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68Ga PSMA PET/CT dans le Cancer Prostatique

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Plan

- Introduction
- FDG et Fluro/Carbone Choline et cancer de la prostate
- PSMA et cancer de la prostate
- Cas clinique
- Quelques messages

Introduction

- Major public health problem

- Second most common cancer in male worldwide

Globocan IARC, 2018

- Europe: 214 cases/1000 men

- outnumbering lung and colorectal cancer

Boyle P, Ferlay. J. Ann Oncol (2005)

- Increasing number of “non-lethal” tumors being diagnosed
- 1 in 6 will be diagnosed, 1 in 35 will die from it. (10% of cancer related deaths in men.)

Major public health problem



Estimated age-standardized incidence and mortality rates (World) in :2018

	World	
	Incidence	Mortality
Lung	31.5	27.1
Prostate	29.3	7.6
Colorectum	23.6	10.8
Stomach	15.7	11.7
Liver	13.9	12.7
Bladder	9.6	3.2
Oesophagus	9.3	8.3
Non-Hodgkin lymphoma	6.7	3.3
Leukaemia	6.1	4.2
Kidney	6.0	2.6

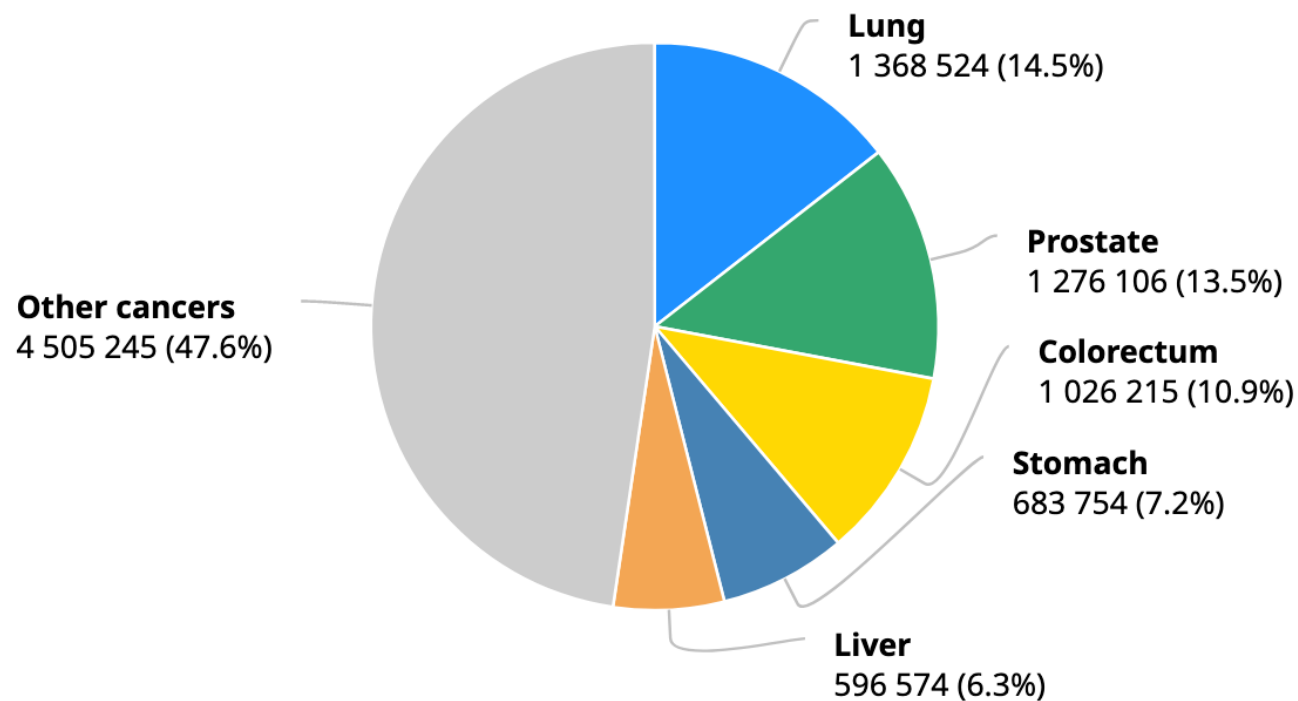
Major public health problem

International Agency for Research on Cancer



**CANCER
TODAY**

Number of new cases in 2018, males, all ages



Total: 9 456 418

Data source: GLOBOCAN 2018
Graph production: Global Cancer Observatory (<http://gco.iarc.fr/>)
© International Agency for Research on Cancer 2019

Major public health problem

World

Source: Globocan 2018

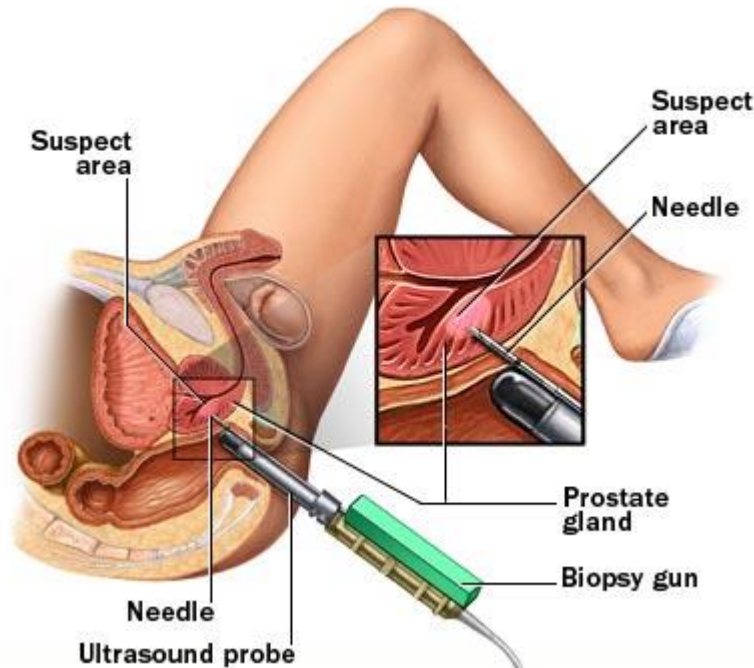


Incidence, Mortality and Prevalence by cancer site

Cancer	New cases				Deaths				5-year prevalence (all ages)	
	Number	Rank	(%)	Cum.risk	Number	Rank	(%)	Cum.risk	Number	Prop.
Lung	2 093 876	1	11.6	2.75	1 761 007	1	18.4	2.22	2 129 964	27.91
Breast	2 088 849	2	11.6	5.03	626 679	4	6.6	1.41	6 875 099	181.78
Prostate	1 276 106	3	7.1	3.73	358 989	8	3.8	0.60	3 724 658	96.73
Colon	1 096 601	4	6.1	1.31	551 269	5	5.8	0.54	2 785 583	36.49
Stomach	1 033 701	5	5.7	1.31	782 685	2	8.2	0.95	1 589 752	20.83
Liver	841 080	6	4.7	1.08	781 631	3	8.2	0.98	675 210	8.85
Rectum	704 376	7	3.9	0.91	310 394	10	3.2	0.35	1 876 453	24.58
Oesophagus	572 034	8	3.2	0.78	508 585	6	5.3	0.67	547 104	7.17
Cervix uteri	569 847	9	3.2	1.36	311 365	9	3.3	0.77	1 474 265	38.98
Thyroid	567 233	10	3.1	0.68	41 071	25	0.43	0.05	1 997 846	26.17

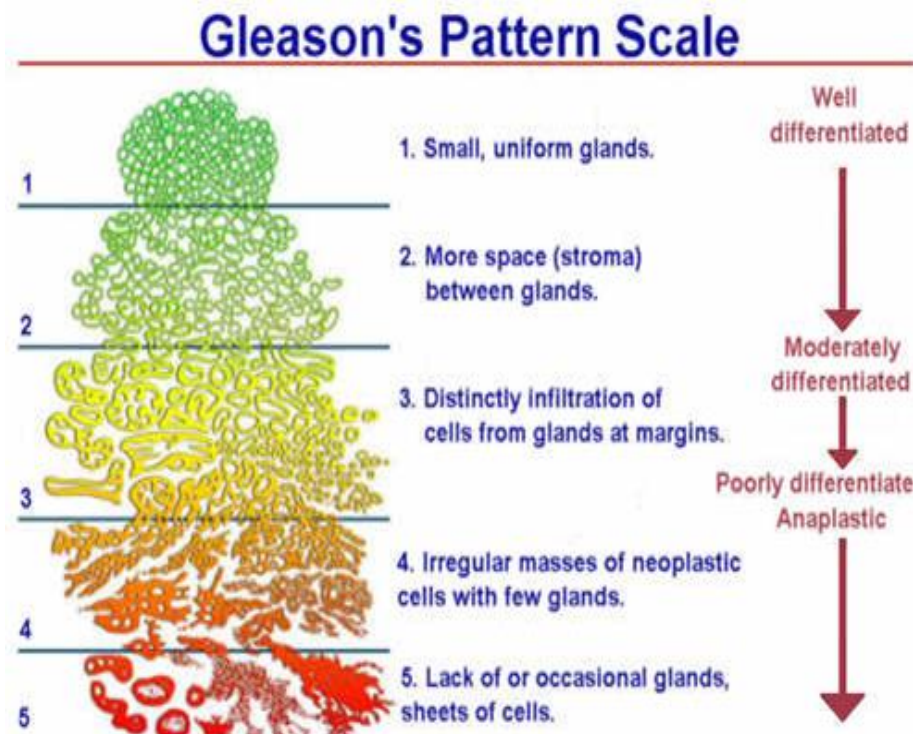
Diagnosis of Prostate Cancer

- Diagnosis by histological findings
 - Transrectal core biopsies with transrectal ultrasound guidance (TRUS) (6-12)



Diagnosis

- Gleason Score (architectural features)
 - to grade the aggressiveness from 2 (1+1) to 10 (5+5)



Under a low-powered microscope, five specific patterns of prostate cancer cells have been identified ("grades"). These are numbered 1 through 5.

Adding the **two most common patterns seen in a prostate biopsy specimen** gives the Gleason score (for example, Gleason 3 + 3 = 6 or Gleason 4 + 3 = 7). The first number represents the most common pattern in the specimen, the second number the next most common pattern.

Predictable method of assessing aggressiveness of prostate cancer. Helpful in categorizing patients for prognosis; for instance, Gleason 4 + 3 = 7 has a less favorable prognosis than Gleason 3 + 4 = 7 due to the 4 in the former example representing a larger portion of the specimen being more poorly differentiated.

Gleason ≤ 6 Well differentiated (slight anaplasia)
Gleason 7 Moderately differentiated (moderate anaplasia)
Gleason 8-10 Poorly differentiated/undifferentiated (marked anaplasia)

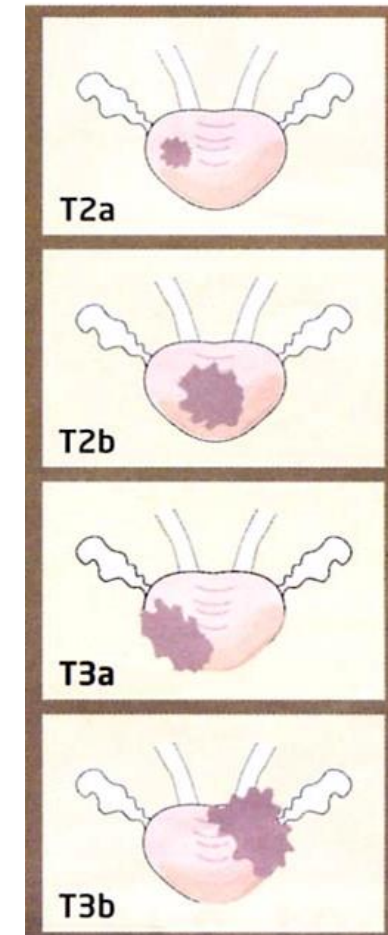
Diagnosis

- PSA **levels at diagnosis**
 - Higher values, increased risk of metastatic disease
 - <10 ng/ml (low risk)
 - 10-20 ng/ml (moderate risk)
 - >20 ng/ml (high risk)

Diagnosis

- TNM clasification

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
T1a	Tumour incidental histological finding in 5% or less of tissue resected
T1b	Tumour incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA] level)
T2	Tumour confined within the prostate ¹
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule ²
T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall



Recurrence risk

■ Low Risk:

- T1-T2a and Gleason score 2-6 and PSA < 10 ng/ml

■ Intermediate Risk:

- T2b-T2c or Gleason score 7 or PSA 10-20 ng/ml

■ High Risk:

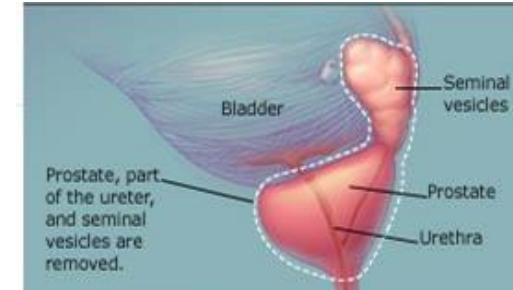
- T3a or Gleason score 8-10 or PSA > 20 ng/ml

■ Very High Risk:

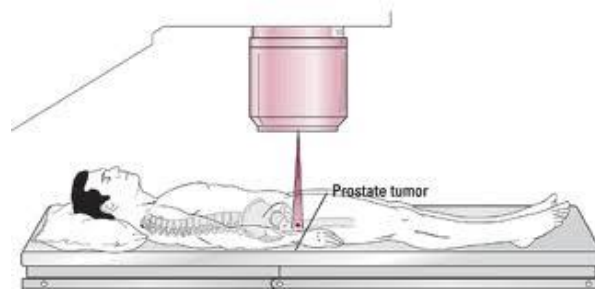
- T3b-T4 (locally advanced)

Localized Prostate Cancer. Curative intent treatment

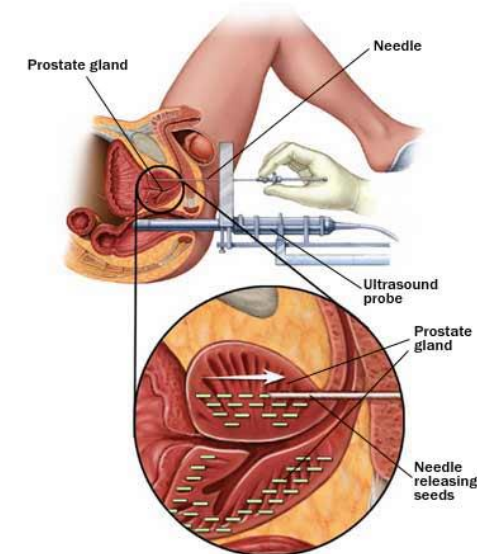
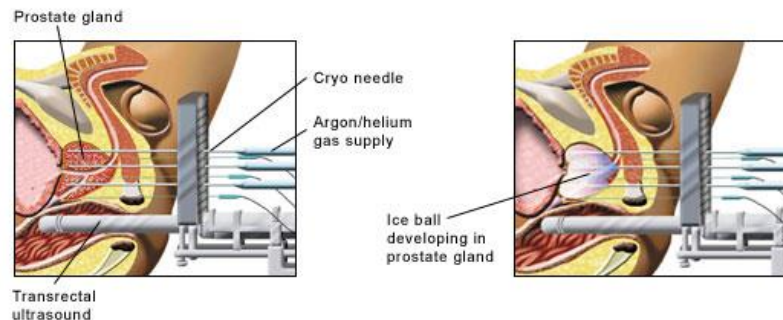
- Radical Prostatectomy (RP)
 - Open surgery
 - Robotic laparoscopic surgery
- External Beam Radiotherapy



- Brachiththerapy



- Cryotherapy



Treatment

- T1c - Except in very young (< 60) or high PSA/Gleason score's, Active Surveillance with no therapy
- T2 - Active Surveillance in low risk patients. Radical prostatectomy or high dose radiation therapy.
- T3 (Stage III) - Usually treated with radiation therapy
- T4- Usually radiation therapy + Hormonal treatment
- Metastatic – Systemic treatment

Biochemical failure / relapse

- 40% rise in PSA at 10 years from primary treatment
 - Locally recurrent (25%)
 - Metastatic disease only (20%)
 - Local + Metastatic (50%)
- Increased probability of distant M1
 - PSAdt < 6m
 - PSA relapse in first 2 years of Radical prostatectomy

Relapse treatment

- Locally realpse:
 - Local salvage treatment
- Metastatic Prostate cancer
 - Most of them respond to androgen deprivation therapy (ADT)
 - Resistance in 1-3 years (CRPC)
 - After resistance to ADT
 - Abiraterone
 - Enzalutamide
 - Chemotherapy (symptoms, survival, not curative).
 - 1st line Docetaxel (PFS 18 months)
 - 2nd Cabacitaxel
 - Isotopes
 - ^{223}Ra in patients with bone “quasi” exclusive metastasis (in Belgium, only after 1th systemic treatment line)
 - ^{177}Lu PSMA and alpha-PSMA treatments such as ^{225}Ac PSMA, are investigational promising treatments.

PET and SPECT (CT) in prostate cancer, a lot of radiotracers

Molecular targets for Urologic Cancer Imaging

Molecular Target	Physiological Process	Modality	Tracer
Glut1, Hexokinase	Glycolysis	PET	¹⁸F-FDG
Choline kinase	Membrane Synthesis	PET	¹¹C-choline ¹⁸F-(m)ethylcholine
L-AAT	Amino Acid Transport	PET	¹¹ C-methionine
Androgen receptor	Hormonal receptor	PET	18F-Fluoro-5α-Dihydrotestosterone
PSMA	Transmembrane protein	SPECT SPECT PET	111In-capromab pendetide (Prostascint) – ^{99m}Tc/¹²³I-PSMA ¹⁸F/⁶⁸Ga-PSMA
CB1	Transmembrane receptor	PET	¹⁸ F-MK-9470
Hydroxyapatite	Bone remodeling “Bone scan”	PET SPECT	¹⁸F-Fluoride ^{99m}Tc-MDP

Diagnosis and initial staging

- **Normal uptake:**

- FDG PET/CT uptake in presumed normal 145 men without known or suspected prostate pathology (SUVmax. 1.1 – 3.7)

Jadvar H et al. Nat Rev Urol. 2009

- **Low specificity :** False-positive results may occur with prostatitis

Incidental prostate hypermetabolism in FDG PET

- 1.5% of all PET
- Biopsy, digital rectal exam, PSA and follow up
 - Cancer positive (median PSA 49) □ SUVmax. 5.7
 - Cancer neg (median PSA 3.2) □ SUVmax. 4.8
- Cannot dif. Benign vs Cancer (**overlap**)

Hwang et al Ann Nucl Med 2012

*Level of ^{18}F -FDG accumulation can overlap in normal prostate tissue, benign prostatic hyperplasia, and prostate cancer tissues, all of which often coexist.

