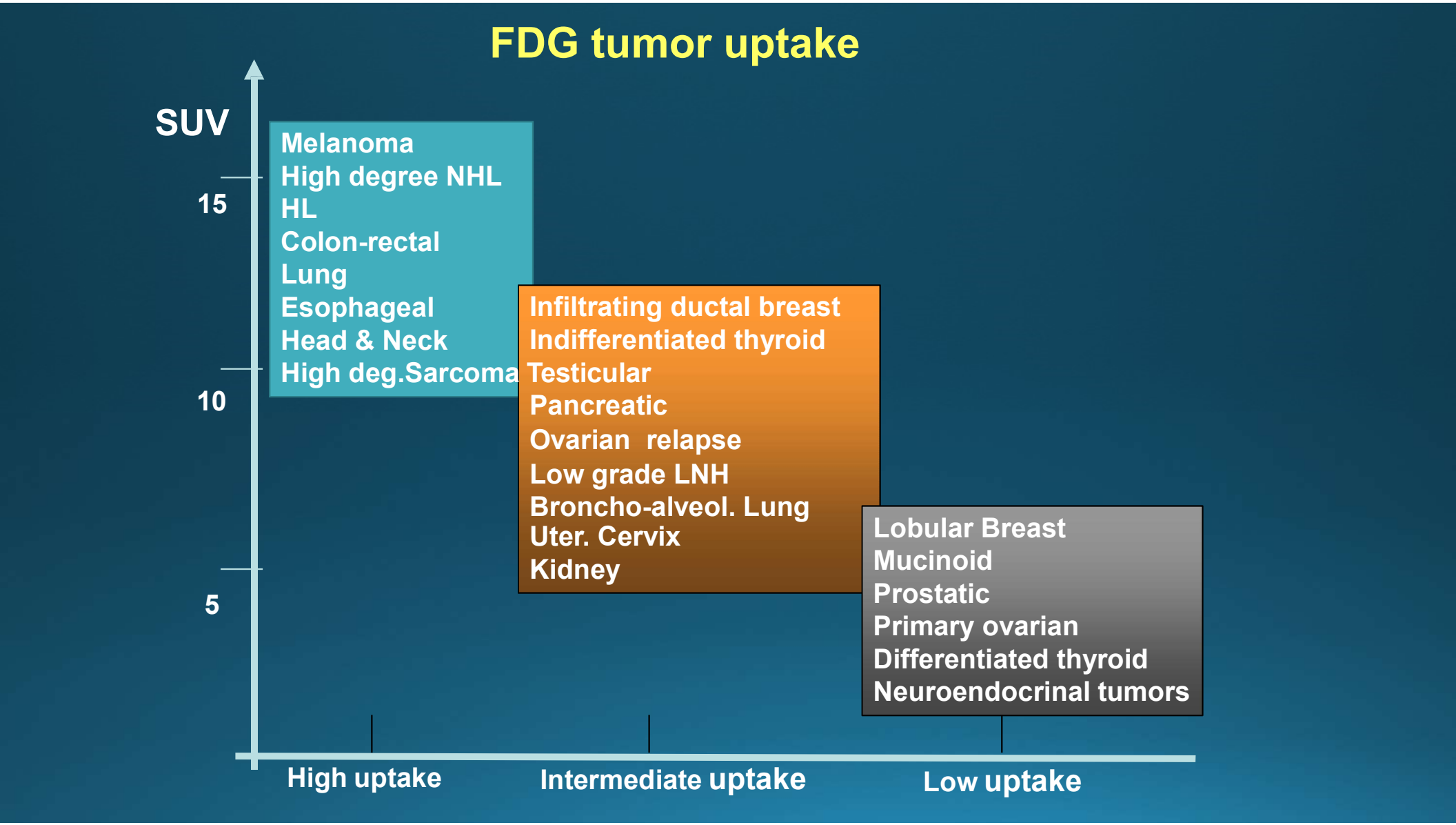
^{18}F-FDG PET/CT
in Oncology

FDG PET in ONCOLOGY

UTILITY in CLINICS

1. Identification and localisation of disease foci
   unknown primary (paraneoplastic syndromes)
2. Diagnosis and "grading" of malignant disease
   staging and restaging TNM
3. Evaluation and monitoring of response to therapy
4. Identification of recurrent disease in comparison with "raising" tumour markers and anatomic/structural changes (CT and MR)
5. RadioTherapy guidance and "management"
6. Guide for biopsy

FDG tumor uptake



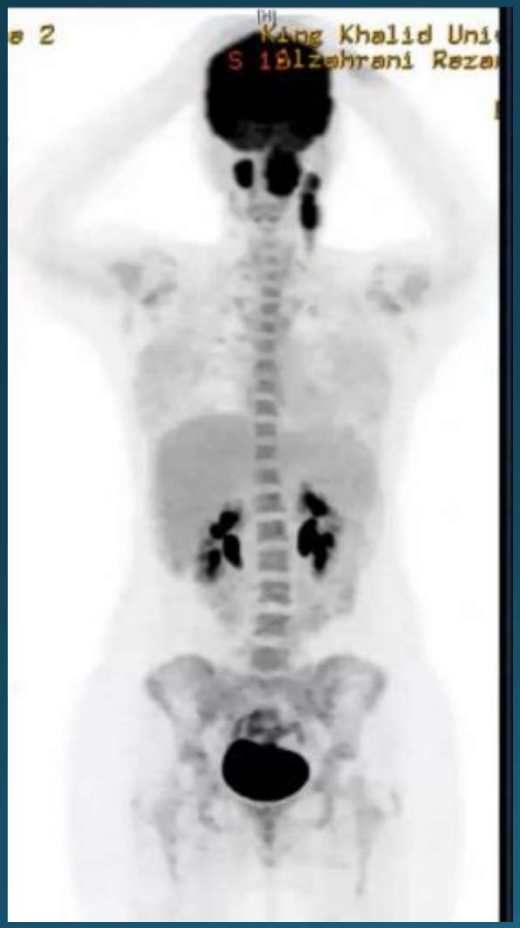
Identification and localisation of disease foci

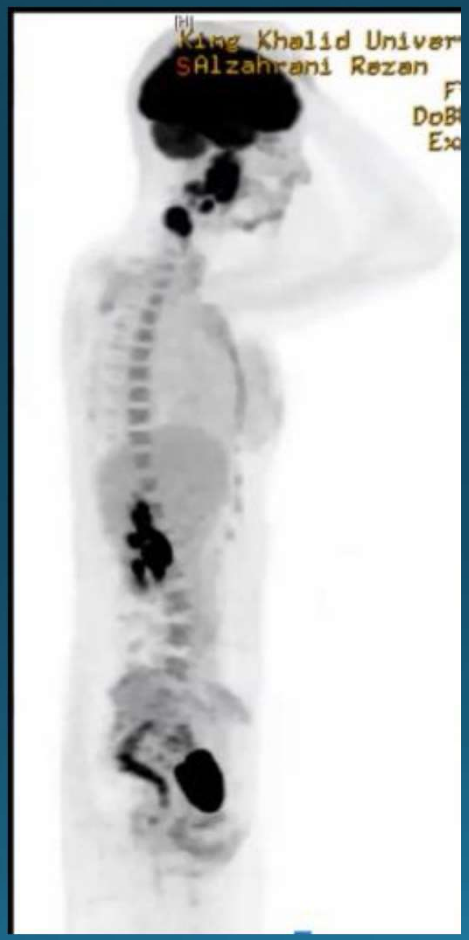
^{18}F-FDG-PET can reveal the primary location of the tumor in 1/3 of patients with cancer of unknown location

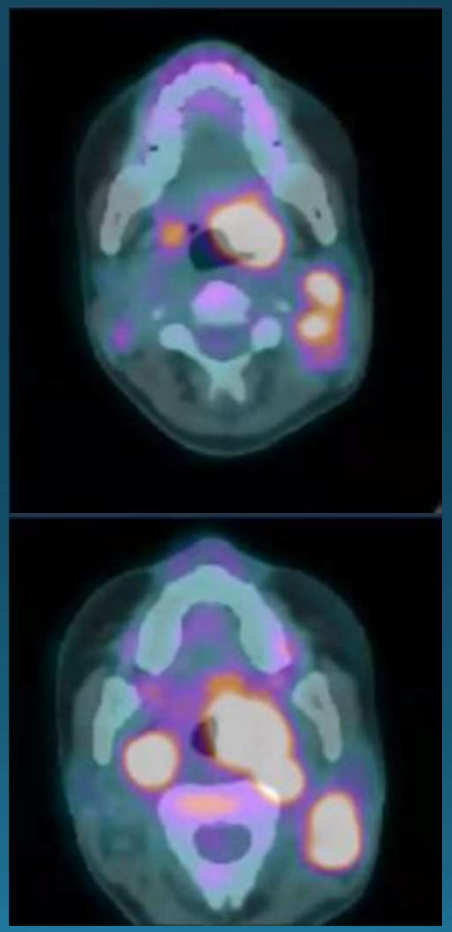
Statistic	CT	PET	CT and PET Side-by-side Evaluation	Intrinsically Fused PET/CT
Sensitivity (%)	19 (8/42)*	28 (11/39)*	31 (13/42)*	35 (15/42)*
Positive predictive value (%)	73 (8/11)	65 (11/17)	81 (13/16)	83 (15/18)
Sensitivity (%)	19 (8/42)*	28 (11/39)*	31 (13/42)*	35 (15/42)*
Positive predictive value (%)	73 (8/11)	65 (11/17)	81 (13/16)	83 (15/18)

Gutzeit A et al Radiology. 2005 Jan;234(1):227-34.