Salminen et al. A Oncol, 2002

Diagnosis and initial staging

- Variable FDG uptake depending on the aggressivity
 - FDG uptake is higher in poorly differentiated primary tumors (Gleason sum score > 7) and higher PSA values (PSA>12 ng/ml)
 - sensitivity 73% in peripheral zone and 20% in central zone.

Minamimoto et al. Ann Nucl Med 2011

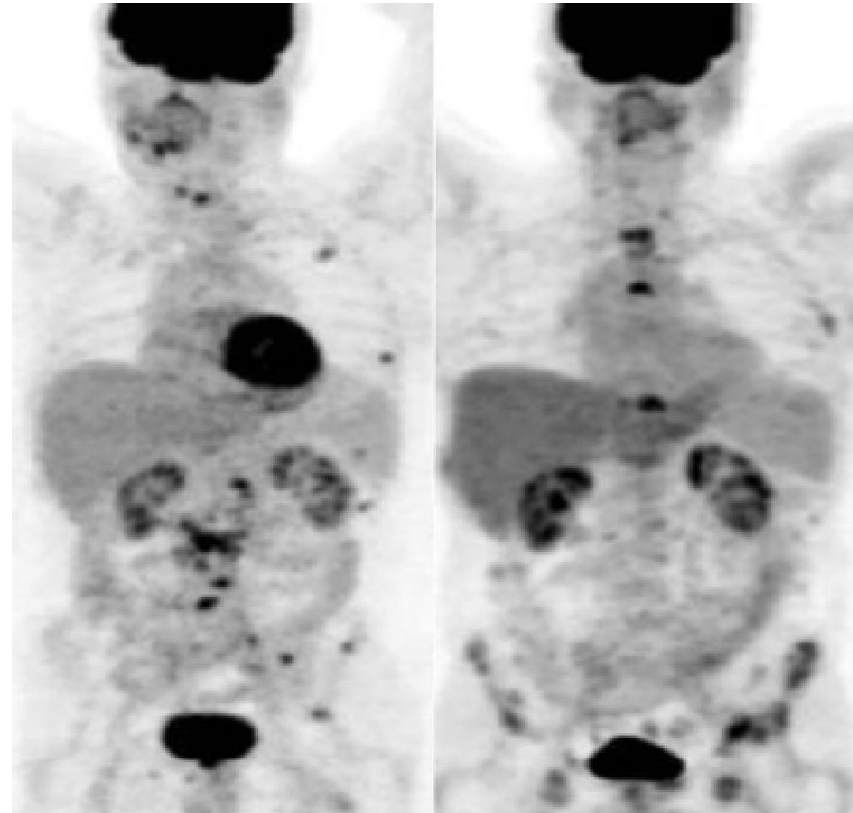
- High locoregional background
 - High level of excreted radiotracer in the adjacent urinary bladder and uretra that may mask any lesions in the vicinity.
- Staging:
 - Few data on staging with FDG (poorly differentiated?)
 - Frequent micrometastatic LN involvement missed

Biochemical recurrence

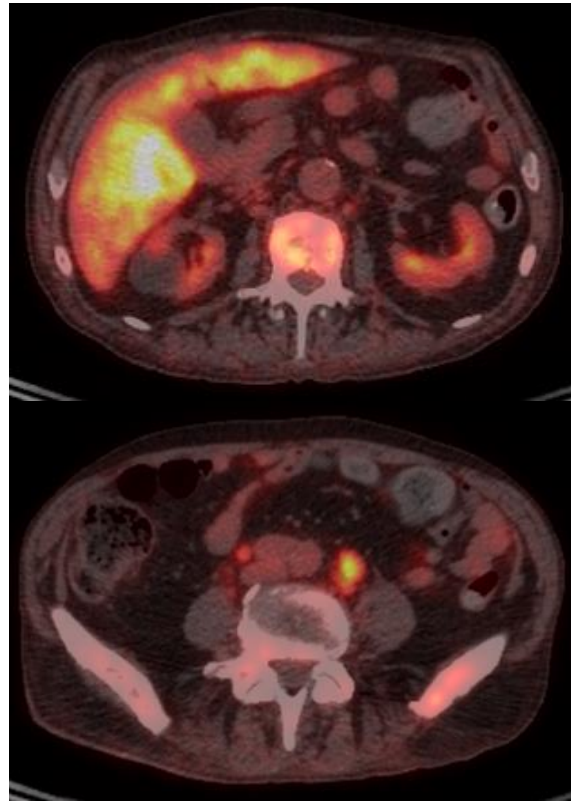
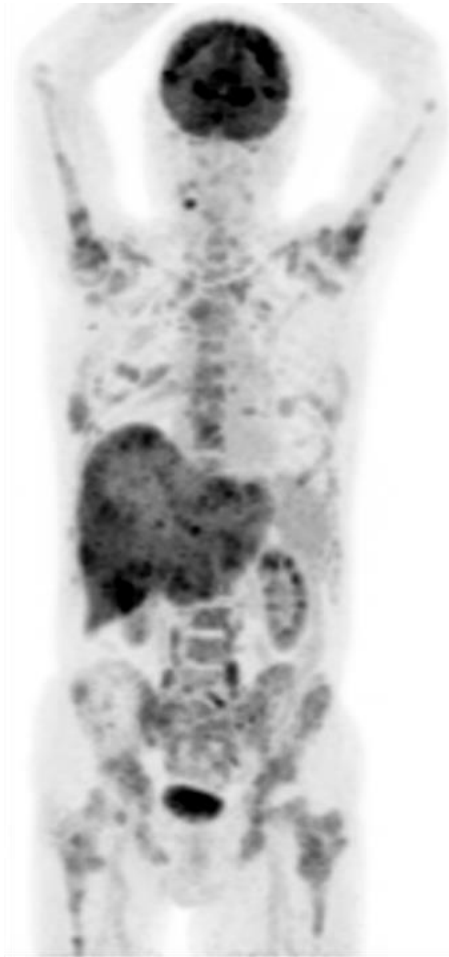
- **PSA increase** after prostatectomy or radiotherapy
- **Standard imaging:** contrast enhanced CT, ^{99m}Tc -bone scan, US, MRI.
- **Treatment:**
 - salvage radiotherapy or surgery for local recurrence
 - Systemic therapy for metastatic disease
- FDG: only 8.1% detection rate

FDG as a prognostic marker

- mCRPC progressing under ADT
 - FDG PET 4w and 12w of chemotherapy
 - **Progressive disease**
 - Δ SUVmax changes
 - increase >33% in FDG
 - or new lesions

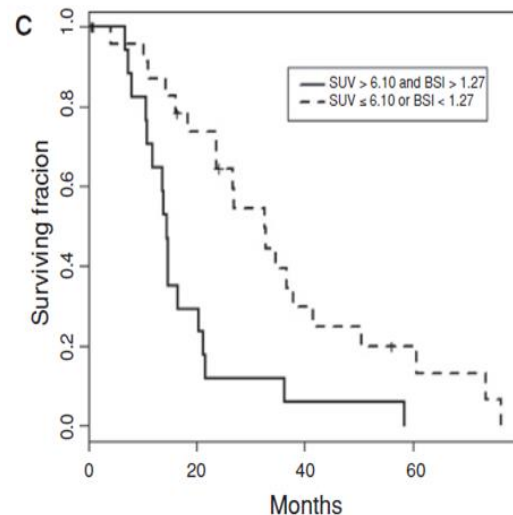


Example, Patient with Prostate Cancer, Gleason 9 (5+4), PSA 234 ng/dl, post 4 different lines of systemic treatment

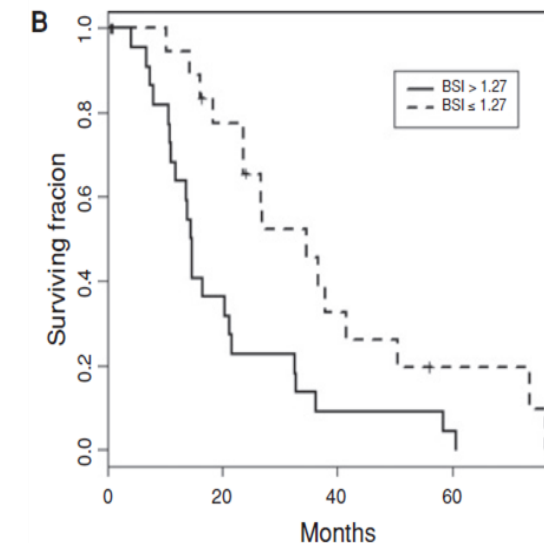
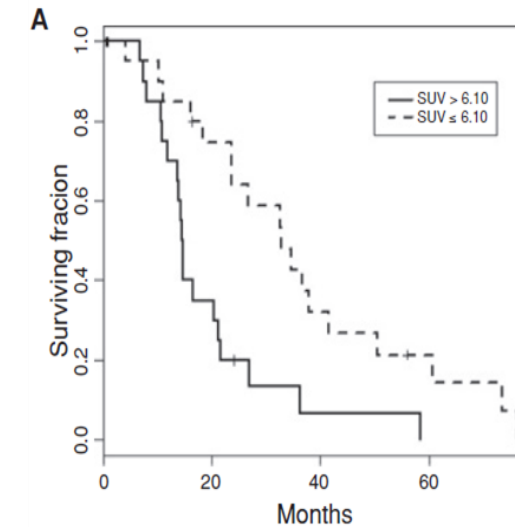


FDG as a prognostic marker

- Baseline FDG PET and ^{99m}Tc -MDP Bone Scan in 43 Progressing mCRPC patients
 - Bone Scan Index (BSI) method for quantitative bone scan interpretation
 - SUVmax (quantify metabolism)
 - correlated with survival



High SUVmax >6 :
median survival:14.4
months
Low SUVmax <6 :
median survival 32.8
months



FDG PET in Prostate Cancer

- Teaching Points:

FDG PET for diagnosis / staging / recurrence detection is **NOT** indicated

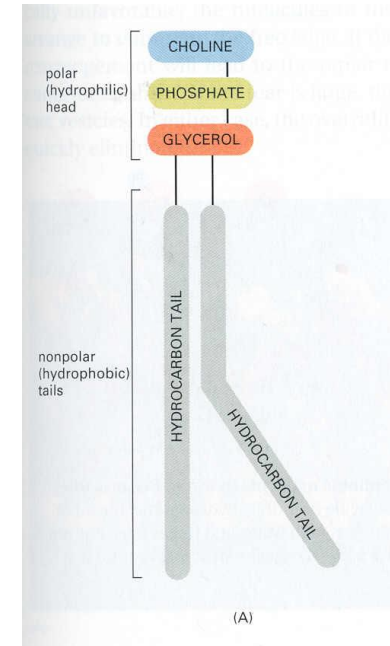
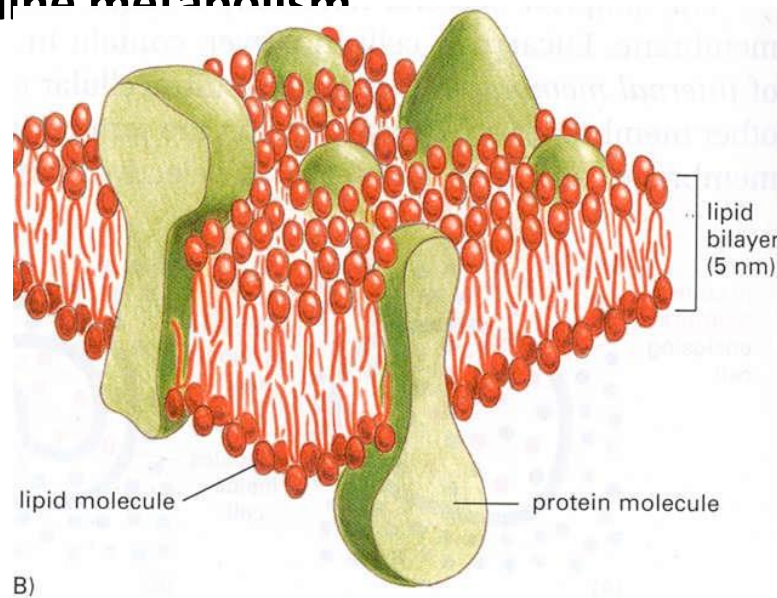
FDG PET-CT might be useful for **treatment and patient outcome** in mCRPC

If poorly differentiated PCa

❓ use of serial FDG PET for treatment monitoring ?

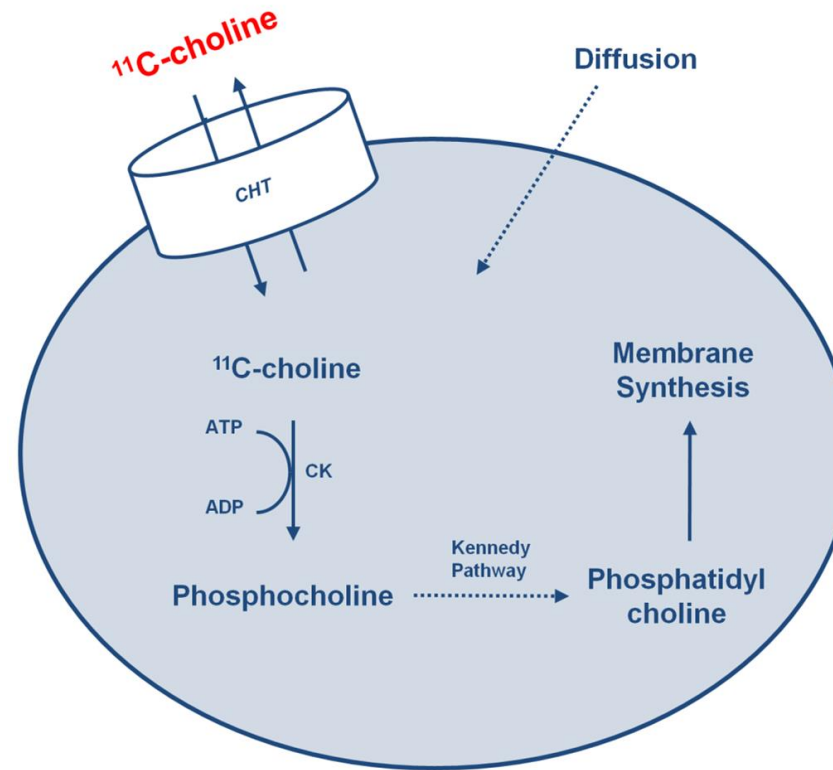
Choline PET Imaging

- **Choline = precursor for lipid layer of cell membrane**
- **Increased uptake of choline in cancer cells**
 - higher proliferation rate
 - upregulation of Choline kinase
- **In vivo- imaging of Choline metabolism**
 - MR spectroscopy
 - choline PET-CT



Cellular choline uptake and retention

Choline is a **substrate** **for** the synthesis of phosphatidylcholine, which is a major **phospholipid** in the cell membrane.



- Accumulation reflects cell **membrane phospholipid** synthesis
- uptake in PCa

Radioactive choline analogues

852

G. Henriksen et al. / Nuclear Medicine and Biology 31 (2004) 851–858

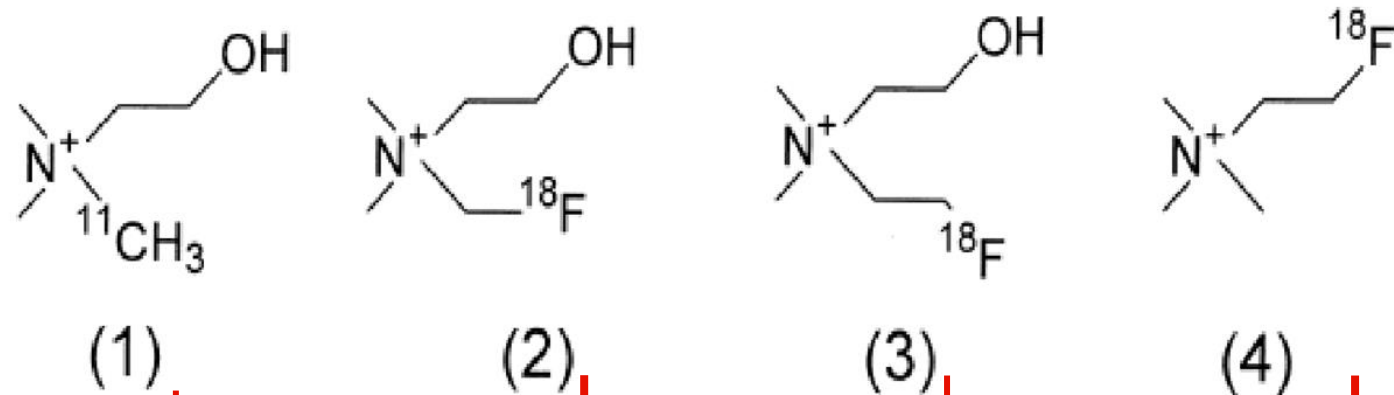


Fig. 1. Structure of [^{11}C]choline (1) ([^{11}C]CHO) and the [^{18}F]labeled choline analogues [^{18}F]fluoromethyl choline (2) ([^{18}F]FMC), [^{18}F]fluoroethyl choline (3) ([^{18}F]FEC), and deshydroxy-[^{18}F]fluorocholine (4) ([^{18}F]dOC).