Nasophargeal cancer with LN metastasis

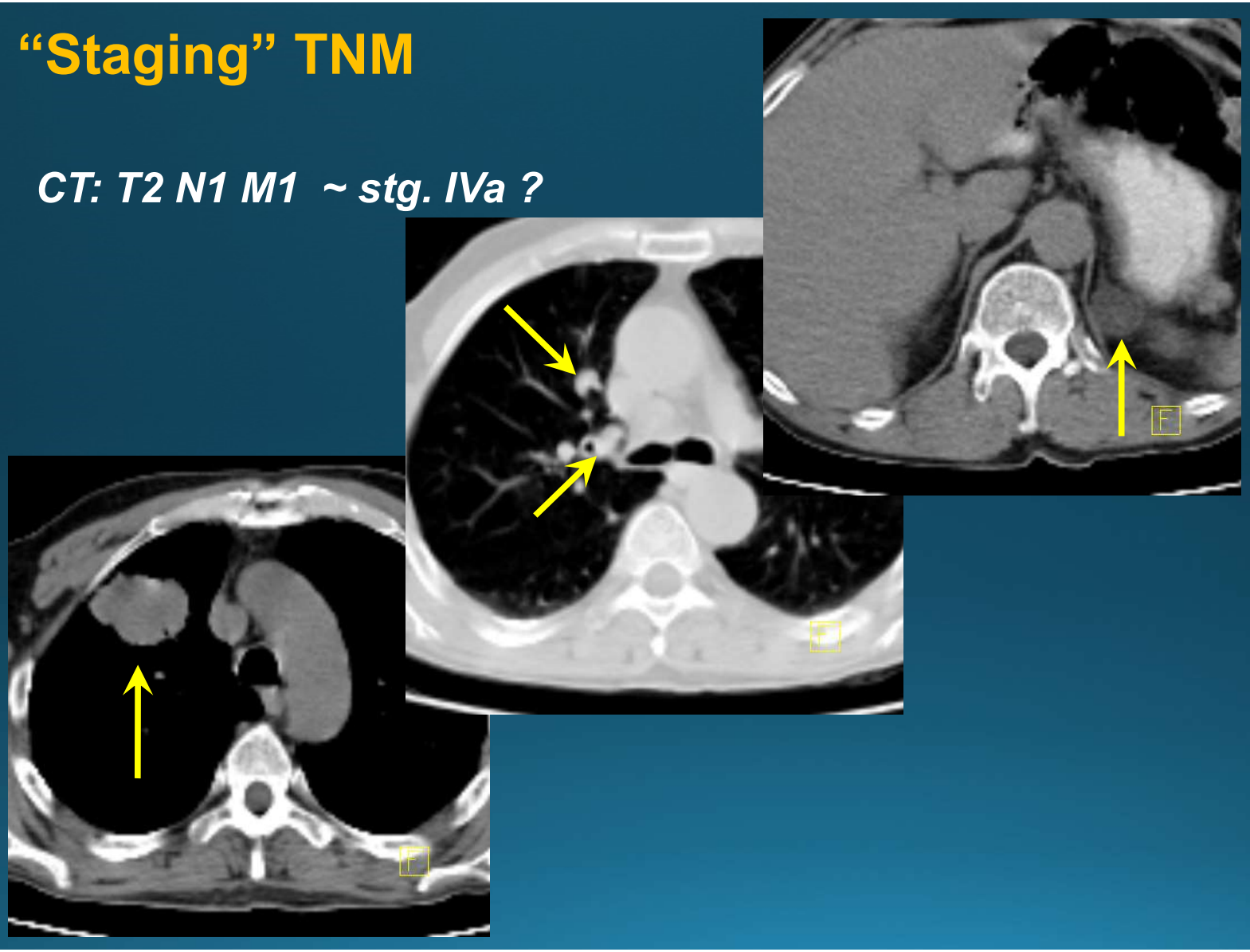






“Staging” TNM

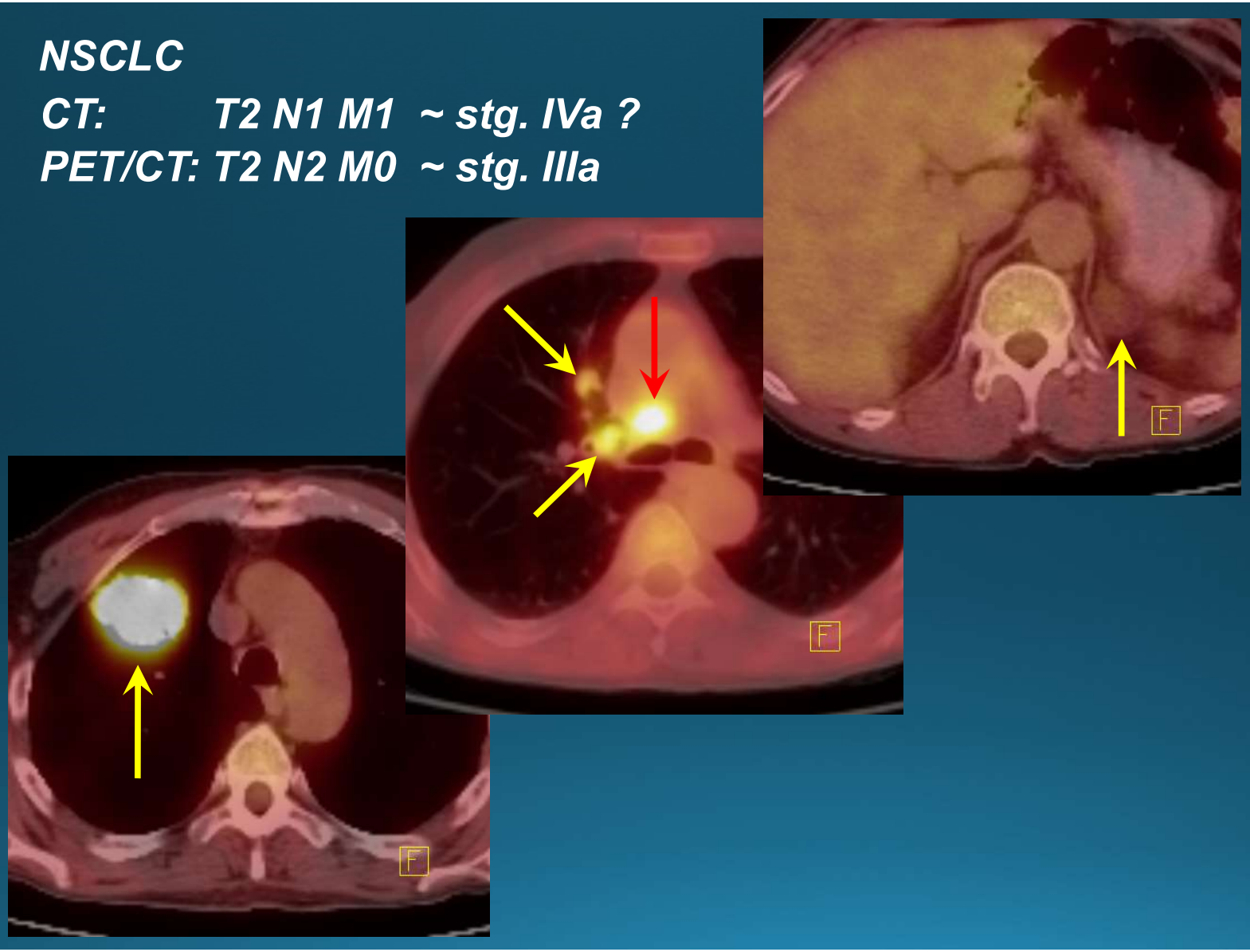
NSCLC CT: T2 N1 M1 ~ stg. IVa ?



NSCLC

CT: T2 N1 M1 ~ stg. IVa ?

PET/CT: T2 N2 M0 ~ stg. IIIa



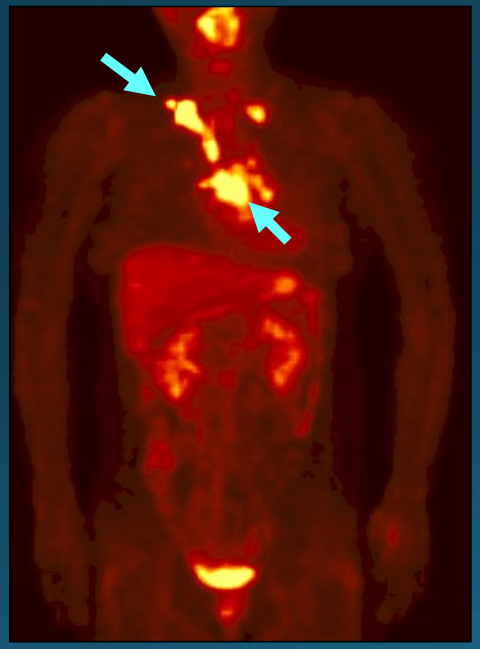
Evaluation and monitoring of response to therapy

- 2 to 3 weeks after chemotherapy
- 6 to 12 weeks after radiotherapy (due to the stunning effect on malignant cells: transiently reduced metabolism and proliferation, false negative finding, or radiation pneumonitis, false positive finding)
- 2-6 months after surgery

Chemotherapy

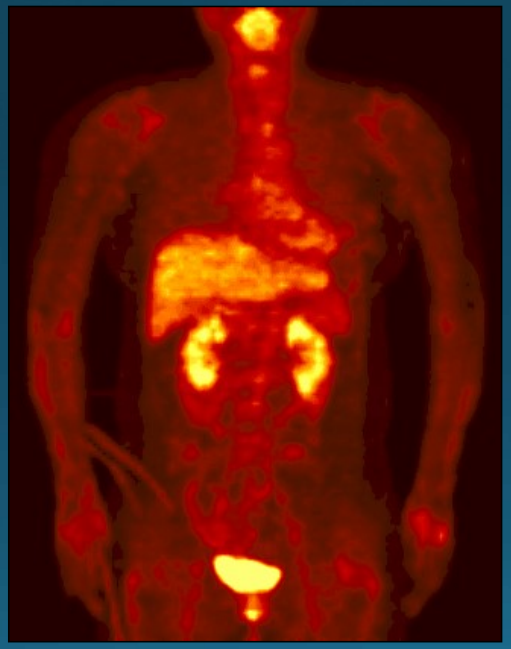
Before

('01.7.25.)