C11- Choline

F18- Fluoro
MethylCholine

F18- Fluoro
EthylCholine

F18- Fluoro
Choline

C11-Choline Biodistribution

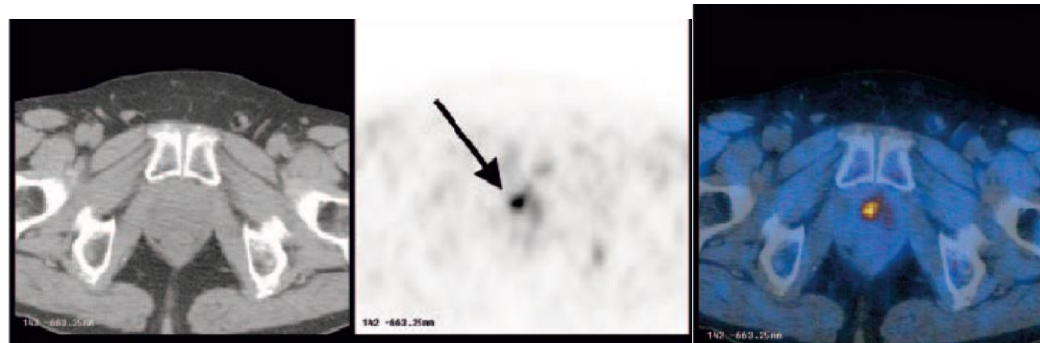


Primary tumor detection

- Histopathology 216 sextants
- Chol PET/CT results for detection of PC
 - Sensitivity 66% (FN low tumor burden)
 - Specificity 81% (FP prostatitis/hypertrophy)
 - Accuracy 71%
 - PPV 71%
 - NPV 55%
- No differences in ^{11}C -Choline uptake between PC/benign
- No correlation between ^{11}C -Choline uptake and tumour grade, Gleason score or PSA

Primary tumor detection

- Major **limits**
 - Choline uptake seems to be **similar** in patients with **benign** prostatic diseases (prostatitis, prostatic hypertrophy) and proven prostate **cancer**.
 - Limited **spatial resolution** of PET-CT devices.



Staging

- NOT accurate enough for evaluation of
 - extracapsular extension
 - seminal vesicle involvement
 - detection of lymph node micrometastases.

Sensitivity
20%

- Major limit: limited spatial resolution of PET-CT devices.

	Patient-based analysis	LN region-based analysis
No. of true-positive cases	3	3
No. of true-negative cases	19	294
No. of false-positive cases	1	1
No. of false-negative cases	13	29
Sensitivity	18.8%	9.4%
Specificity	95%	99.7%
PPV	75%	75%
NPV	59.4%	91.0%

LN = lymph node; NPV = negative predictive value; PPV = positive predictive value.

Future Indication for
SLN SPECT-CT?

–lymph node metastasis outside
the generally recommended
surgery regions
–impact on survival

Budiharto, Eur Urol 2011

* Choline PET imaging in predicting stage at presentation cannot be recommended for a routine clinical use.

Choline-PET for biochemical recurrence

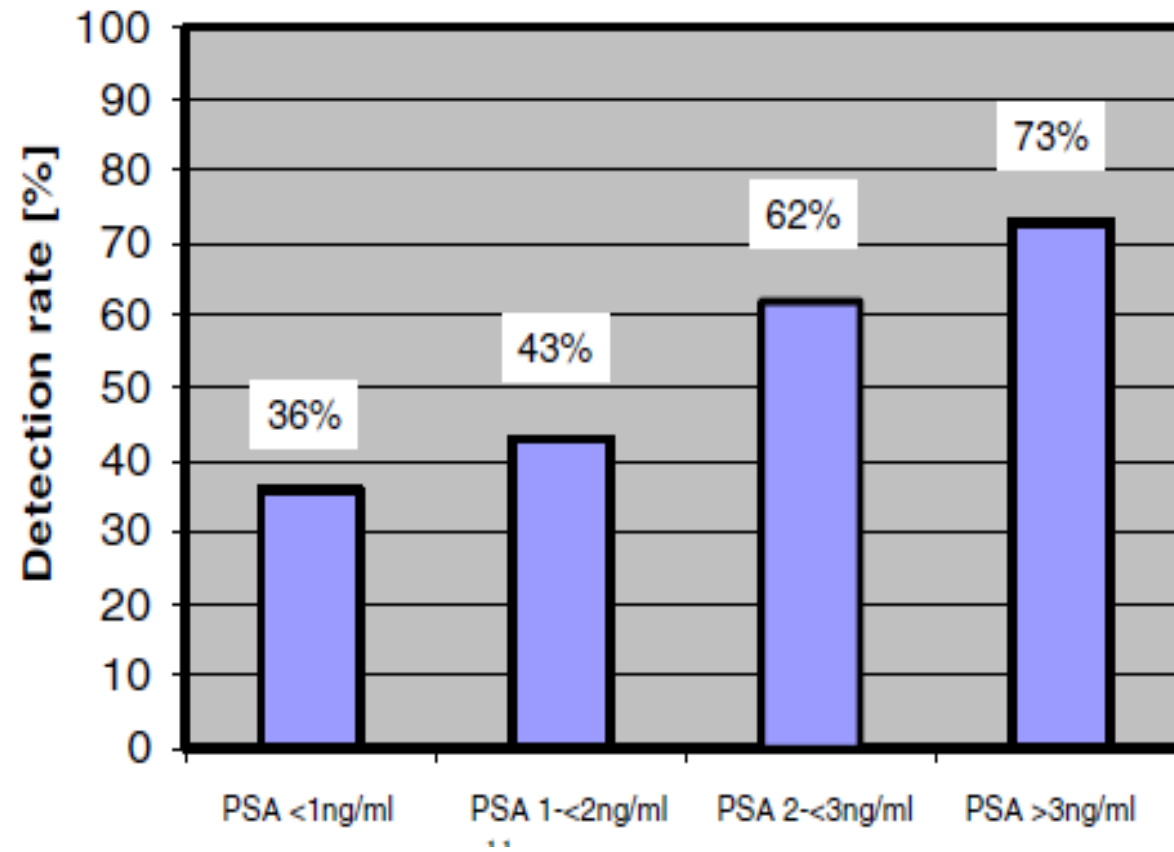


Detection PCa recurrence

- ^{11}C and ^{18}F -Choline studies
 - Sensitivity ranges 38%-98% for detection biochemical recurrence.
 - **Heterogeneity** of patient population in terms of PSA levels
 - Which is the trigger **PSA level** to indicate choline PET?
 - Pre-test probability
 - Increase Sensitivity
 - Decrease False Negative

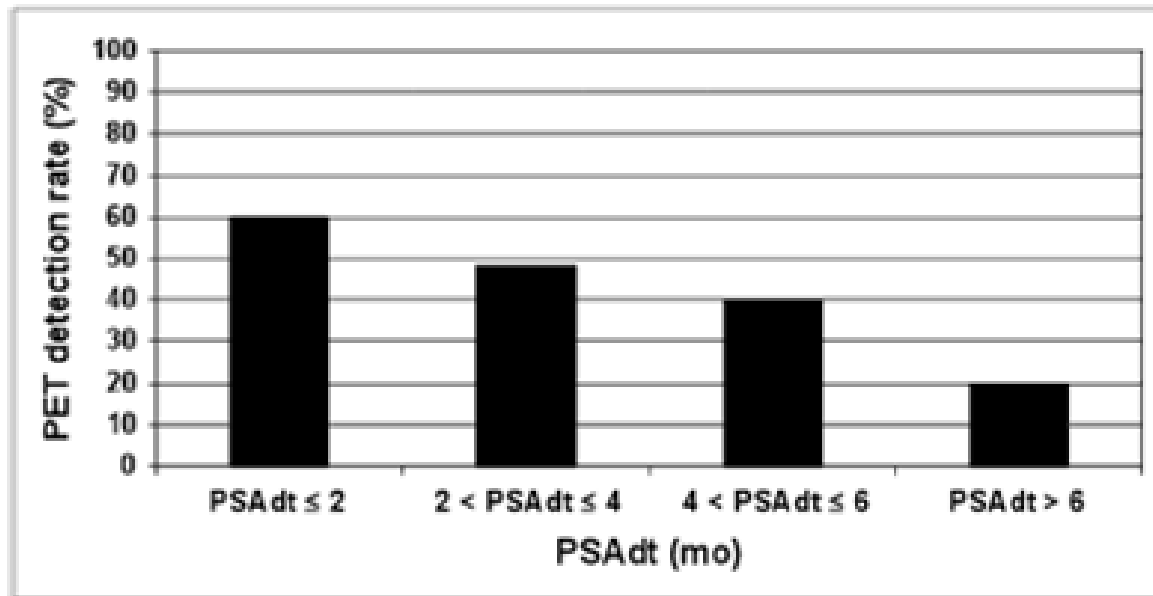


Detection PCa recurrence



Detection PCa recurrence

- Probability of positive PET in 190 men with PSA relapse (0.2-25 ng/ml) after RP.



Castelluci JNM 2011

- Another study 129 patients biochemical relapse:
 - Detection rate >1ng/ml: 87%
 - FP: 24%

Detti, JCCO, 2013

Detection PCa recurrence: ^{18}F Choline

N=358 Overall accuracy 88%

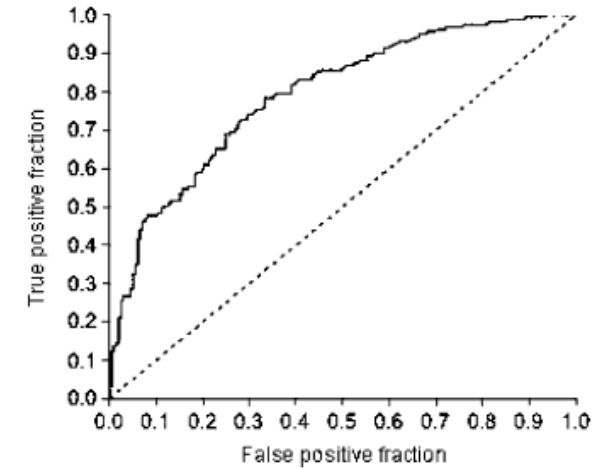
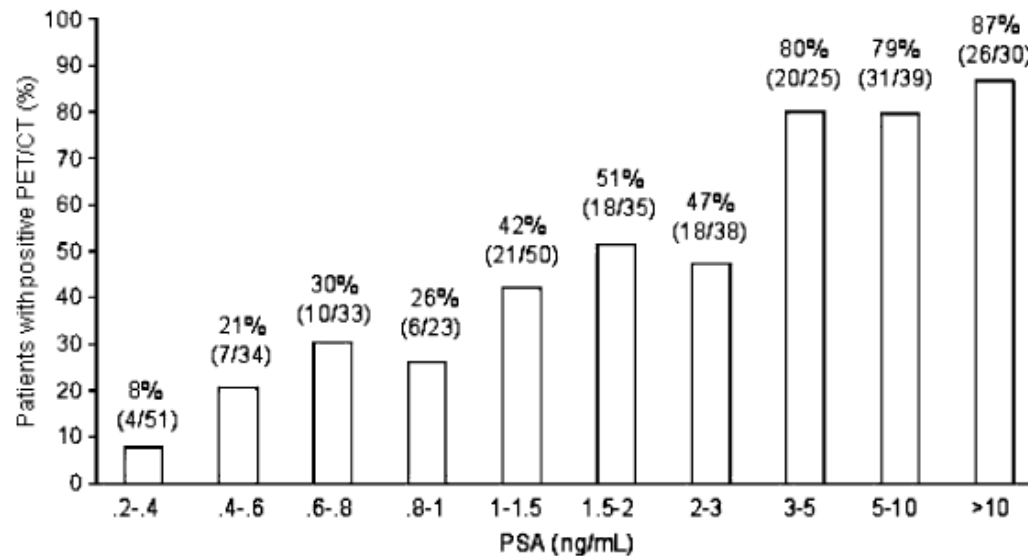


Fig. 3 ROC curve showing the frequency of true-positive and false-positive ^{11}C choline PET/CT scans in relation to PSA levels

Giovachini, EJNM&MI 2010

- ^{18}F choline study:

cut-off PSA 1.74; S: 82%, E: 75%

Graute et al, EJNM&MI 2012

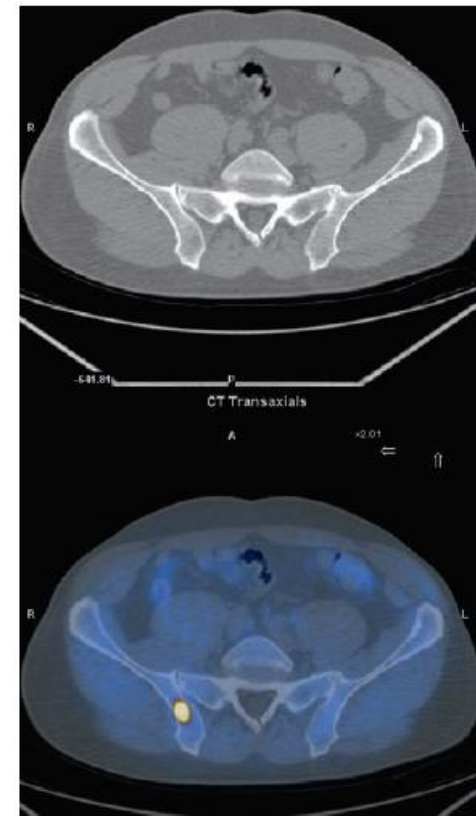
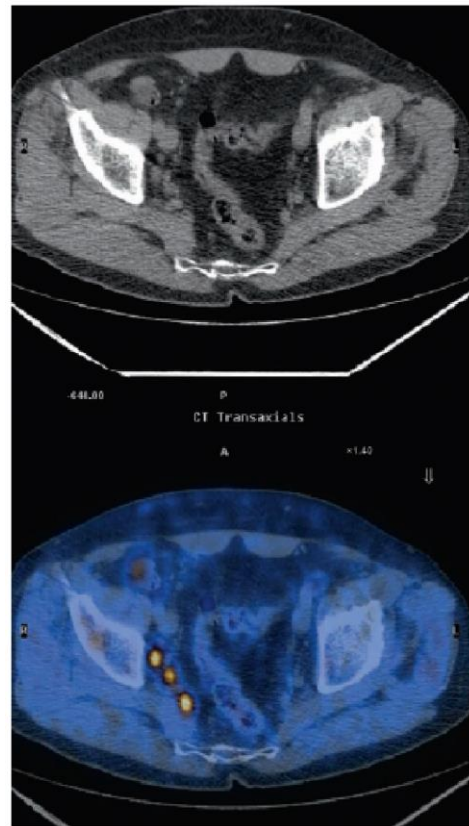
AUC: 0.79

Cut-off: 1.4 ng/ml

Detection PCa recurrence with Choline PET

- Indication for a Choline PET in biochemical recurrence:

- PSA > 1ng/ml
- PSAdt < 6 months



Choline PET in PCa

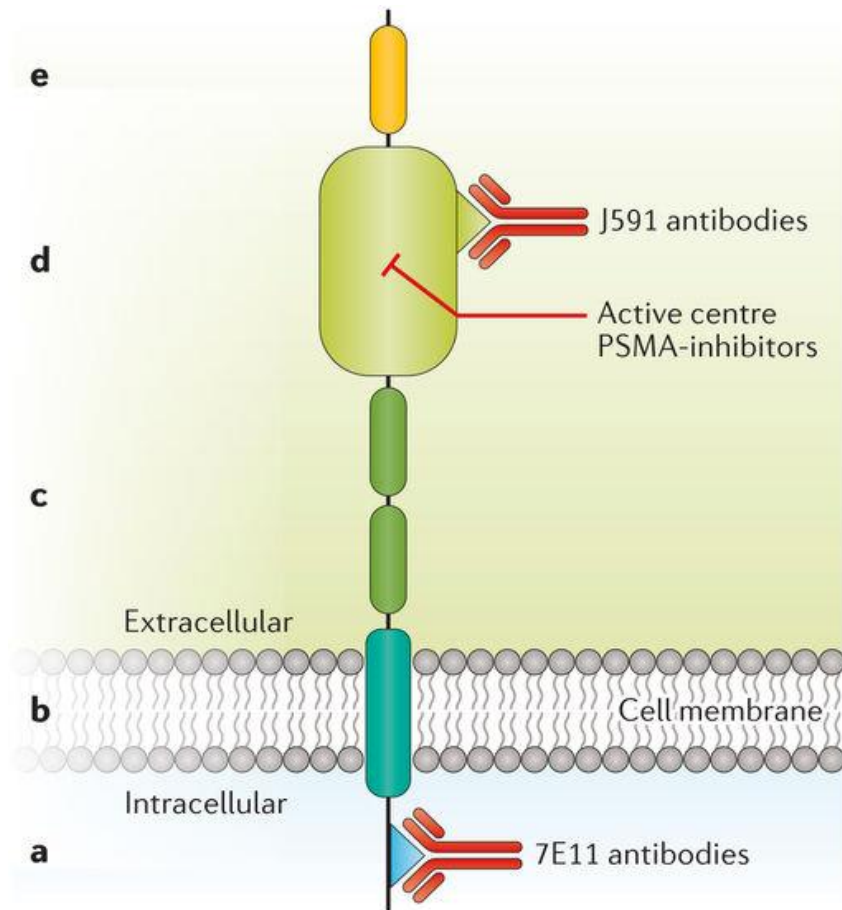
- Take home messages
 - **No** routine indication in newly diagnosed PCa
 - Promising for **detection of PCa recurrence**
 - Result of positive PET can be predicted
 - $\text{PSA} < 2.0 \text{ ng/mL}$ & $\text{PSA}_{\text{dt}} > 6$ à 7 months: low sensitivity
 - **Combine** Choline PET with
 - $^{99\text{m}}\text{Tc}$ -SPECT/CT or ^{18}F -fluoroide PET
 - complementary
 - “Reduced” sensitivity choline PET under ADT
 - **Similar** results for ^{11}C -Chol and ^{18}F -Chol

Prostate-specific membrane antigen
(PSMA)

Prostate-specific membrane antigen (PSMA)

- Prostate-specific membrane antigen (PSMA) is a **cell surface protein** with a significantly increased expression in prostate cancer cells
- Advantage:
 - Transmembrane location with a large extracellular domain
- This protein therefore provides a **promising target** for prostate carcinoma-specific imaging and therapy

PSMA



Nature Reviews | Urology

^{99m}Tc

Protein membrane. 750 amino acids

¹¹¹In

Clin Cancer Res. 1997 Jan;3(1):81-5.