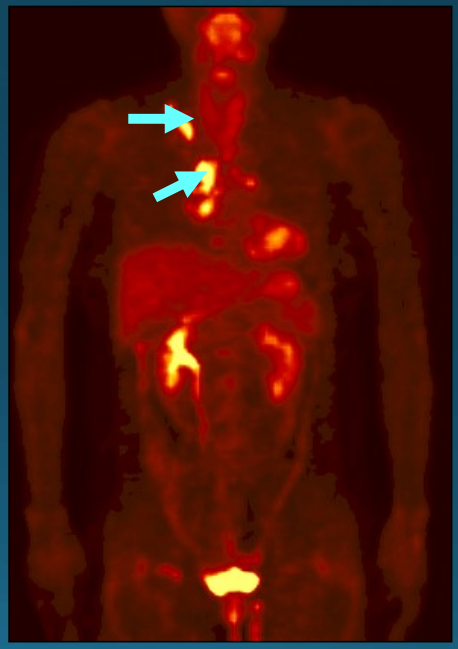
After

('01.12.14.)



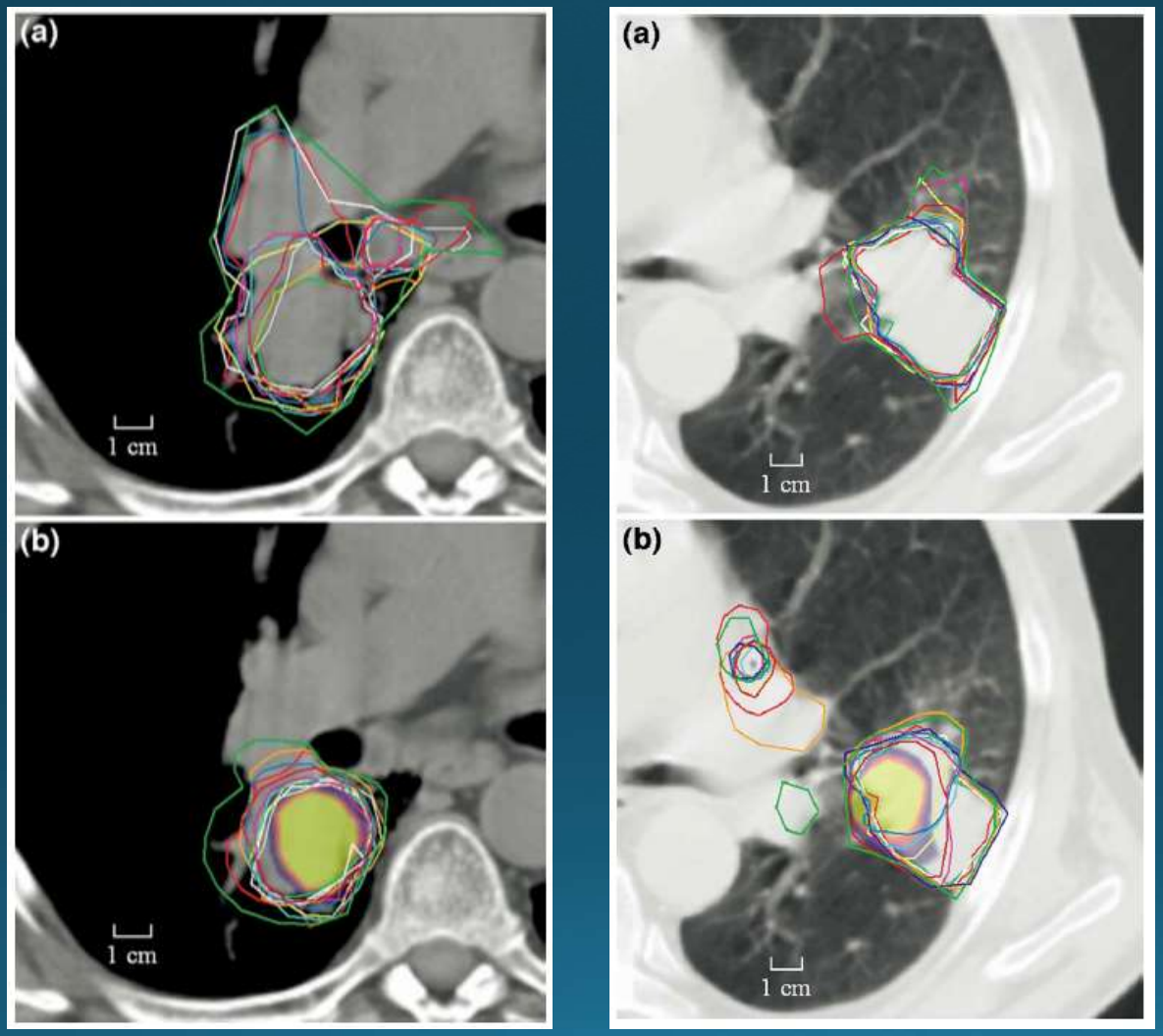
Relapse

('02.4.16.)

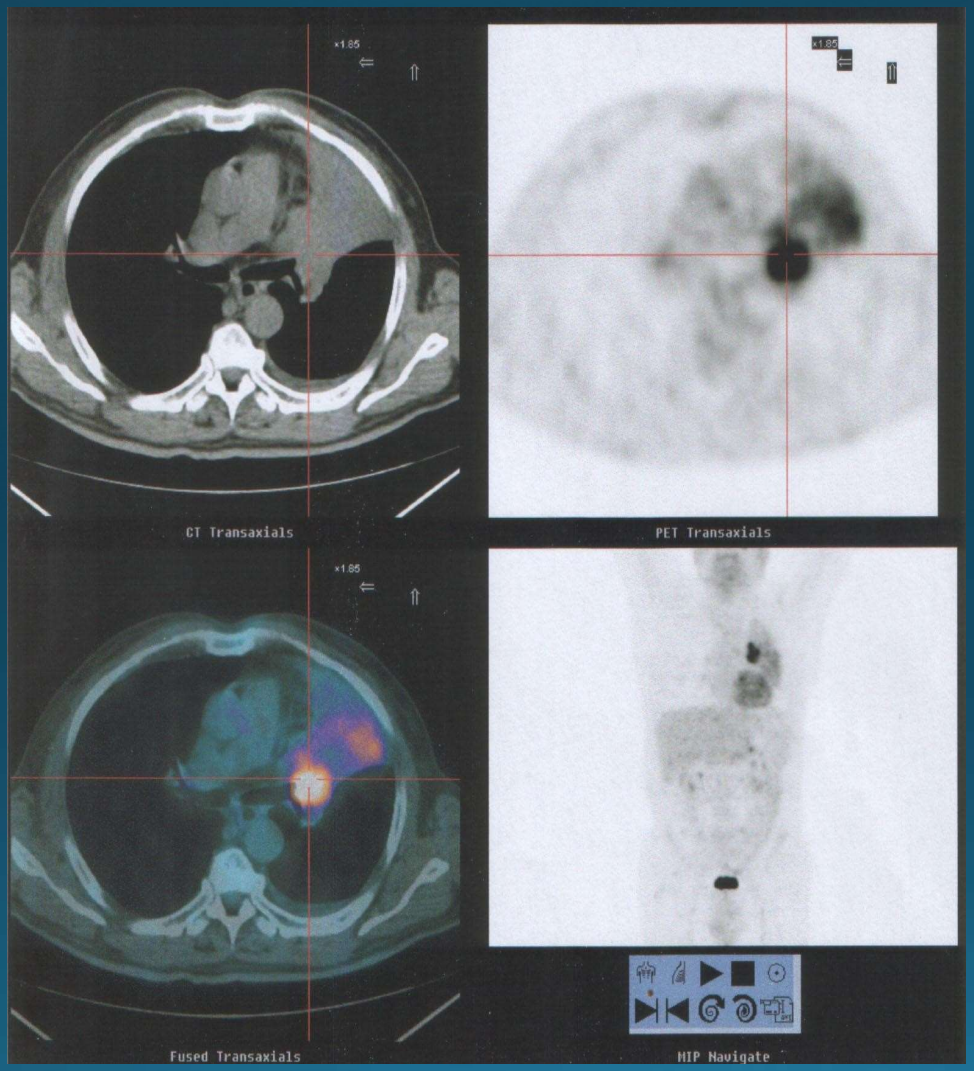


RadioTherapy guidance and management

- More precise planning of the beam field depending on the metabolic and biological activity in the malignant tumor itself
- Fusion functional-morphological imaging using PET/CT significantly improves the accuracy of planning the air field:
- In NSCLC, the removal of atelectasis and infection zones from the air field, and the shift and increase of the dose to the area of lymph nodes that accumulate FDG.



Steenbakkers R. Int J Radiat Oncol Biol Phys. 2006;64:435.



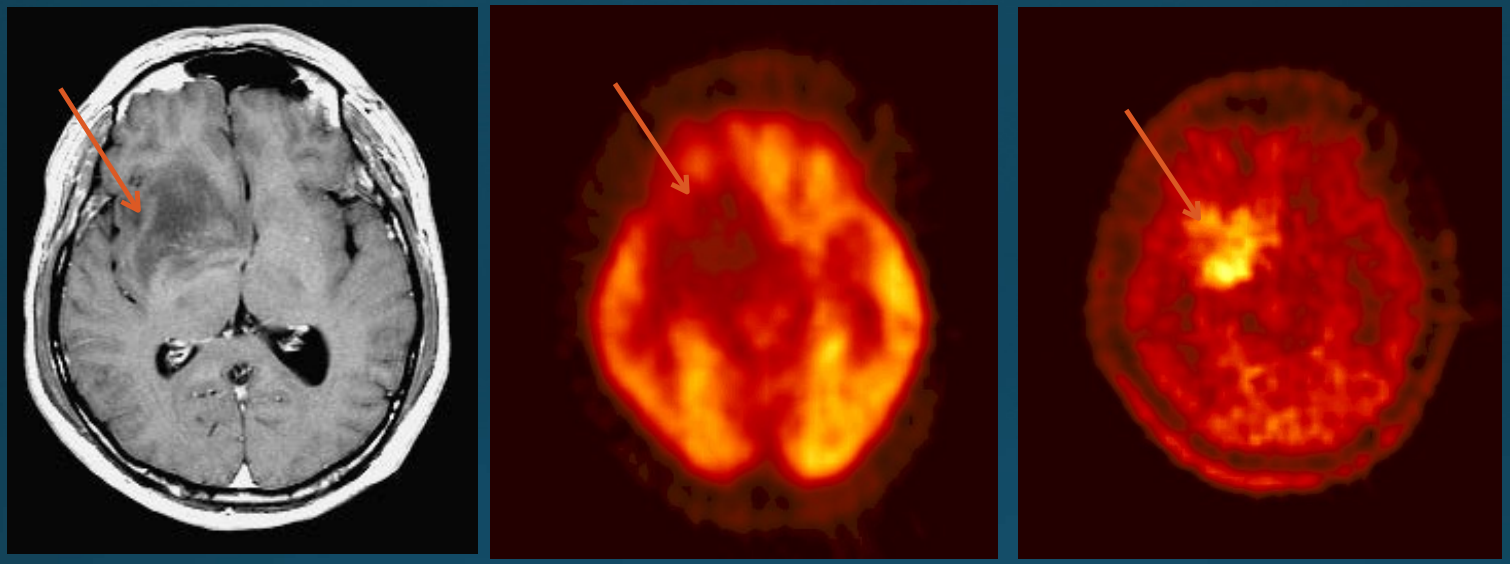
NSCLC. atelectasis

Post-therapy
Pre-therapy
SUVmax
16.1
SUVmax
25.5

Indications of PET CT

Breast Cancer*	Staging*, restaging*, and monitoring response to therapy*
Colorectal Cancer	Diagnosis*, staging* and restaging*
Esophageal Cancer	Diagnosis*, staging* and restaging*
Head & Neck Cancers (excluding CNS and thyroid)	Diagnosis*, staging* and restaging*
Lung Cancer (Non-Small Cell)	Diagnosis*, staging* and restaging*
Lymphoma	Diagnosis*, staging* and restaging*
Melanoma (Excludes evaluation of regional nodes)	Diagnosis*, staging* and restaging*
Solitary Pulmonary Nodule	Characterization of indeterminate single pulmonary nodule
Thyroid Cancer*	Restaging
Cervical Cancer*	Staging as an adjunct to conventional imaging