¹⁷⁷Lu

PSMA is expressed in endothelial capillary cells of neo-angiogenesis in peritumoral areas

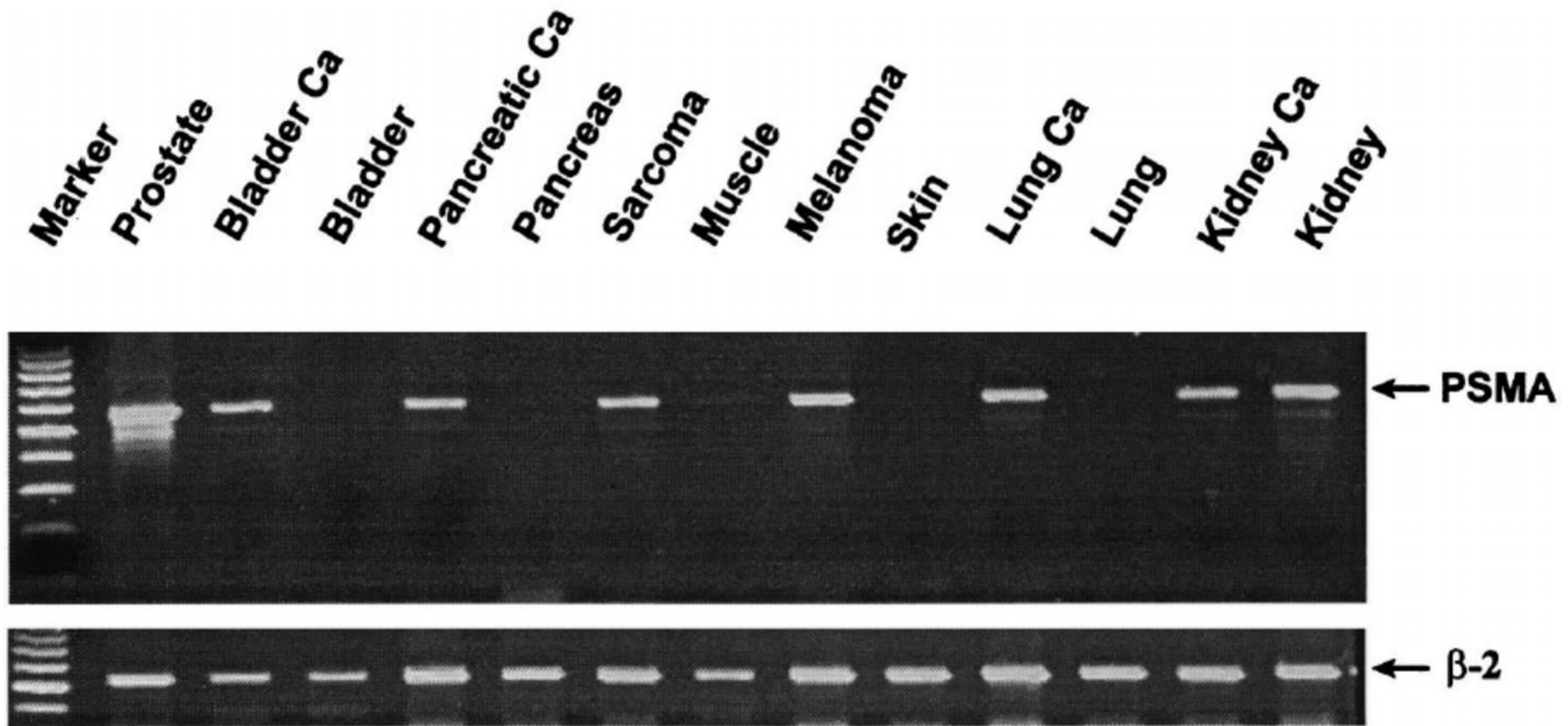
⁶⁸Ga

⁶⁴Cu

²²⁵Ac

²¹³Bi

Nature Reviews Urology 13, 226–



Lancet. 1997 May 31;349(9065):1601.

Clin Cancer Res October 1999 5; 2674

Intratumoral heterogeneity expression of PSMA proteins

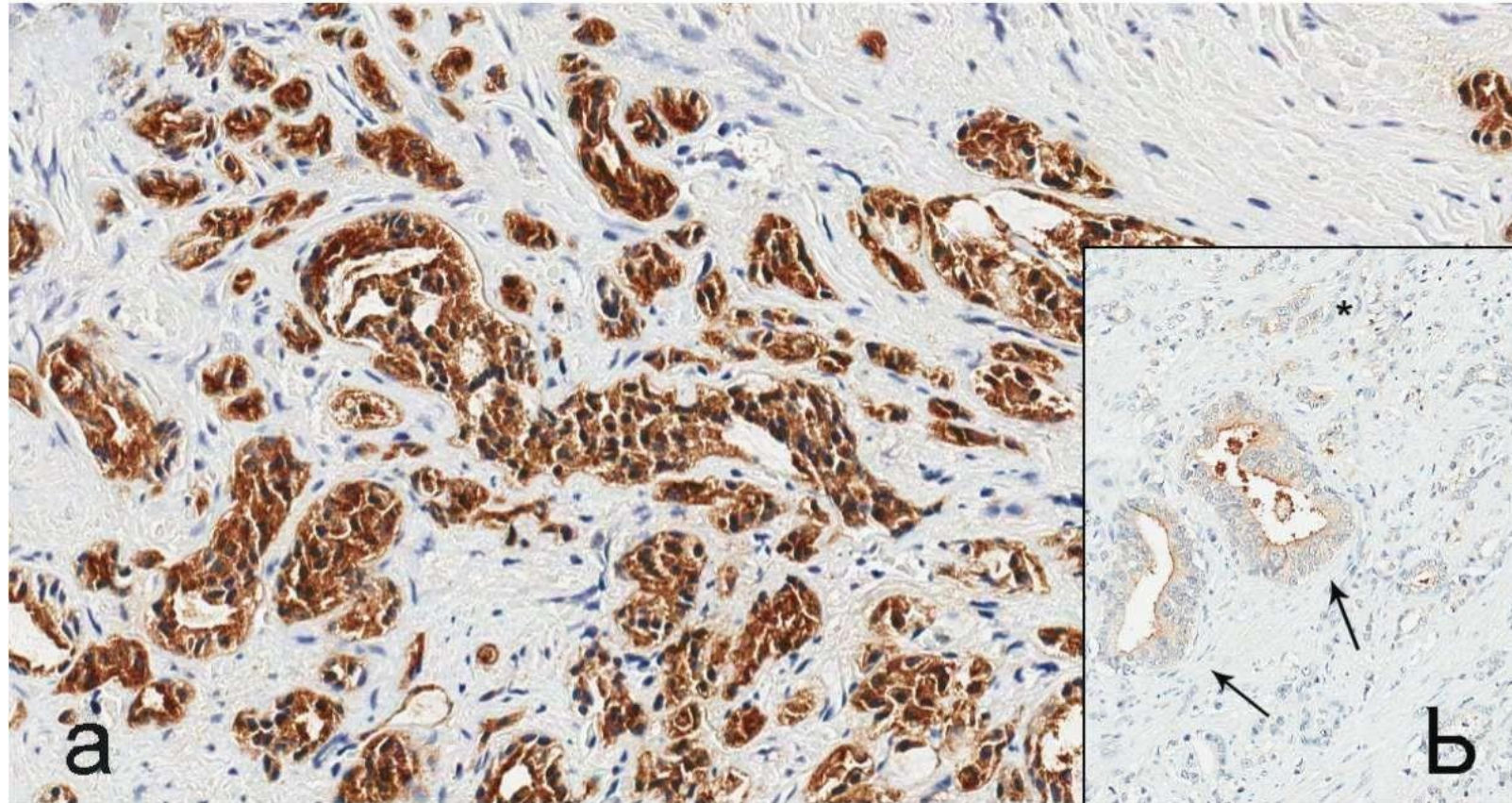
Table 1 Summary of PSMA expression and cellular localization data in primary prostate cancer and metastasis (differentiated according to the site of metastasis)

	PSMA positive fraction	PSMA	PSMA intensity (mean±SD)		
	(mean%±SD)	negative/total	Apical	Cytoplasmic	Membranous
Primary tumor	67.84±28.04	2/51	2.33±1.11	1.39±0.86	1.35±0.84
Metastasis total	63.9±37.82	8/51	2.12±1.23	1.38±1.08	1.13±0.9
Metastasis bone	63.91±38.18	6/31	2.27±1.19	1.47±1.12	1.05±0.85
Metastasis other	63.89±38.25	2/20	1.81±1.32	1.22±1.03	1.13±0.9

Table 2 Summary of PSMA expression and cellular localization data according to the Gleason score of the primary tumor

Gleason score	No. of patients	Primary PSMA (mean%±SD)	Metastasis PSMA (mean±SD)	PSMA intensity (mean±SD)		
				Apical	Cytoplasmic	Membranous
6	8	63.75±30.2	69.37±43.3	1.87±1.1	1.00±0.8	1.50±1.2
7	8	64.37±23.2	31.6±43.3	2.12±1.1	1.37±1.0	1.31±1.1
8	21	67.14±32.8	65.76±36.4	2.28±1.3	1.55±1.1	1.31±0.9
9	6	65.8±21.0	84.1±9.2	2.58±1.3	1.25±1.0	1.08±0.8
10	8	83.75±20.6	70.62±31.2	3.00±1.3	1.50±1.2	1.56±1.1

Mannweiler et al Pathol Oncol Res 2009;15_167-172

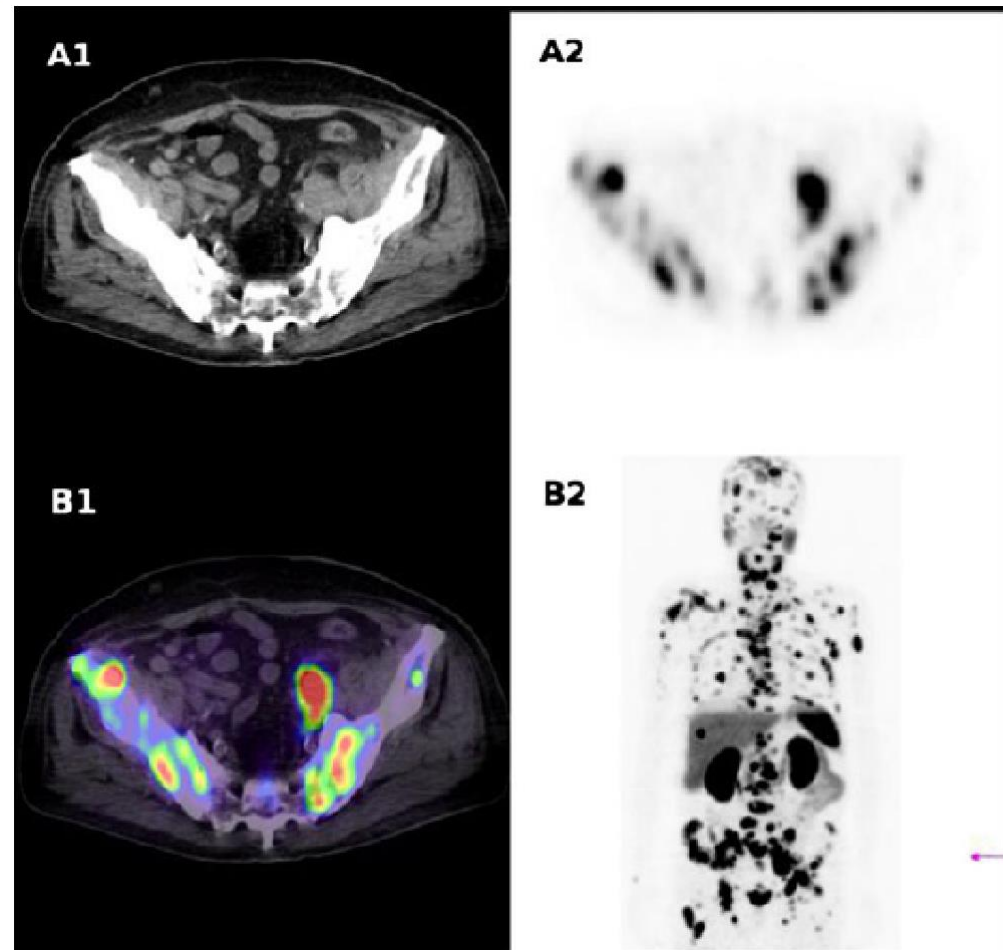
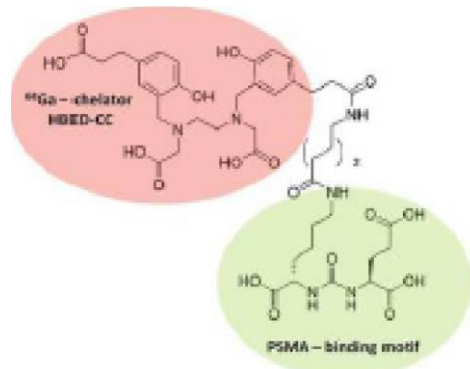


Rybalov et al. Int J Mol Sci 2014,15,6046-6061

Figure 1. PSMA staining in prostate cancer tissue. (a) Membranous and cytoplasmic brown staining for PSMA in prostate cancer cells, 400× magnification; (b) focal brown staining for PSMA in prostate cancer cells (arrows) amidst negative cancer tissue (*), 200× magnification.

Prostate-specific membrane antigen (PSMA)

PET imaging with a [^{68}Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions



Patient preparation

Table 1 Protocol example for ^{68}Ga -PSMA PET/CT image acquisition and reconstruction

Patient preparation	Hydration with e.g. oral intake of 500 mL of water 2 h prior to acquisition
Activity	1.8–2.2 MBq ^{68}Ga -PSMA per kilogram bodyweight
Administration	i.v., Flushing with at least the same volume of saline
Concomitant medication	Furosemide (20 mg i.v.)
Uptake time	60 min (acceptable range: 50 to 100 min)
Patient position	Arms elevated above the head
CT Protocol	FOV: base of the skull base to mid-thigh; Phase: portal venous (80 s after contrast agent, 1.5 mL per kilogram bodyweight)
PET Protocol	FOV and acquisition: from mid-thigh to base of the skull base; 3–4 min per bed position
PET Reconstruction	Ordered subsets expectation maximization; attenuation correction from CT data

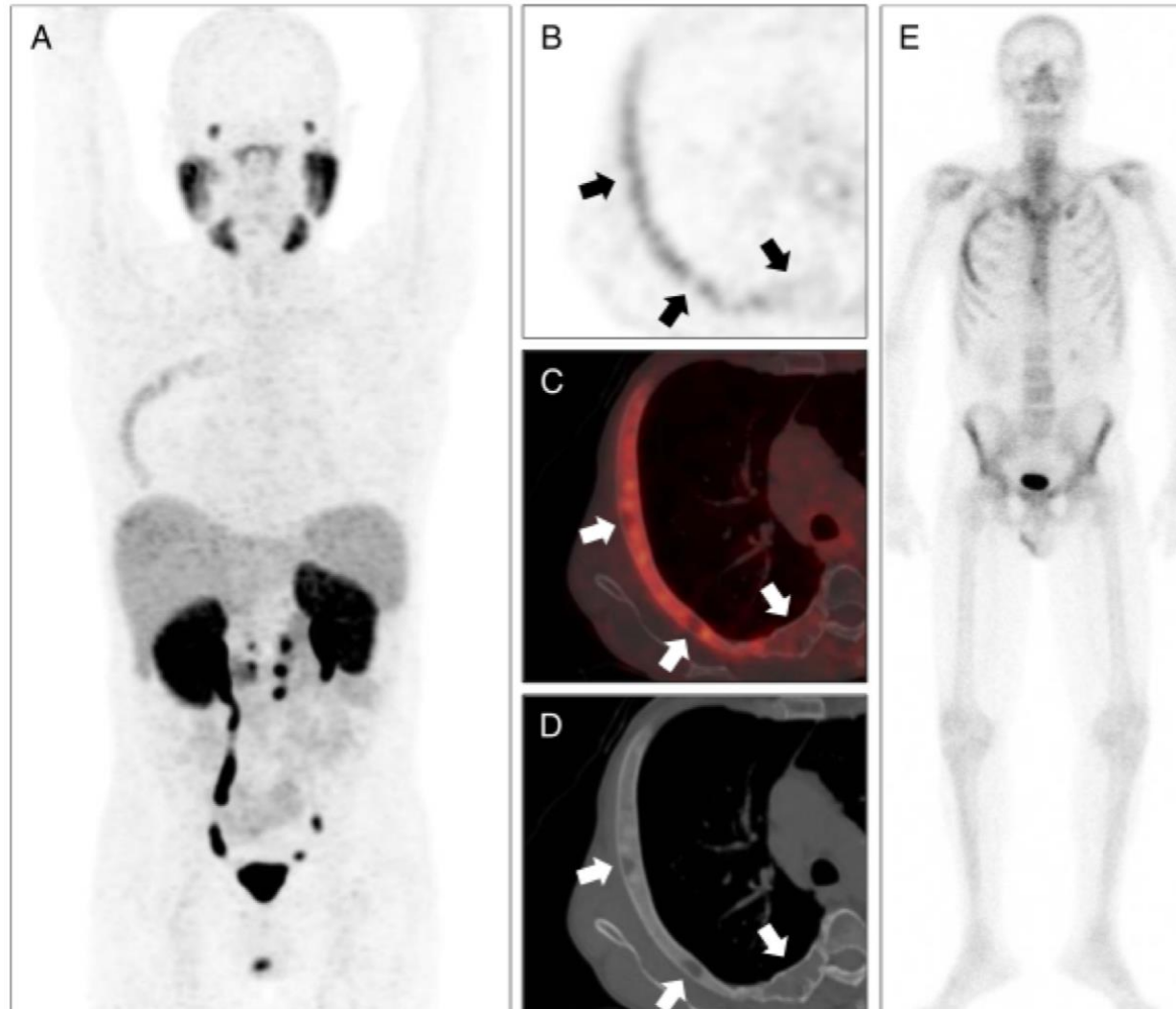
Is PSMA specific for prostate cancer?

- PSMA membrane protein also over expressed in:
 - Normal tissues: salivary glands, colon, duodenum
 - Other malignancies: colon, kidney, thyroid, lung, ...
 - Benign pathologies: Prostatitis, Paget, TBC, Fibrous dysplasia, ...

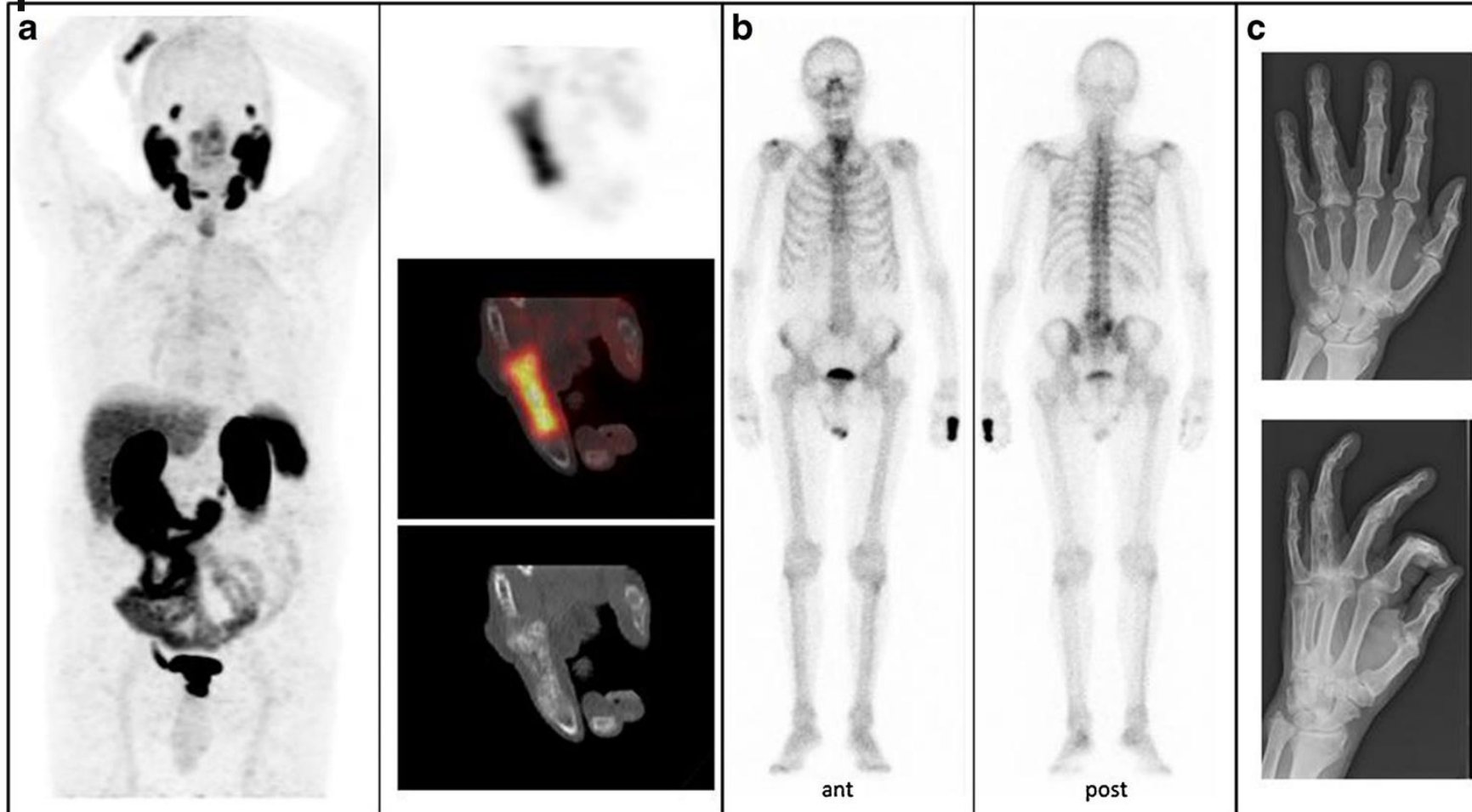
Normal ^{68}Ga PSMA PET imaging biodistribution



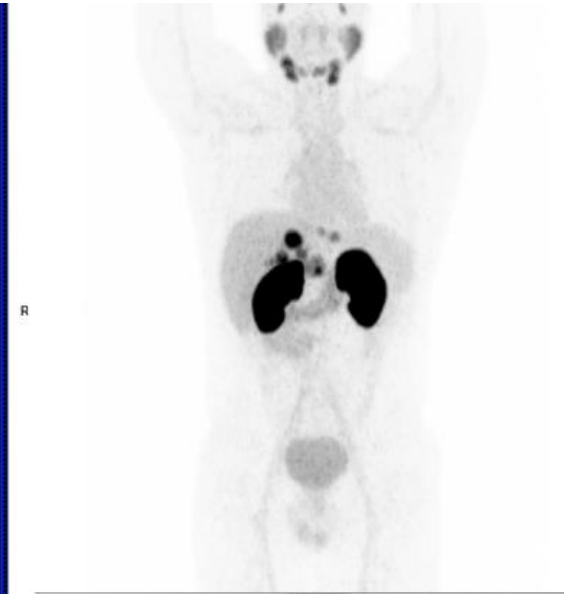
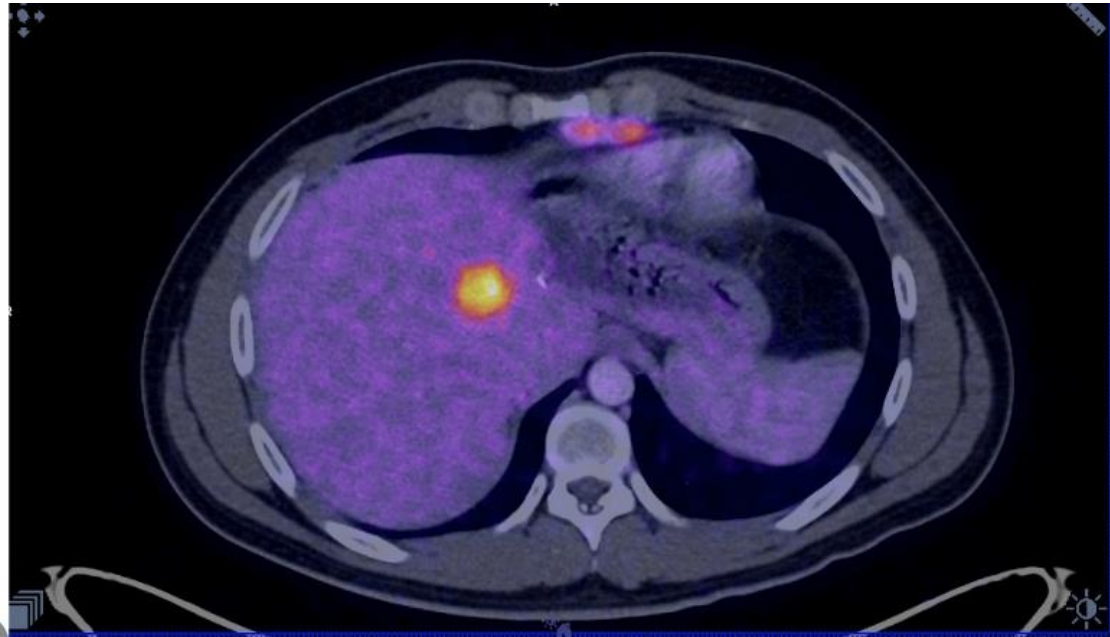
68Ga-PSMA PET/CT Uptake in Fibrous Dysplasia



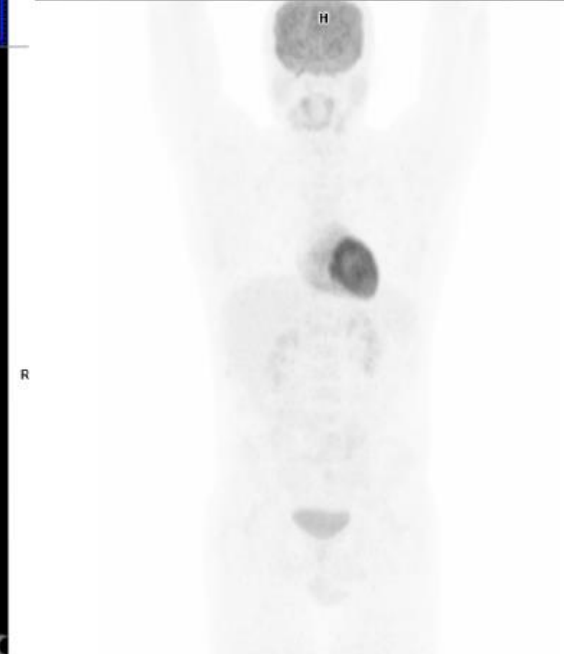
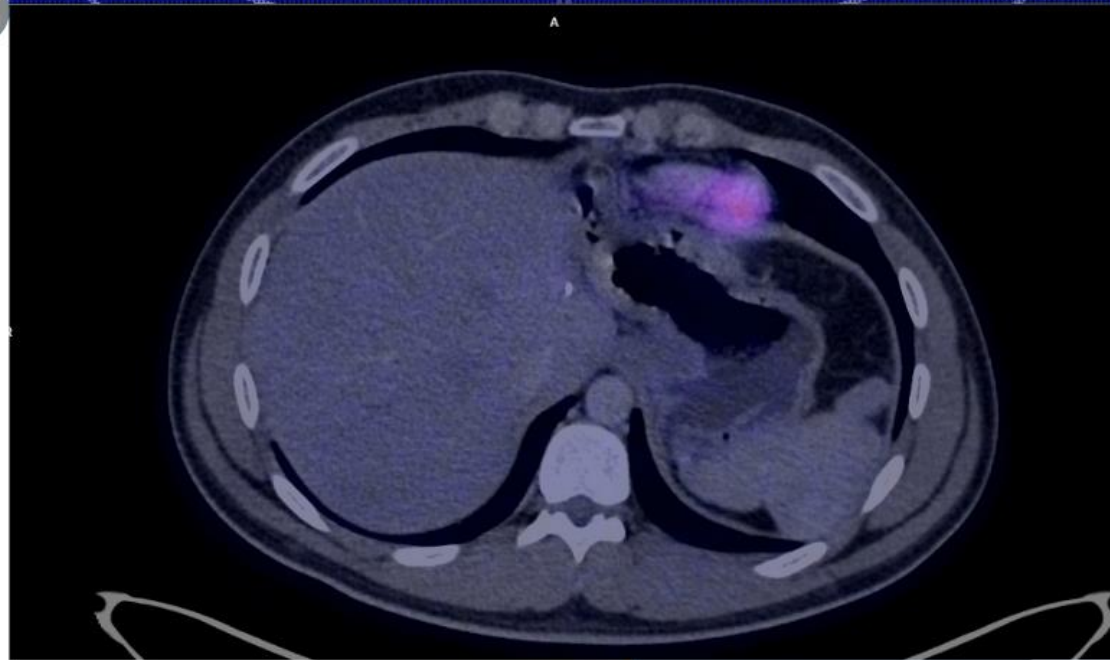
Paget bone disease demonstrated on 68Ga-PSMA ligand PET/CT



68GaPSMA
PET/CT



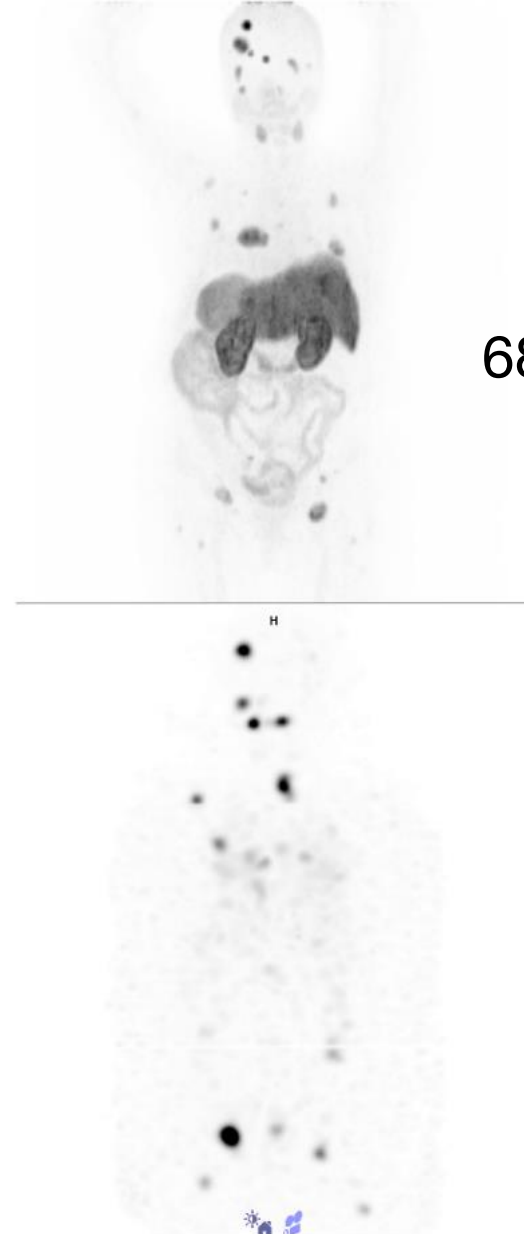
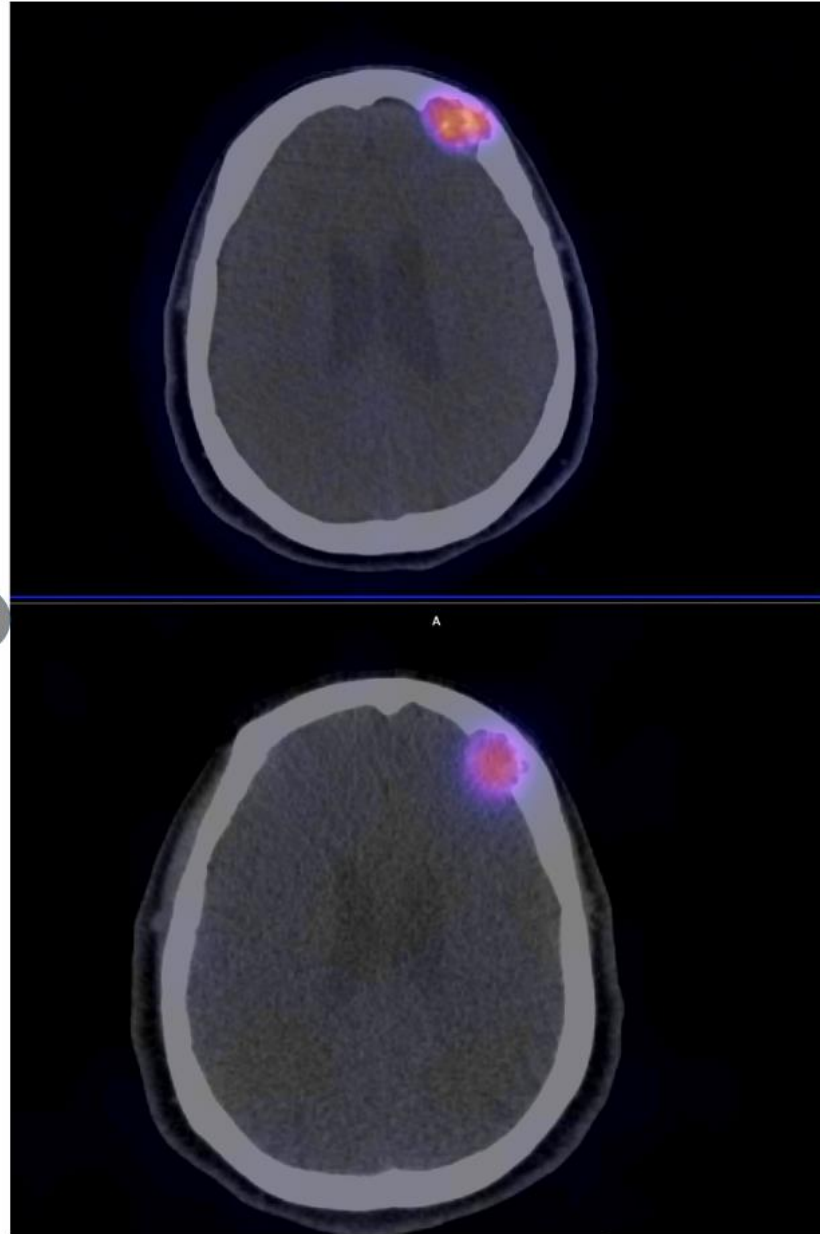
18FDGP PET/CT



hepatocarcinoma

Thyroid cancer

10



68GaPSMA PET/CT

131I SPECT/CT

Prostate-specific membrane antigen (PSMA)

Biodistribution, Tumor Detection, and Radiation Dosimetry of ^{18}F -DCFBC, a Low-Molecular-Weight Inhibitor of Prostate-Specific Membrane Antigen, in Patients with Metastatic Prostate Cancer