Brain tumors

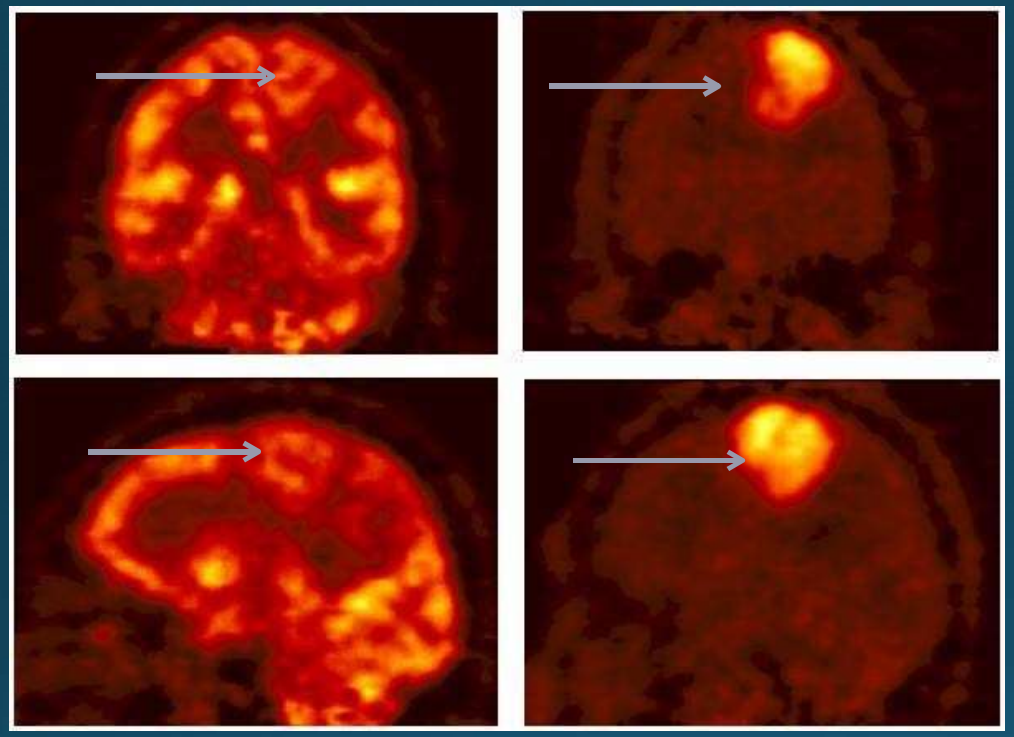


MRI ^{18}F-FDG ^{11}C-metionine

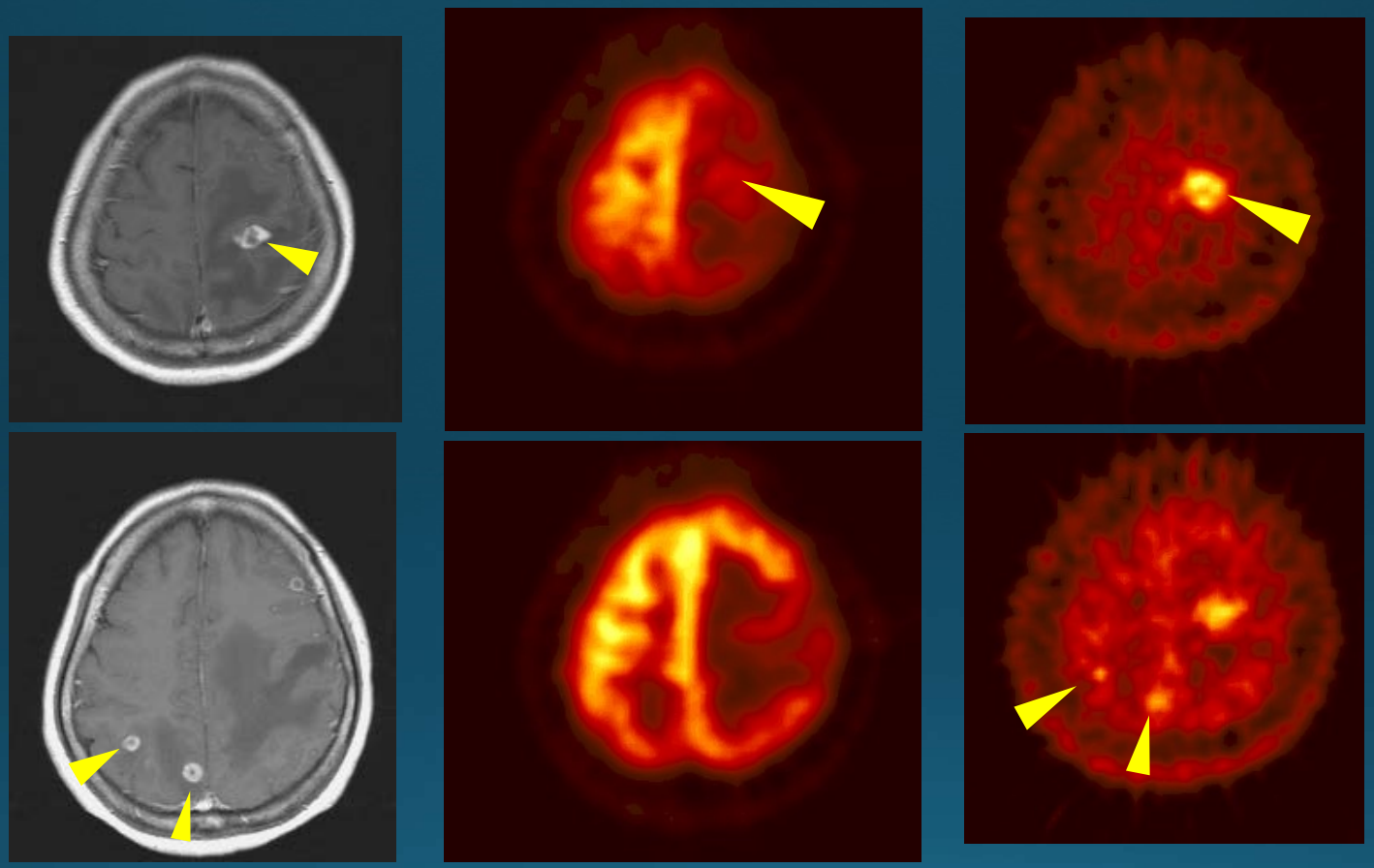
Astrocitoma

^{18}F-FDG negative uptake

^{11}C-метионин positivie uptake



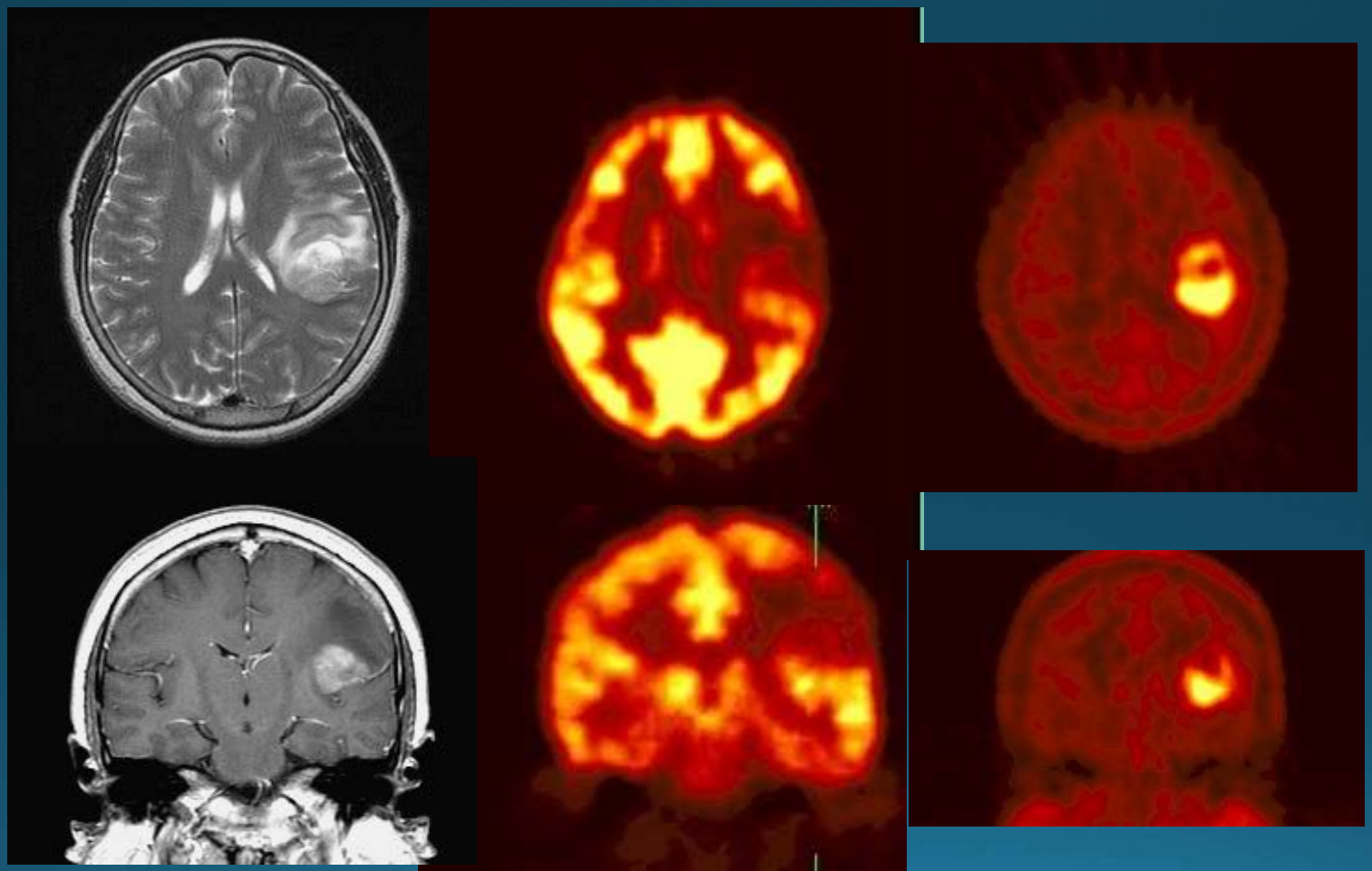
accumulation of FDG in the tumor (left, arrows) does not differ from physiological methionine (right) accumulates in the tumor much more intensively than in the surrounding brain tissue (anaplastic oligodendroglioma).



^{11}C-methionine

Brain metastases (non small cell lung carcinoma)