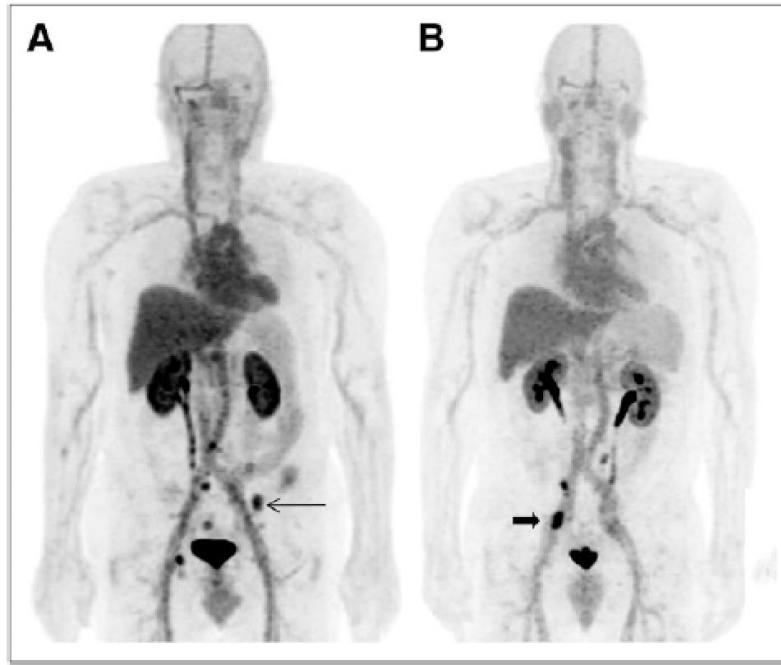
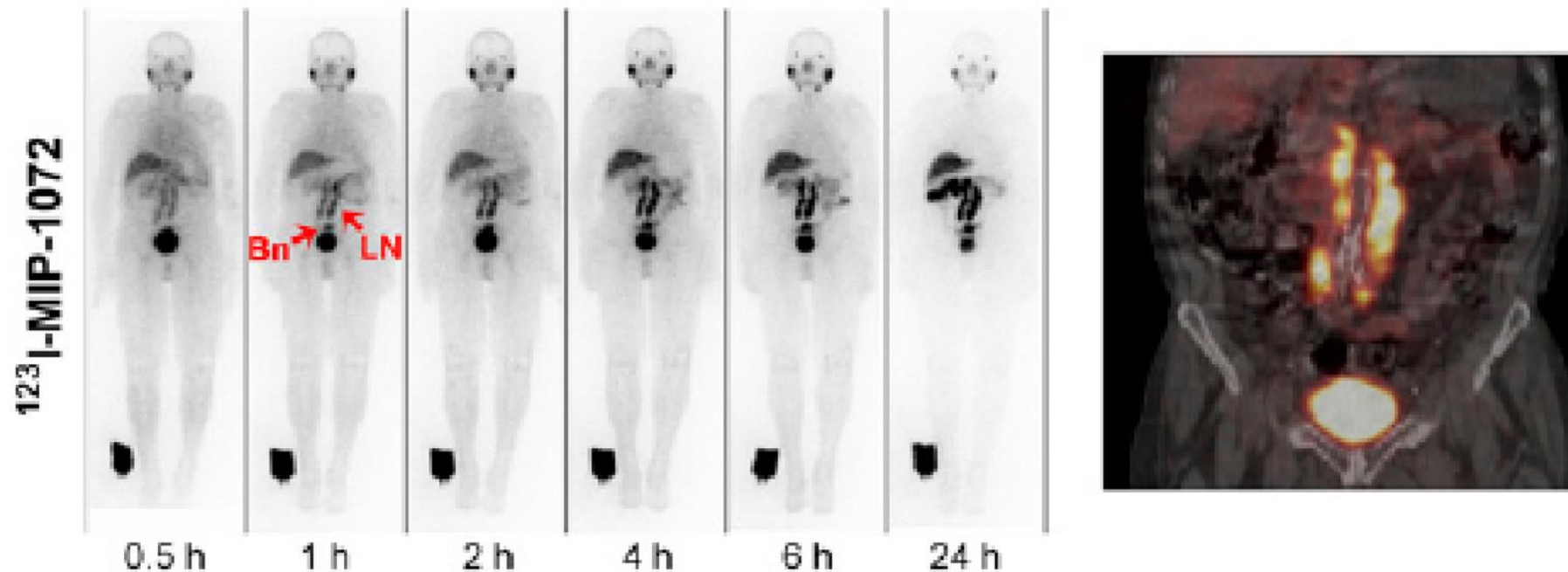


FIGURE 2. ^{18}F -DCFBC PET anterior projection maximal-intensity-projection images at 2 h after injection in patient 1, with several bone metastases (arrow) (A), and patient 5, with LN metastases (arrow) (B), as confirmed by correlation to CT portion of PET/CT exam.

Prostate-specific membrane antigen (PSMA)

First-in-Man Evaluation of 2 High-Affinity PSMA-Avid Small Molecules for Imaging Prostate Cancer

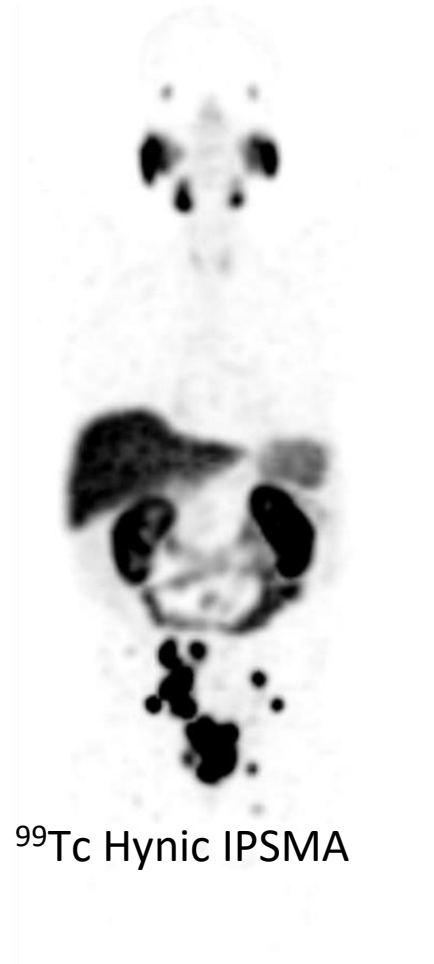
• ^{123}I -MIP



^{99}Tc Hynic IPSMA

77 year-old
Gleason score 5+4.
Retroperitoneal and pelvic lymph node
and prostatic gland positive for prostate
adenocarcinoma.

MIP SPECT



^{99}Tc Hynic IPSMA

MIP PET



^{68}Ga PSMA 11

Courtesy Dr Osvaldo Garcia, INIM, Mexico

^{99}Tc Hynic IPSMA

83 year-old male
Gleason score 4+4.
Metastatic disease in bone lesion and
retroperitoneal and pelvic lymph node

MIP SPECT



^{99}Tc Hynic IPSMA

MIP PET



^{68}Ga PSMA 11

Local detection and Primary staging using ^{68}Ga PSMA PET/CT

- MRI has emerged as the imaging technique of choice for detection of prostate cancer after inconclusive or negative biopsy findings, as well as for local staging regarding capsule penetration or seminal vesicle involvement
- The goal of primary staging is to detect metastatic spread to the first landing sites primarily lymph nodes, bone or other, visceral, organs. Indicated mainly in intermediate-risk to high-risk prostate cancer patients
- Published data on primary staging with PSMA ligands is still very limited and further research is needed before drawing robust conclusions

The EAU–EANM–ESTRO–ESUR–SIOG Guidelines on Prostate Cancer

6.2.6.6 Recommendations for the management of persistent PSA after radical prostatectomy

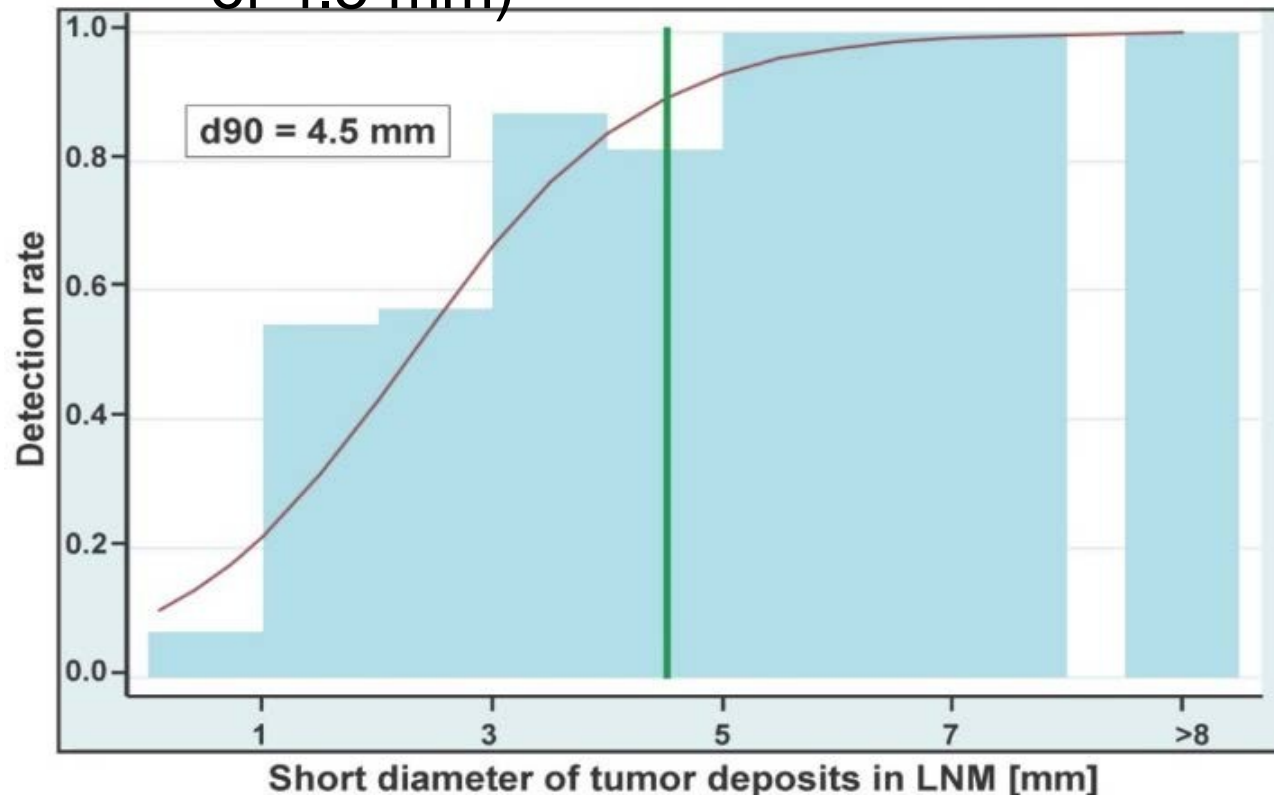
Recommendations	Strength rating
Offer a prostate-specific membrane antigen positron emission tomography (PSMA PET) scan to men with a persistent PSA > 0.2 ng/mL to exclude metastatic disease.	Weak
Treat men with no evidence of metastatic disease with salvage radiotherapy and additional hormonal therapy.	Weak

6.3.4.4 Guidelines for imaging in patients with biochemical recurrence

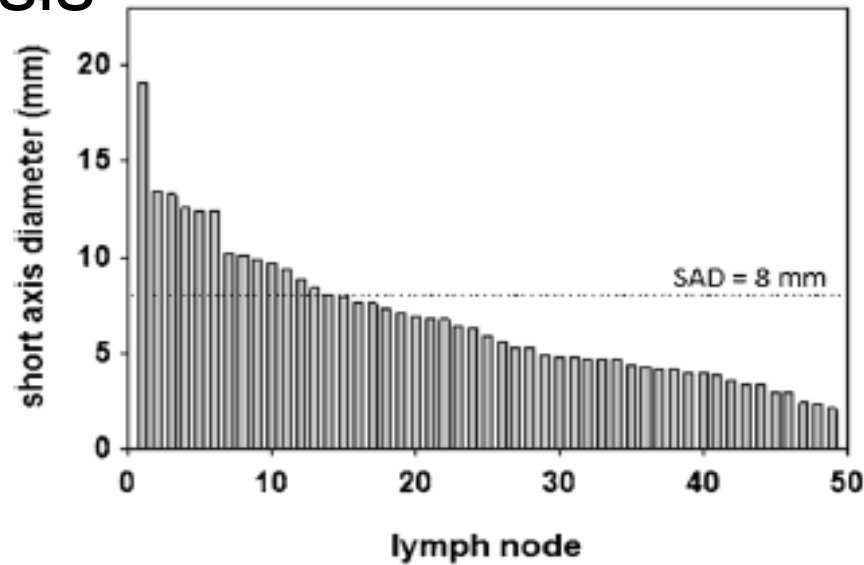
Prostate-specific antigen (PSA) recurrence after radical prostatectomy	LE	Strength rating
Perform PSMA PET/CT if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.	2b	Weak
In case PSMA PET/CT is not available, and the PSA level is ≥ 1 ng/mL, perform Fluciclovine PET/CT or Choline PET/CT imaging if the results will influence subsequent treatment decisions.		Weak
PSA recurrence after radiotherapy		
Perform prostate multiparametric magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	3	Strong
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	2b	Strong

How big do the lymph nodes metastasis need to be, to be detected with ^{68}Ga PET/CT PSMA?

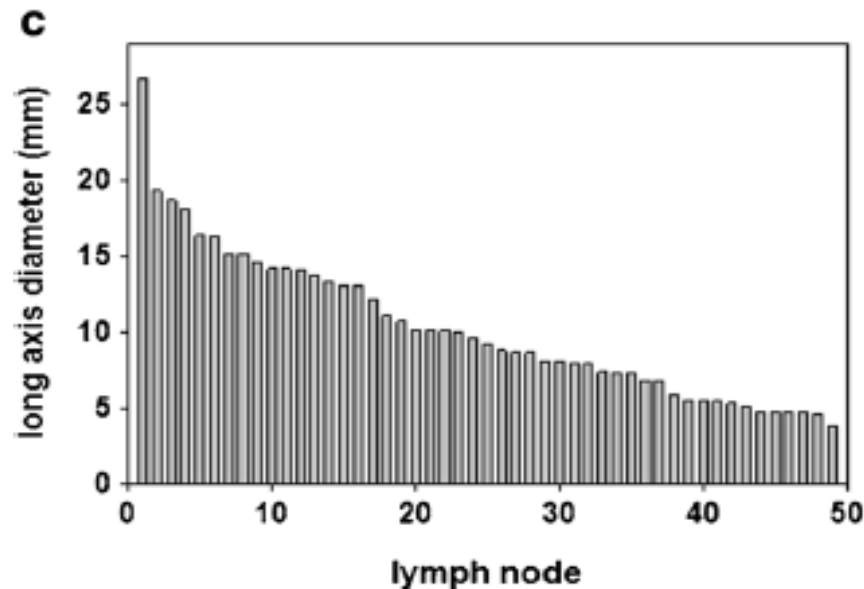
Detection rate of 50% for lymph nodes of 3.7 mm (tumor of 2.3 mm) of 90% for lymph nodes of 6.0 mm (tumor of 4.5 mm)



^{68}Ga PSMA is better than CT in detection of lymph node metastasis

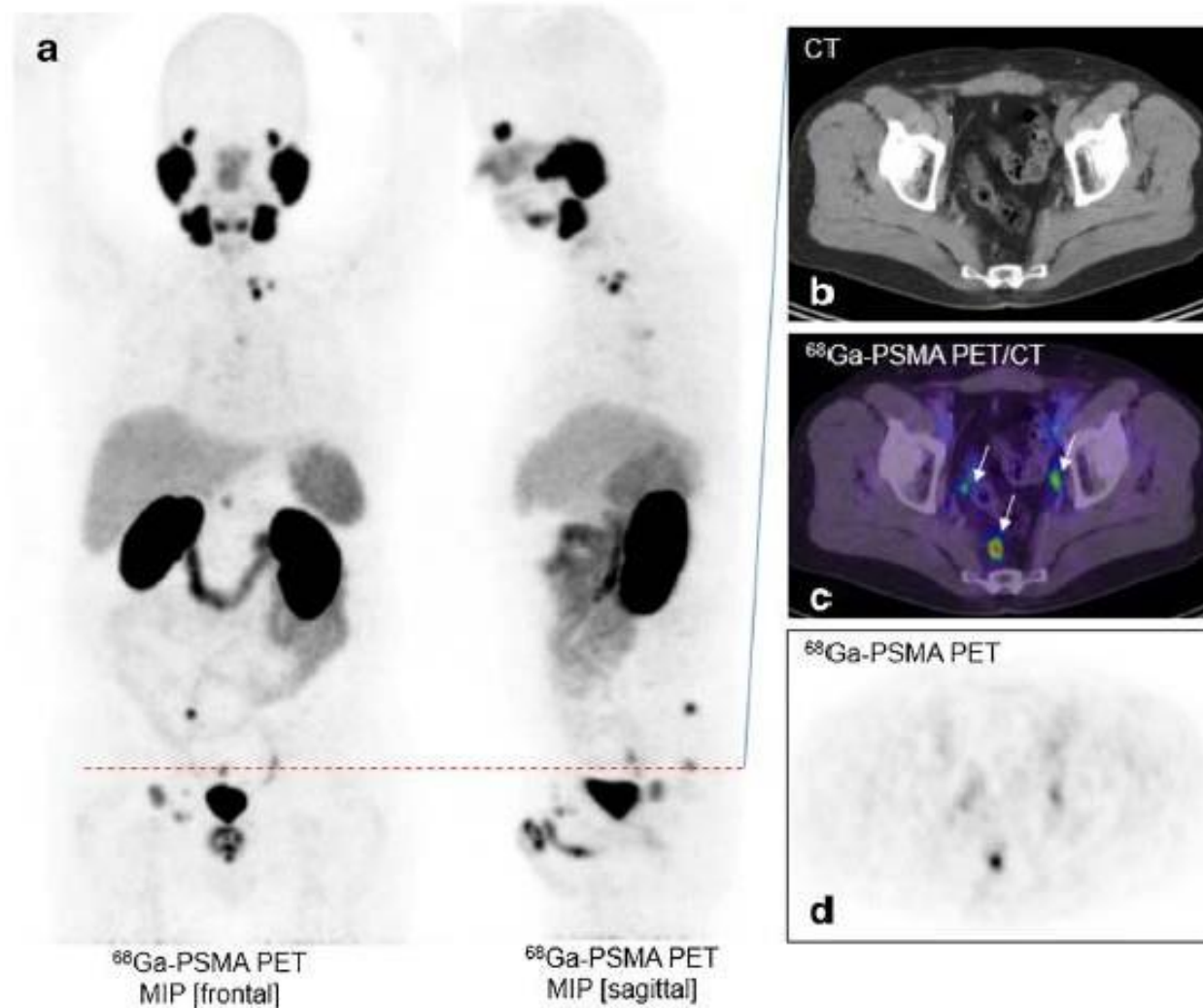


^{68}Ga –PSMA PET-CT detects metastasis in “not enlarged radiological” lymph nodes



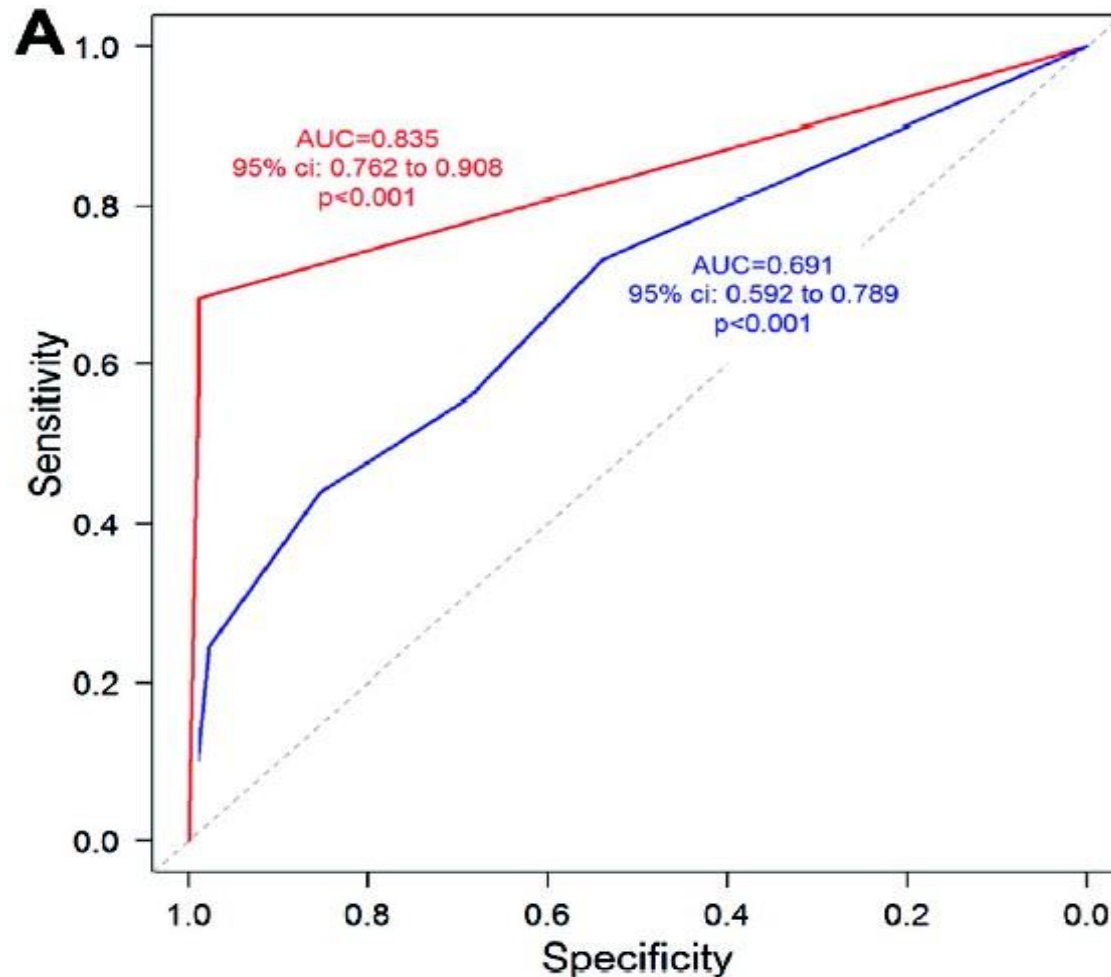
PSMA vs C. T

Detection of lymph node metastasis

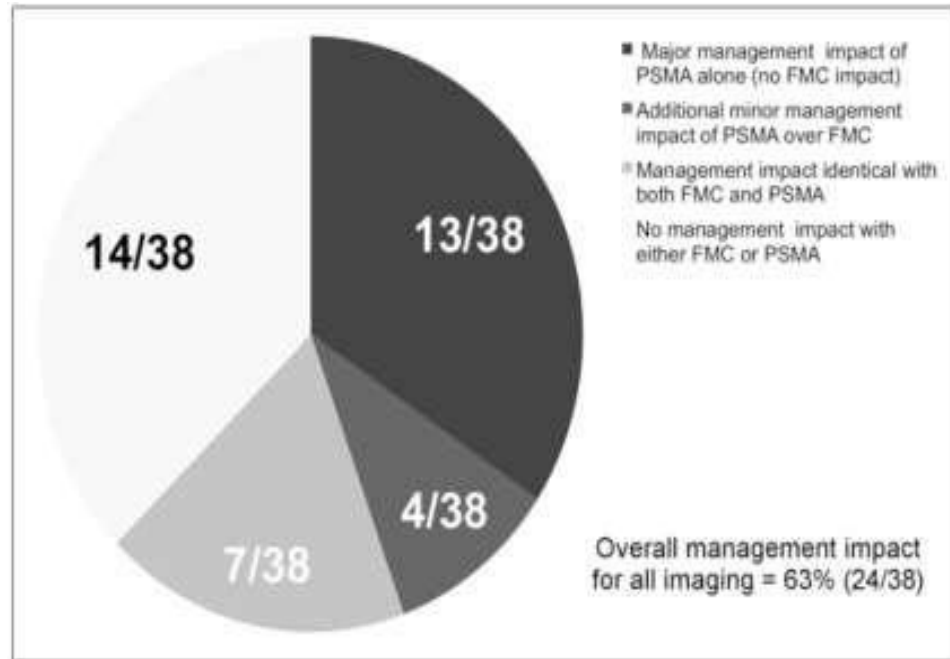


Lymph nodes staging in initial diagnosis of prostate cancer

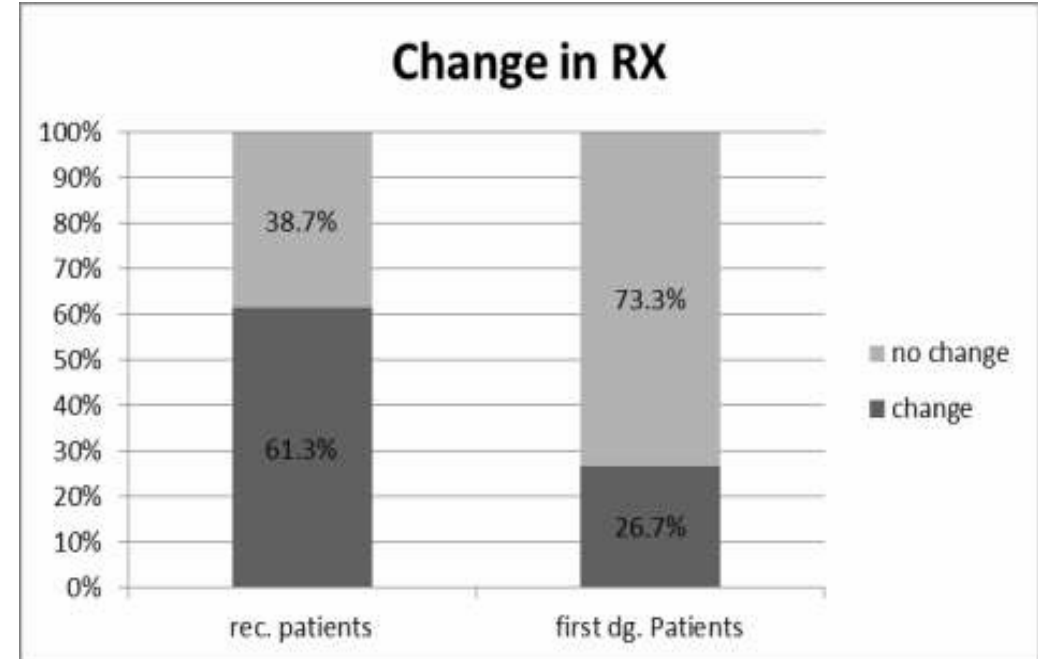
- 130 patients
- Comparison of **PSMA** with morphological imaging (**CT** and **MRI**)



PSMA PET and clinical therapy changes



Morigi JNM 2016



Sterzing EJNM 2016

- However, these therapy changes increase the PFS and OS? What about adverse events linked to largest/boosted irradiated regions?

PSMA PET/CT: Diagnostic Sensitivity

248
patients

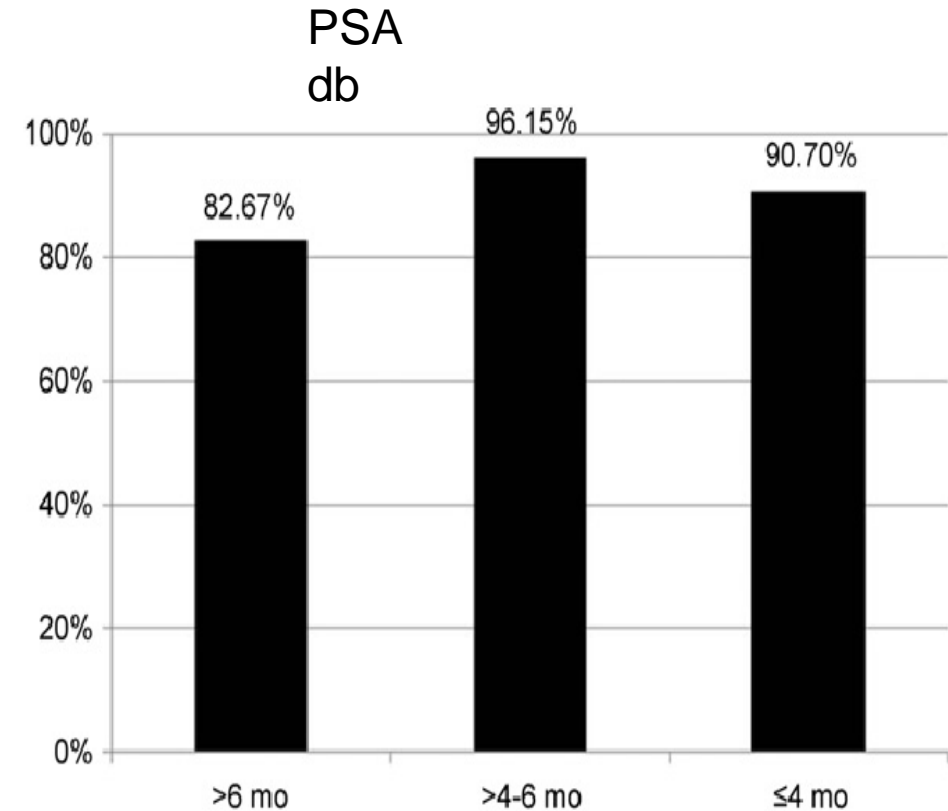
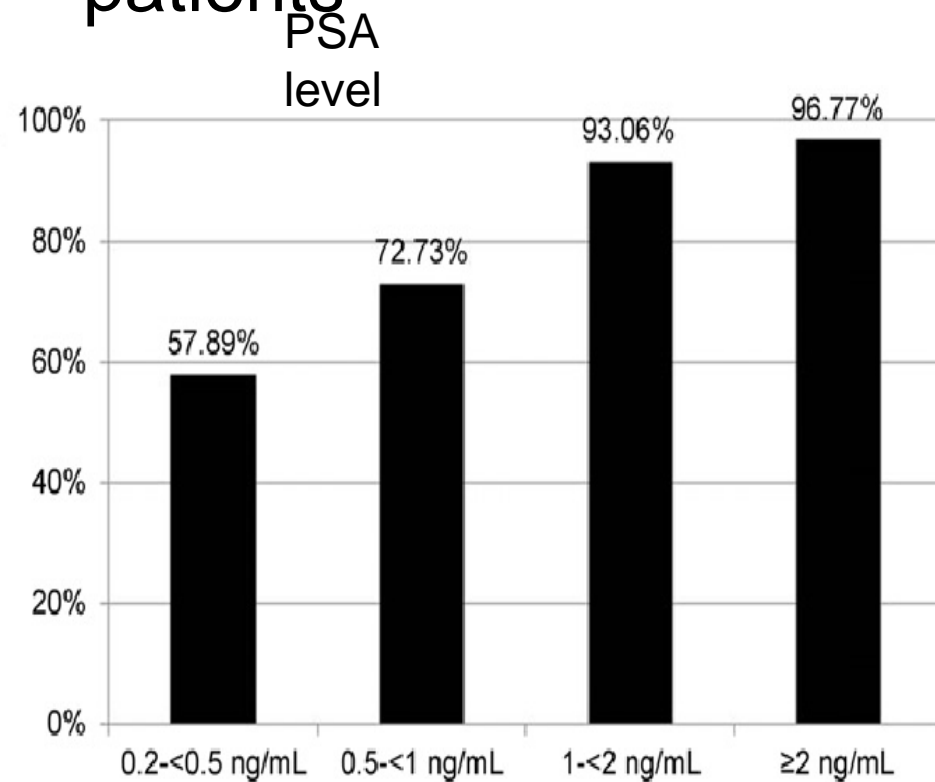
TABLE 2
Different Regions Involved by Recurrent PC in ^{68}Ga -PSMA
Ligand PET/CT

Region	No. of patients
Local recurrence	87 (35.1)
Lymph node metastases	
Abdominopelvic	130 (52.4)
Supradiaphragmatic	13 (5.2)
Bone metastases	89 (35.9)
Other (e.g., lung, liver) metastases	13 (5.2)

Data in parentheses are percentages.