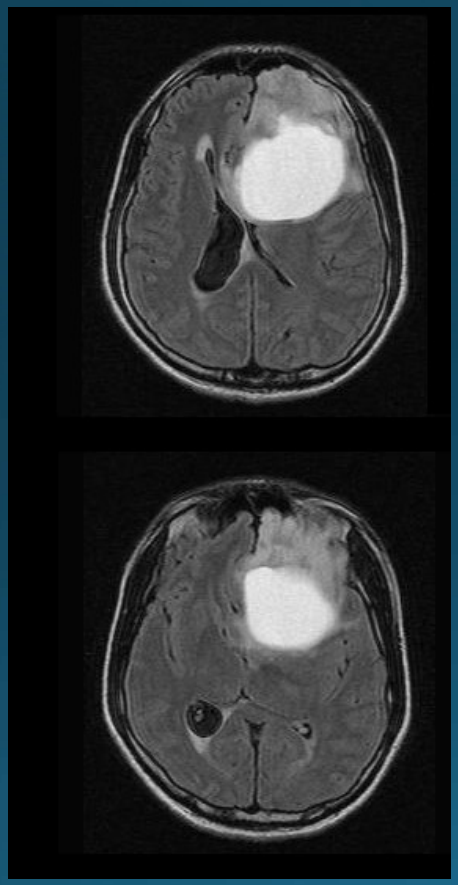
Glioblastoma multiforme

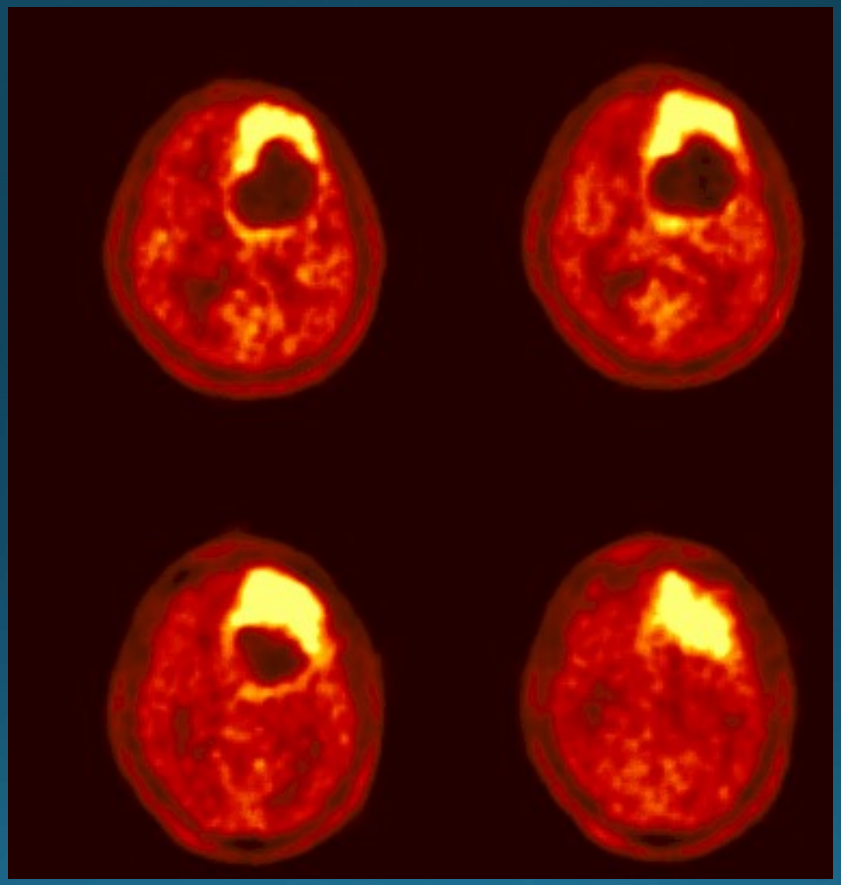


MRI ^{18}F-FDG ^{11}C-methionine

праћење ефекта радиотерапије

MRI



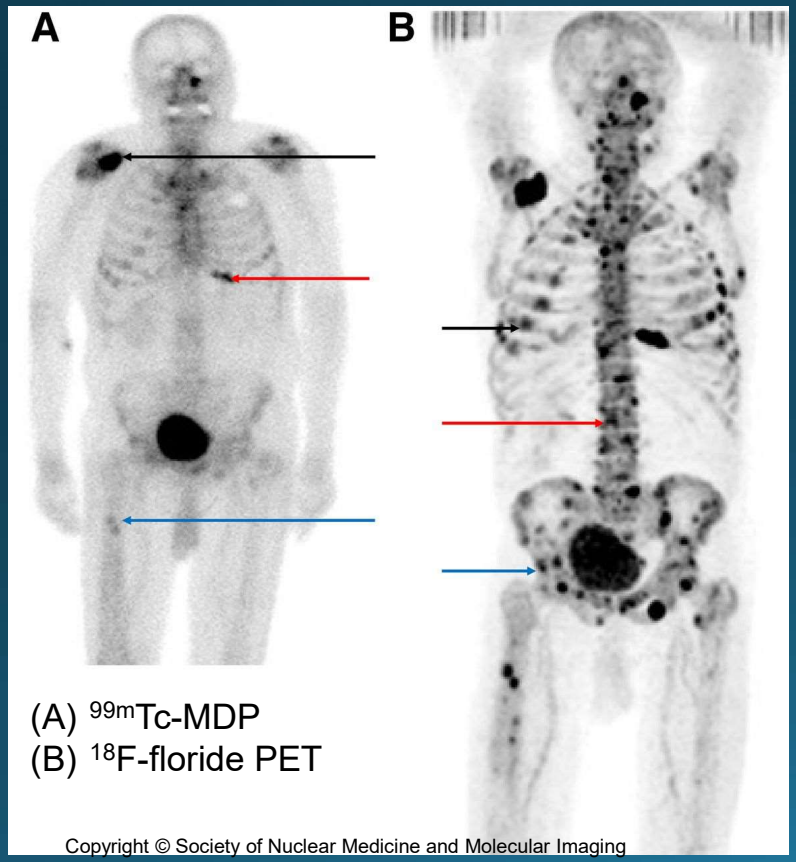


^{11}C-methionine

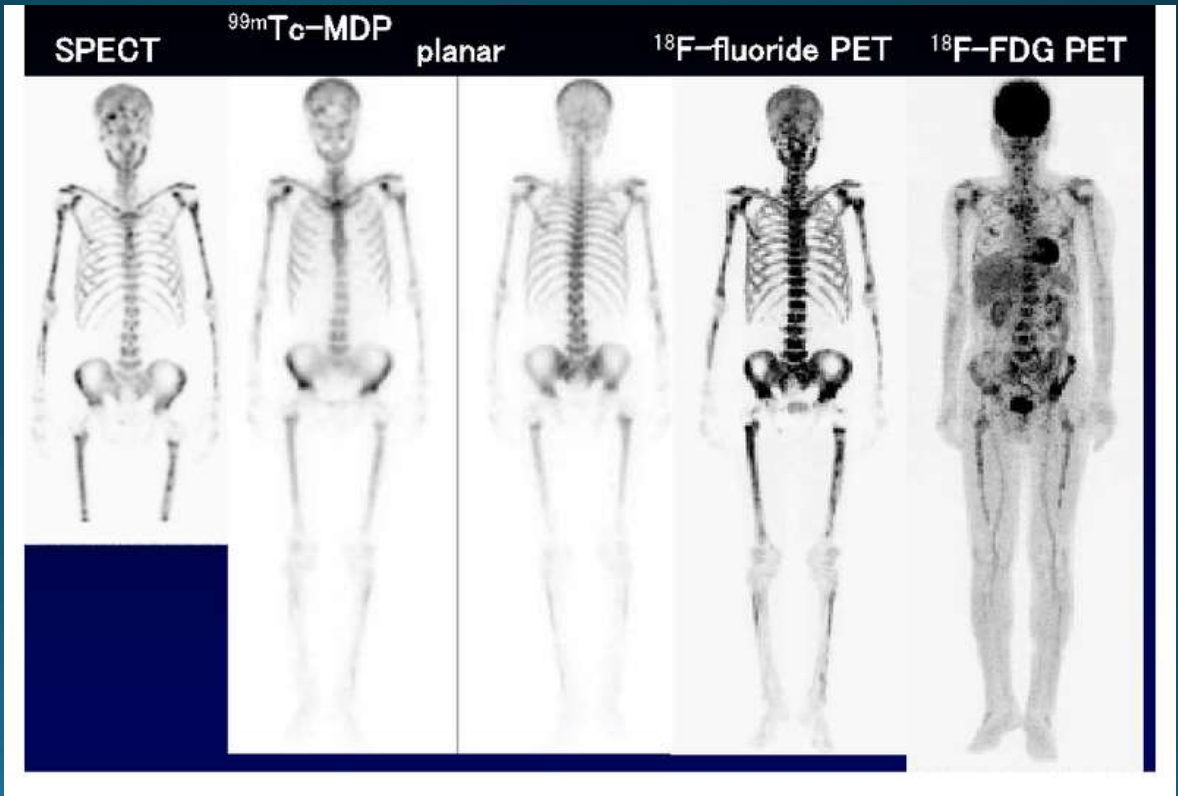
Тумор високог степена малигнитета са зоном некрозе у којој изостаје накупљање РФ

Bone metastases ^{18}F-Na Fluoride

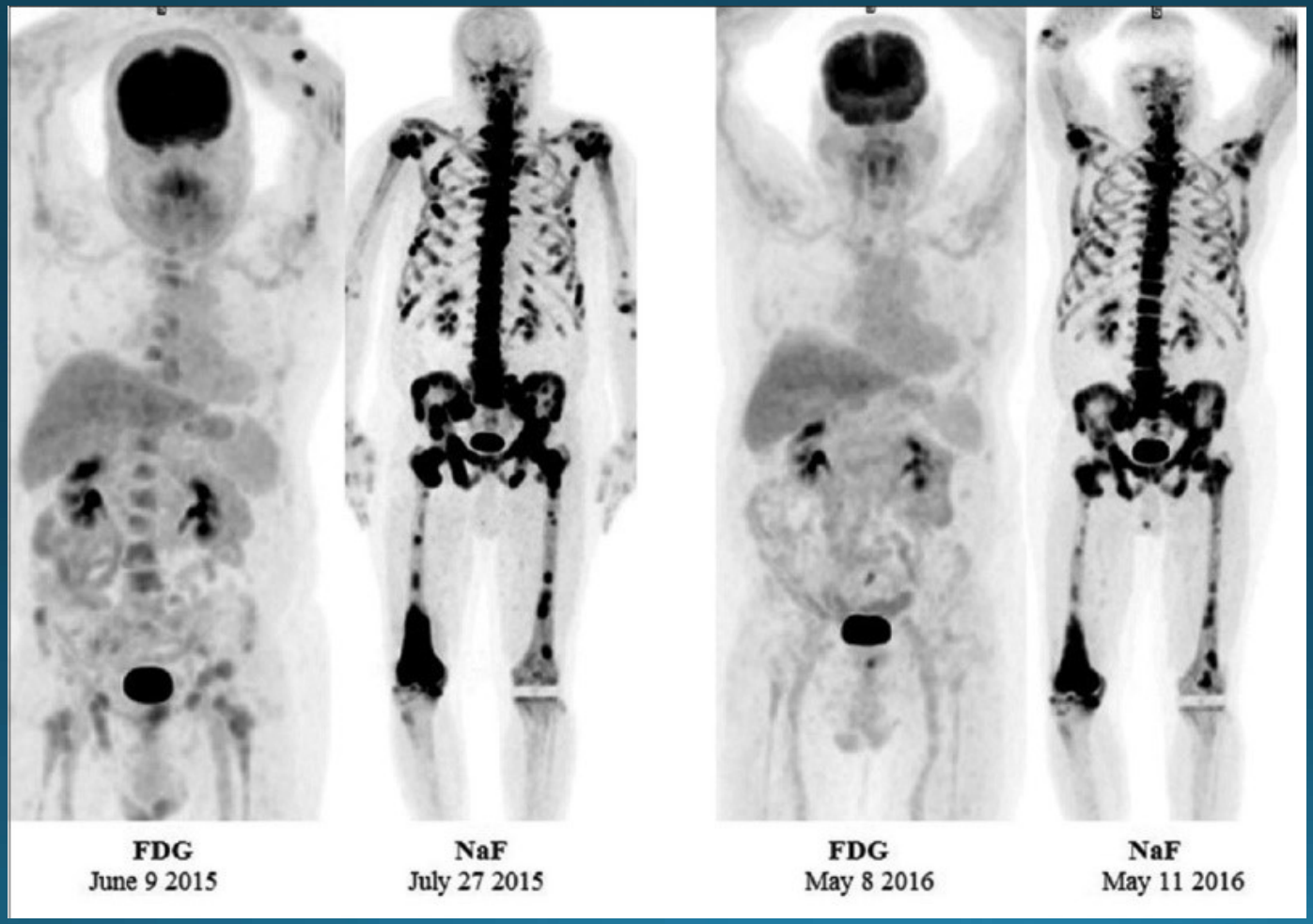
$$2F^- + Ca_{10}(PO_4)_6(OH)_2 \rightarrow Ca_{10}(PO_4)_6F_2 + 2OH^-$$



(A) ^{99m}Tc-MDP
(B) ^{18}F-floride PET



Bone metastases ^{18}F-Na Fluoride

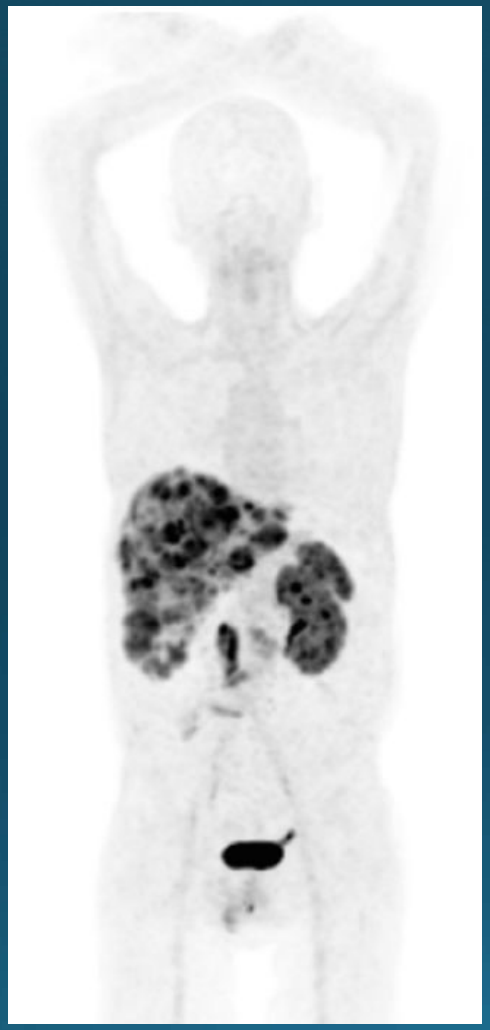


Somatostatin receptor PET tracers: Ga-68

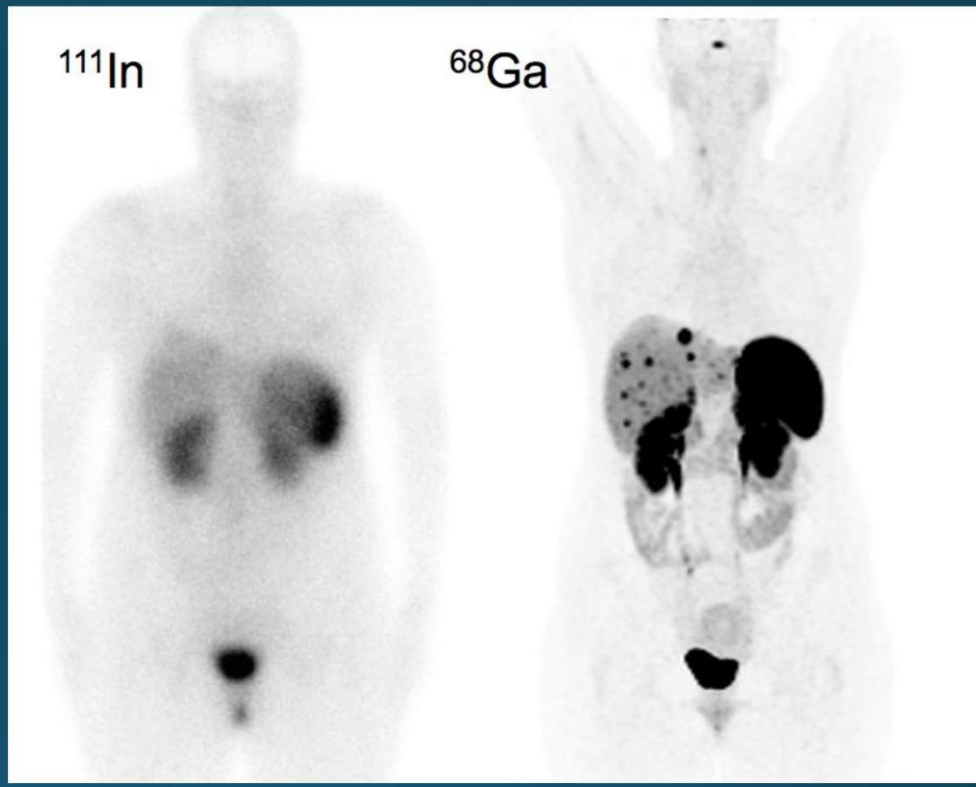
Somatostatin has 5 receptors. Ga-68 is more sensitive.
Higher lesion detection rate than what is achieved SSTR PET, than somatostatin receptor SPECT, CT, or MR imaging.
Sensitivity: 70-100% (depends on density of somatostatin receptors in the tumor).
Indications: Tumours with high expression of receptors of somatostatin.
1. Gastroenteropancreatic tumours (e.g. carcinoids, gastrinoma, insulinoma, glucagonoma, VIPoma,
2. Sympathoadrenal system tumours (pheochromocytoma, paraganglioma, neuroblastoma,ganglioneuroma).
3. Medullary thyroid carcinoma.
4. Pituitary adenoma.
5. Medulloblastoma.
6. Merkel cell carcinoma.
7. Small-cell lung cancer

	Well-differentiated		Poorly differentiated
Grade (ENETS)	Low (G1)	Intermediate (G2)	High (G3)
Ki-67 index (%)	≤2	3-20	>20
Anatomic imaging		more rapid growth on serial imaging	
Functional imaging	Octreoscan SPECT or SSTR PET +ve		FDG PET +ve

NET with extensive metastatic lesions throughout the body



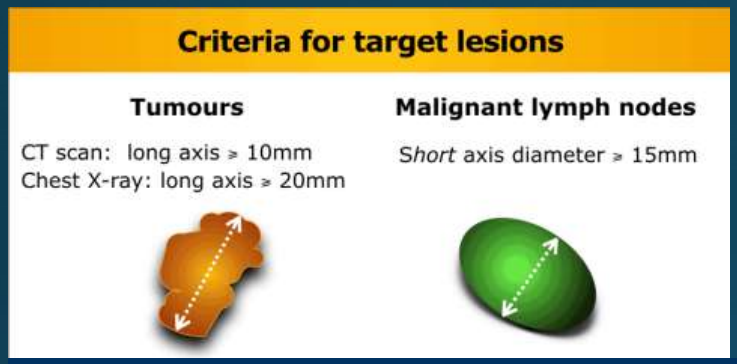
NET with multiple metastatic disease confined to the liver and abdominal cavity

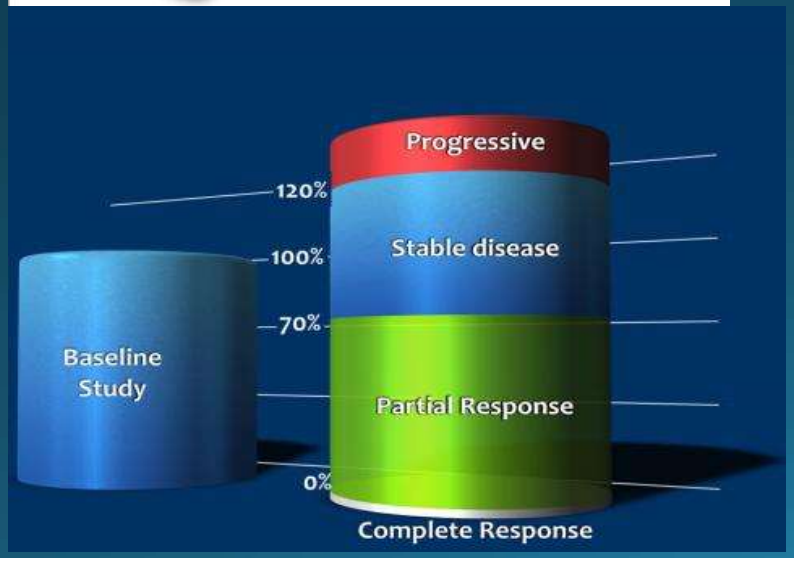


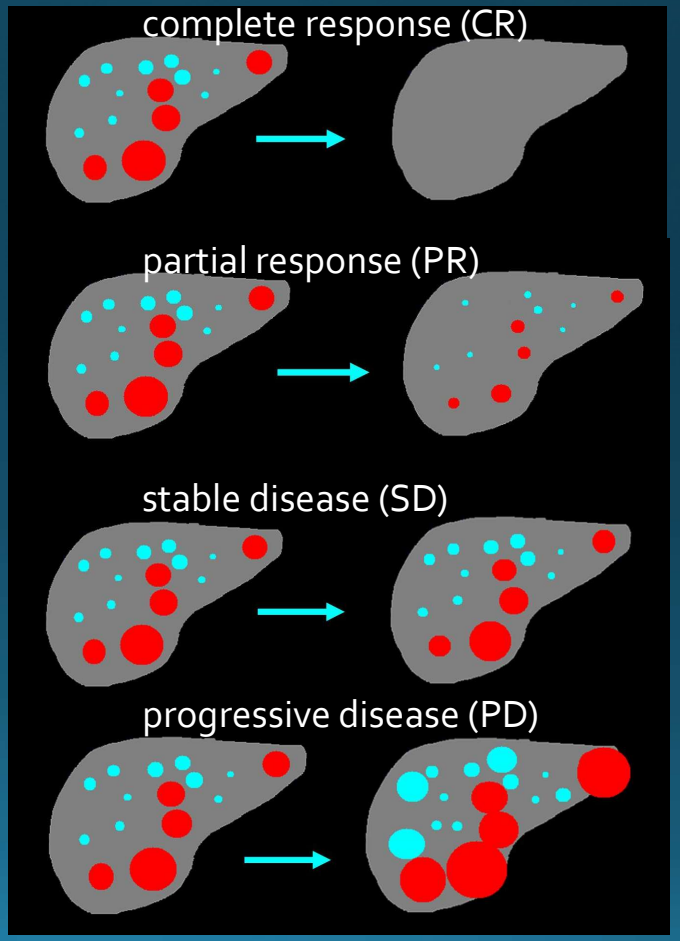
Carcinoid tumor: Positive 68Ga-DOTA-NOC and Negative 111In-Octreoscan.
Ga DOTA-NOC Findings: Multiple metastatic lesions in the liver.

Evaluation and monitoring of response to therapy

RECIST (Response Evaluation Criteria in Solid Tumours) v.1.1 - MDCT
SLD-sum of lenght diameter



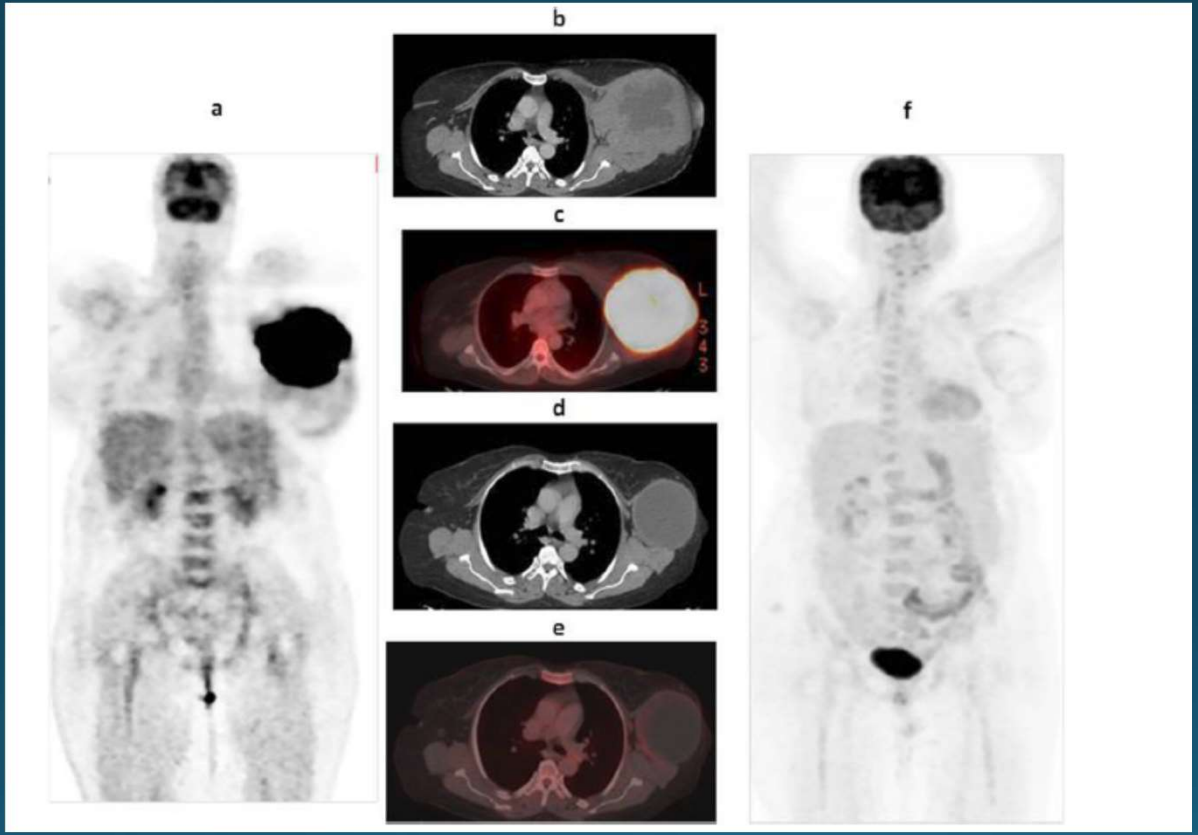




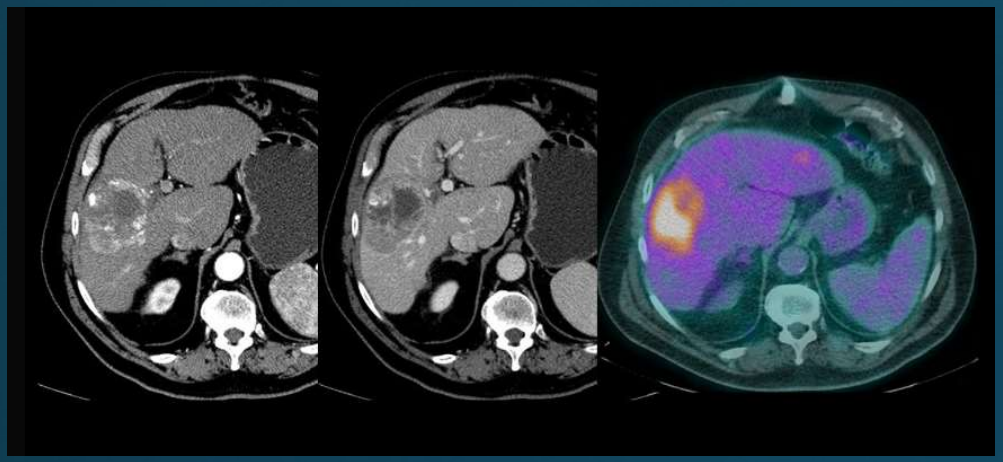
Evaluation and monitoring of response to therapy

CRITERIA	RECIST 1.1	PERCIST
Complete response (CR)	Disappearance of all lesions No new lesions	Disappearance of all metabolically active lesions
Partial response (PR)	30 % decrease in the sum of diameters of the target lesion	30% and a 0.8-unit decline in SUL peak between the most intense lesion before treatment and the most intense lesion after treatment, although not necessarily the same lesion
Progression desease (PD)	20% increase in the sum of diameters of the target lesions	30% and 0.8-unit increase in SUL peak or new lesions or 75% increase in total lesion glycolysis
Stable Desease (SD)	Neither PR or PD	Neither PR or PD

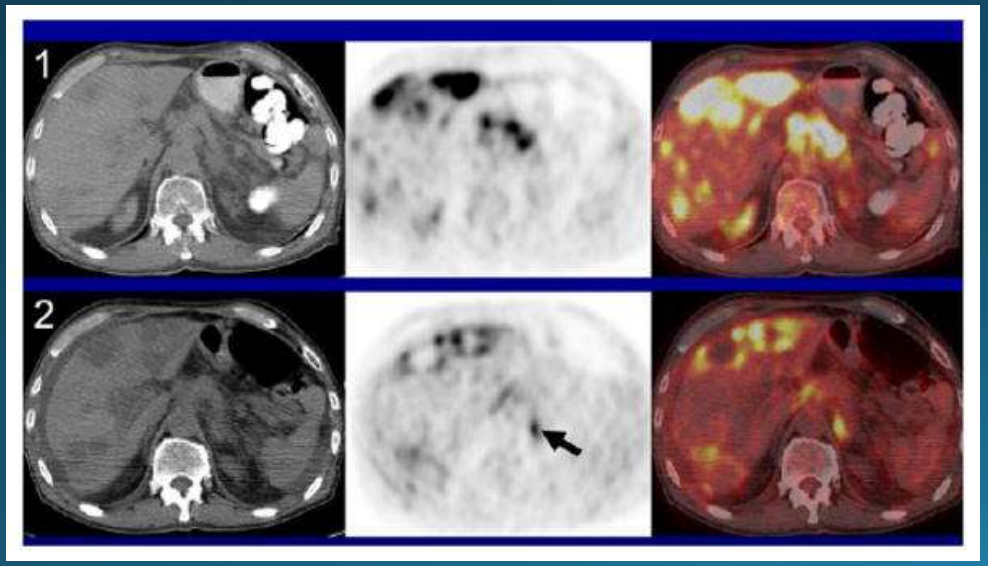
NHL (large B cell type).



A) Left axila 16 x 16 x 15 см , SUV-19
F) Post-therapy– negative uptake 10 x 9,5 x 9,3 см
PR-RECIST
CR-PERCIST



HCC post -therapy
RECIST-SD
PERCIST-PR



Pancreatic cancer post-therapy
RECIST-PR
PERCIST-PD

CONCLUSION

Integrated PET/CT provides:

- More precise staging than all the other imaging techniques
- Allows better selection of patients for new modalities of treatment
- Helps in re-staging after induction therapy
- It is cost-effective
- Precise delineation – EBRT Planning
- Helps in follow up evaluation by differentiating Residual or recurrent tumor from Post-treatment scarring

But....

CONCLUSION

^{18}F-FDG-PET/CT

- False positive results (High metabolic activity in):
  - Inflammation, infection
  - Granulomatous diseases (Sarcoidosis…)
  - Benign tumors
  - Brown fat… Artifacts….

Instead of CONCLUSION

^{18}F-FDG-PET/CT

- False negative results:
  - Small lesions < 8-10mm (limited spatial resolution of PET)
  - Necrotic tissue
  - Bronchoalveolar carcinoma, carcinoid….
  - Hyperglycemia, hyperinsulinemia, corticosteriod therapy