68GaPSMA PET/CT: Diagnostic Sensitivity

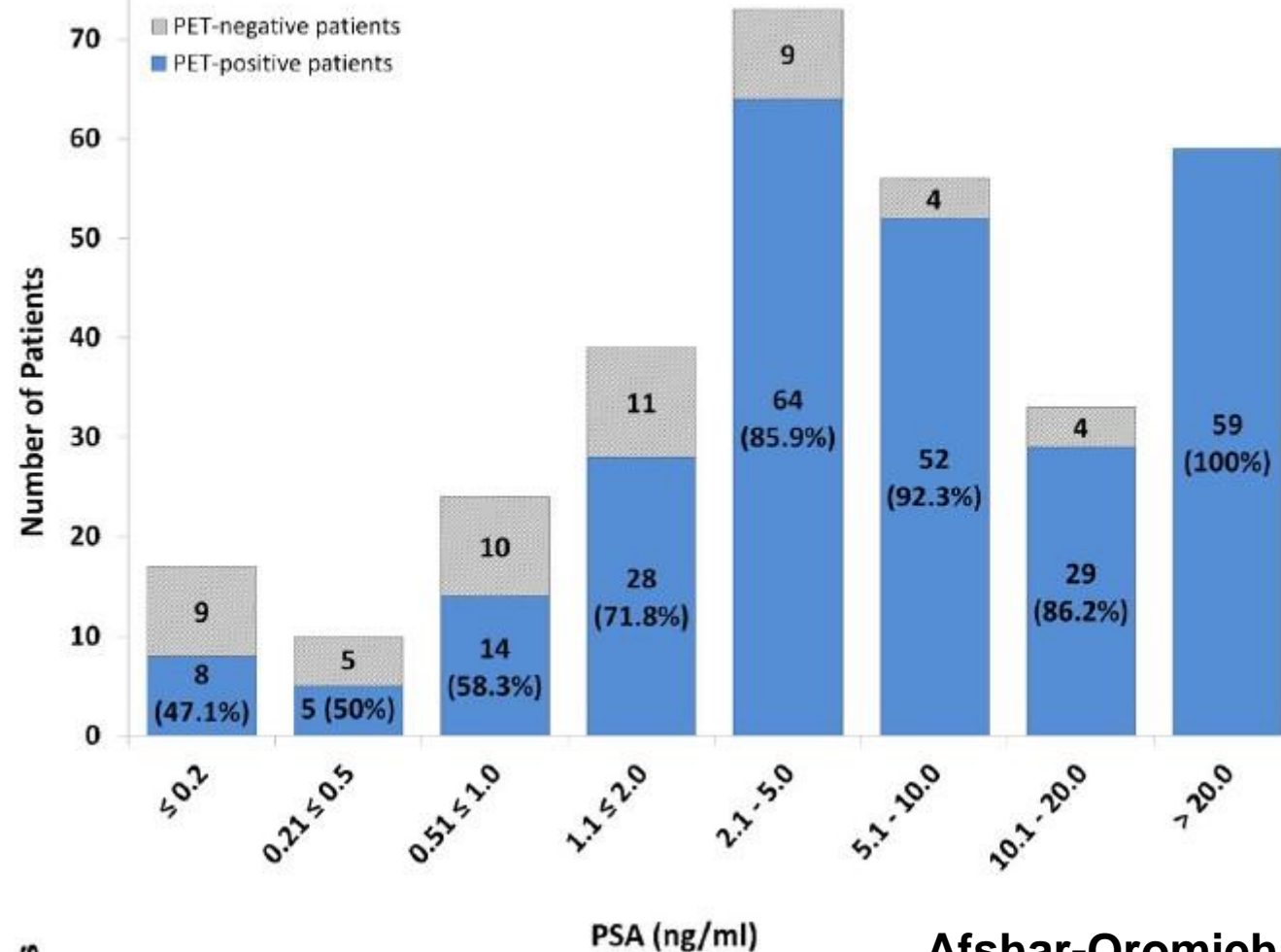
248
patients



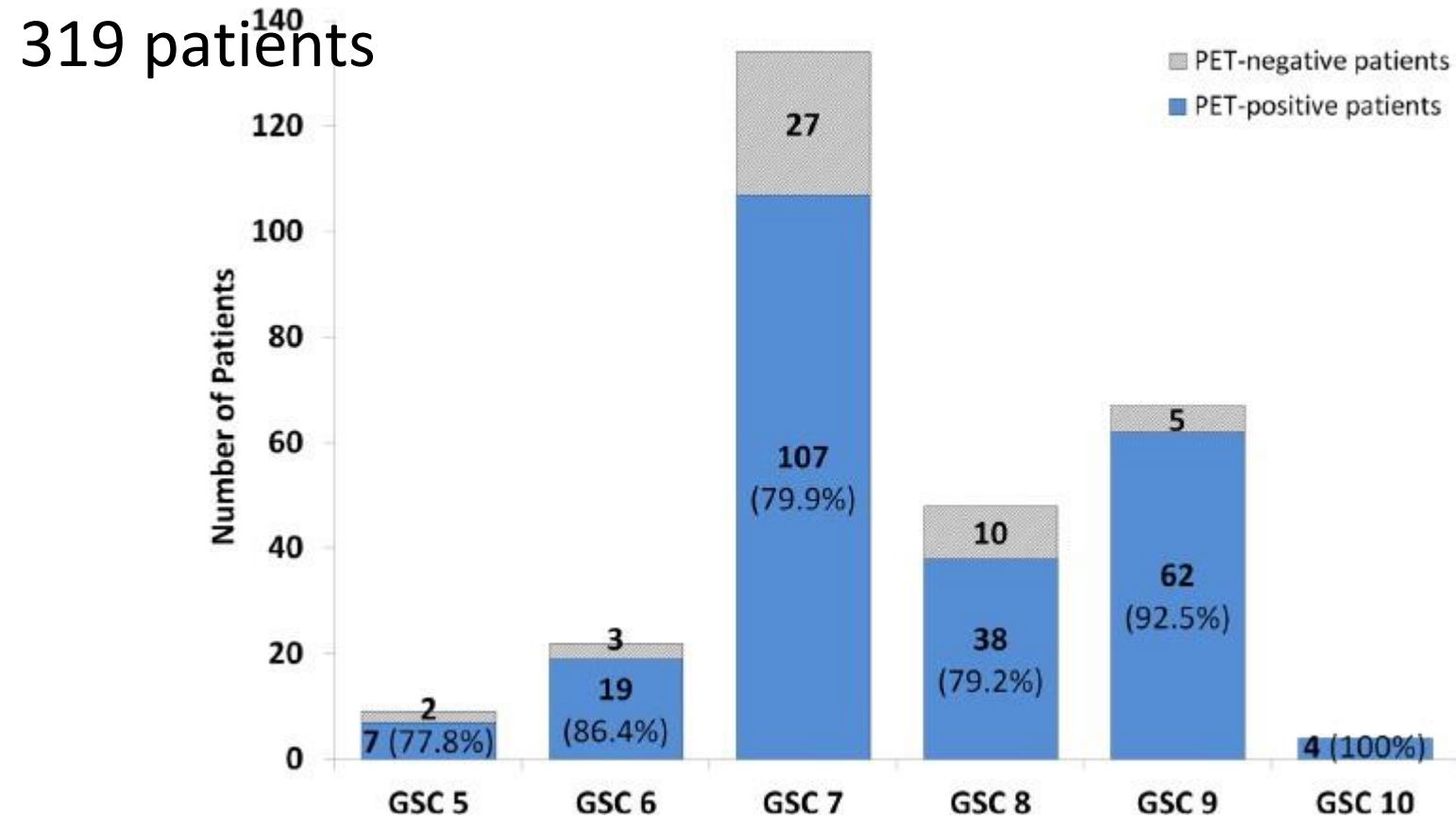
Positive PSMA PET-CT

PSA cut-off value?

319 patients



Positive PSMA PET-CT correlation with Gleason score?



Sensitivity of 68Ga PSMA PET/CT and biochemical recurrence

Systematic review and meta-analysis of 10 studies, 1309 patients

PSA

level:

- 42% for PSA < 0.2 ng/ml,
- 55% for PSA 0.2–0.99 ng/ml
- 75% for PSA 1.00– 1.99 ng/ml
- 95% for PSA > 2.00 ng/ml

dt:

- 64% for PSAdt >6mo
- 92% for PSAdt <6mo

Sensitivity is NOT accuracy

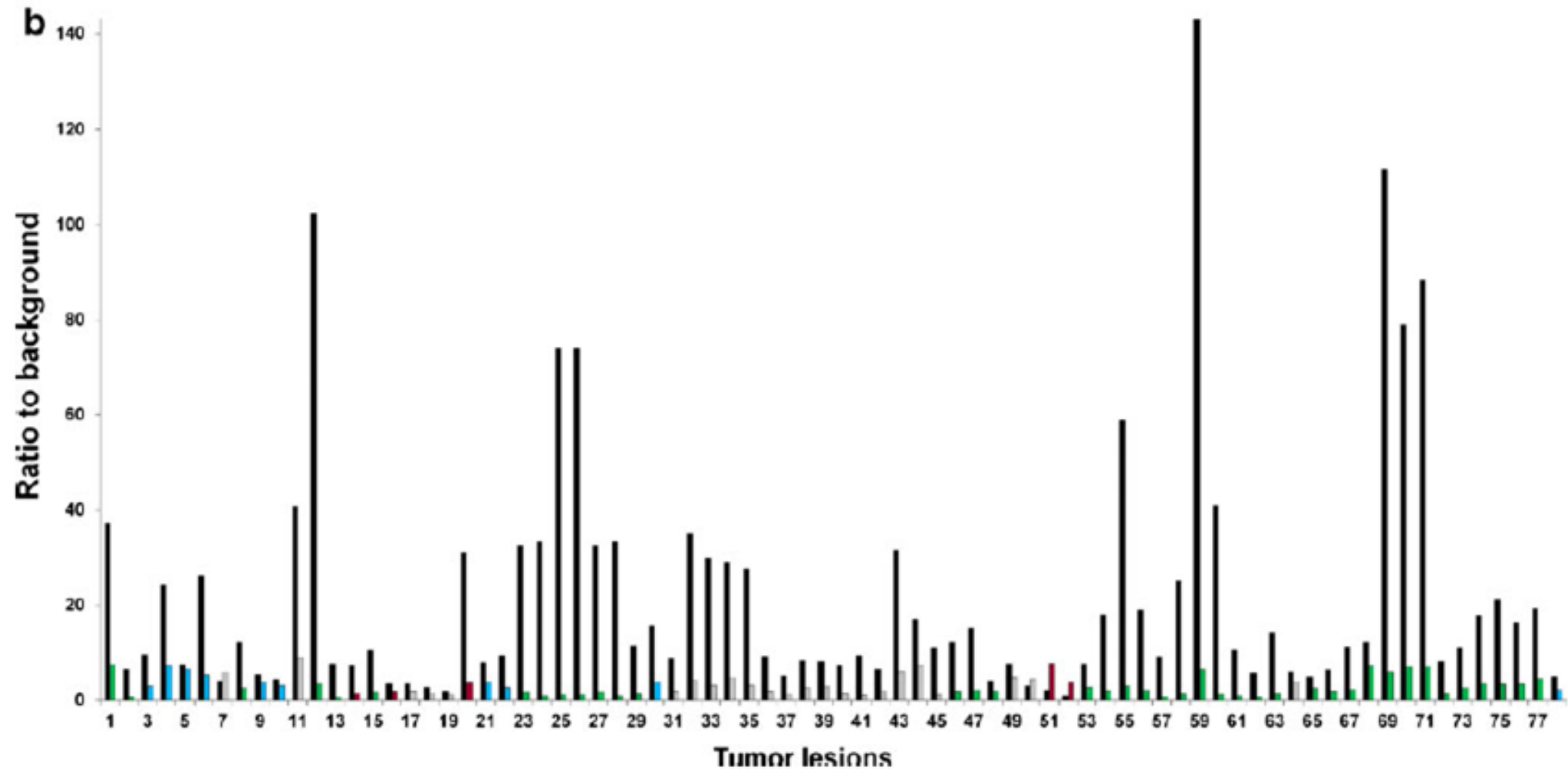
P S M A vs C T detection of metastasis

TABLE 4
Malignant Lesions Exclusively Identified in ⁶⁸Ga-PSMA PET or CT

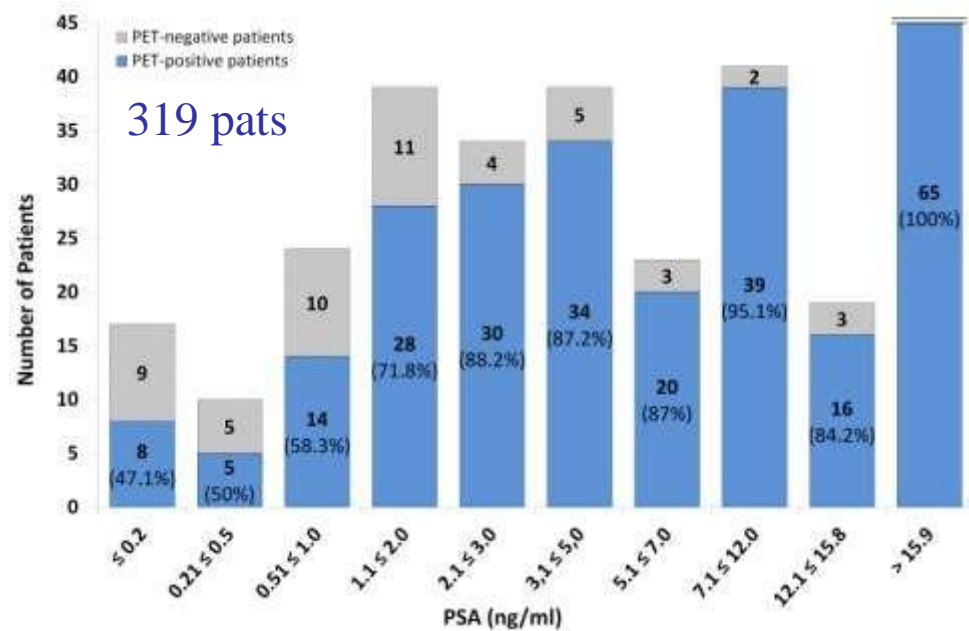
Region/combination of regions	No. of patients with positive findings exclusively demonstrated in ⁶⁸ Ga-PSMA		No. of patients with additional involved regions exclusively demonstrated in ⁶⁸ Ga-PSMA	
	PET	CT	PET	CT
LR only	18		11	
LN metastases only	31	1	17	2
Bone metastases only	9	1	24	7
LR + LN metastases	7		2	
LR + bone metastases	6		1	
LN + bone metastases	4		5	
LR + LN + bone metastases	1			
Other (e.g., lung, liver metastases)	5	1	1	17
Total	81 (32.7%)	3 (1.2%)	61 (24.6%)	17 (6.9%)

^{68}Ga -PSMA

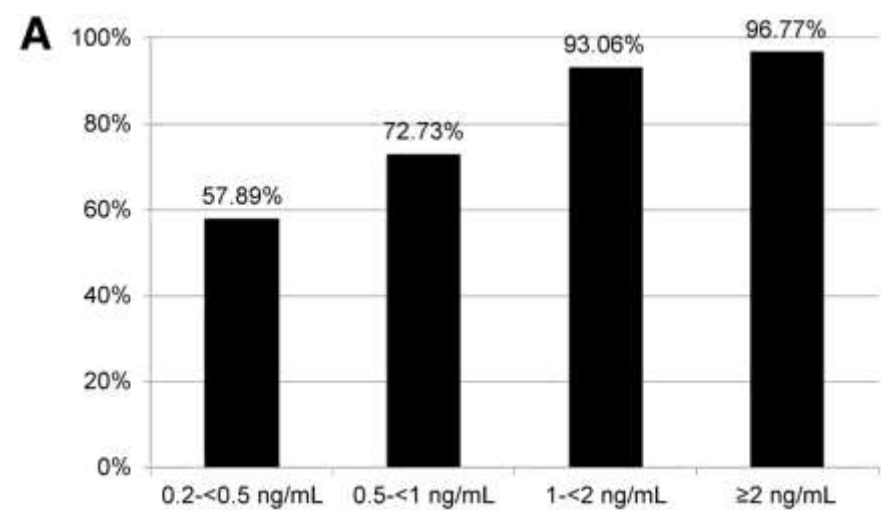
- PSMA vs Choline PET



The difference in sensitivity between PSMA PET and Choline PET could have huge consequences for therapy “salvage” planning



Afshar-Oromieh et al. EJNMMI 2015



Eiber JNM 2015

TABLE 2
Detection Rates of ¹⁸F-Fluoromethylcholine and ⁶⁸Ga-PSMA

PSA level (ng/mL)	¹⁸ F-fluoromethylcholine	⁶⁸ Ga-PSMA	<i>P</i>
<0.5	12.5% (2/16)	50% (8/16)	0.03
0.5–2.0	36% (5/14)	71% (10/14)	0.02
>2.0	63% (5/8)	88% (7/8)	0.18
Total	32% (12/38)	66% (25/38)	<0.001

Morigi JNM 2016

^{68}Ga -PSMA

- PSMA vs Choline PET



Choline PET



PSMA PET

Courtesy Images from
Prof U. Haberkorn

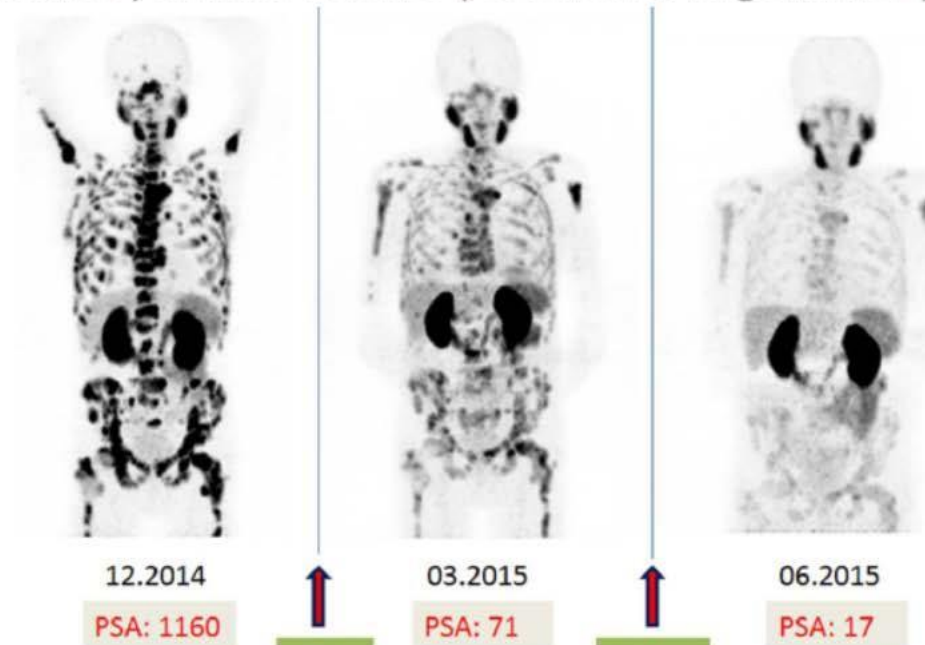
Theranostics

- **The same target for diagnostics as for therapy:**
 - Theragnostics is a treatment strategy that combines therapeutics with diagnostics and includes a wide range of subjects, including personalized medicine, pharmacogenomics, and molecular imaging to develop efficient new targeted therapies with adequate benefit/risk to patients and a better molecular understanding of how to optimize drug selection.
 - Furthermore, theragnostics aims to monitor the response to the treatment, to increase drug efficacy and safety. In addition, theragnostics could eliminate the unnecessary treatment of patients for whom therapy is not appropriate, resulting in significant drug cost savings for the healthcare system.

Therapeutic response and side effects of repeated radioligand therapy with ^{177}Lu -PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer

Hojjat Ahmadzadehfar¹, Elisabeth Eppard¹, Stefan Kürpig¹, Rolf Fimmers², Anna Yordanova¹, Carl Diedrich Schlenkhoff¹, Florian Gärtner¹, Sebastian Rogenhofer³, Markus Essler¹

Therapie-Regime:
24 Pat. 6 GBq



Cas clinique

Homme de 80 ans. Prostatectomie radicale à l'âge de 68 ans pour un adenocarcinome T2N0, Gleason 8 (4+4)
Déprivation hormonale avec taux de testostérone très faibles.

PSA au nadir <0.01 ng/ml.

En 7 ans post prostatectomie, augmentation du PSA allant de <0.01 ng/ml en janvier 2016, 0.12 en avril 2016 et 0.22 ng/ml en juin 2016.

En votre opinion:

A-L'augmentation du PSA est un erreur du laboratoire, il ne faut rien faire

B-Faire une RNM pour exclure une récurrence locorégionale.

Cas clinique

Homme de 80 ans. Prostatectomie radicale à l'âge de 68 ans pour un adenocarcinome T2N0, Gleason 8 (4+4)
Déprivation hormonale avec taux de testostérone très faibles.

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La RNM de juillet 2016 ne montre pas de lésion suggestive de récidence locorégionale. Taux de PSA fin juillet 2016: 0.26 ng/ml

En votre opinion:

A- On doit proposer réaliser une scintigraphie osseuse

B- On doit proposer réaliser une tomographie par émission de positons.

Cas clinique

Homme de 80 ans. Prostatectomie radicale à l'âge de 68 ans pour un adénocarcinome T2N0, Gleason 8 (4+4)
Déprivation hormonale avec taux de testostérone très faibles.

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La RNM de juillet 2016 ne montre pas de lésion suggestive de récurrence locorégionale. Taux de PSA fin juillet 2016: 0.26 ng/ml.

Avec ce niveau de PSA, la sensibilité de la scintigraphie osseuse (Corps entier + SPECT/CT double champs Centré sur le tronc) est très faible donc cet examen n'est pas recommandé à cet stade.

En votre opinion:

A- Il est préférable réaliser une tomographie par émission de positons au Ga68 PSMA

B- L'examen de choix est une tomographie par émission de positons à la Choline (F18 ou C11).

Cas clinique

Homme de 80 ans. Prostatectomie radicale à l'âge de 68 ans pour un adenocarcinome T2N0, Gleason 8 (4+4)
Déprivation hormonale avec taux de testostérone très faibles.

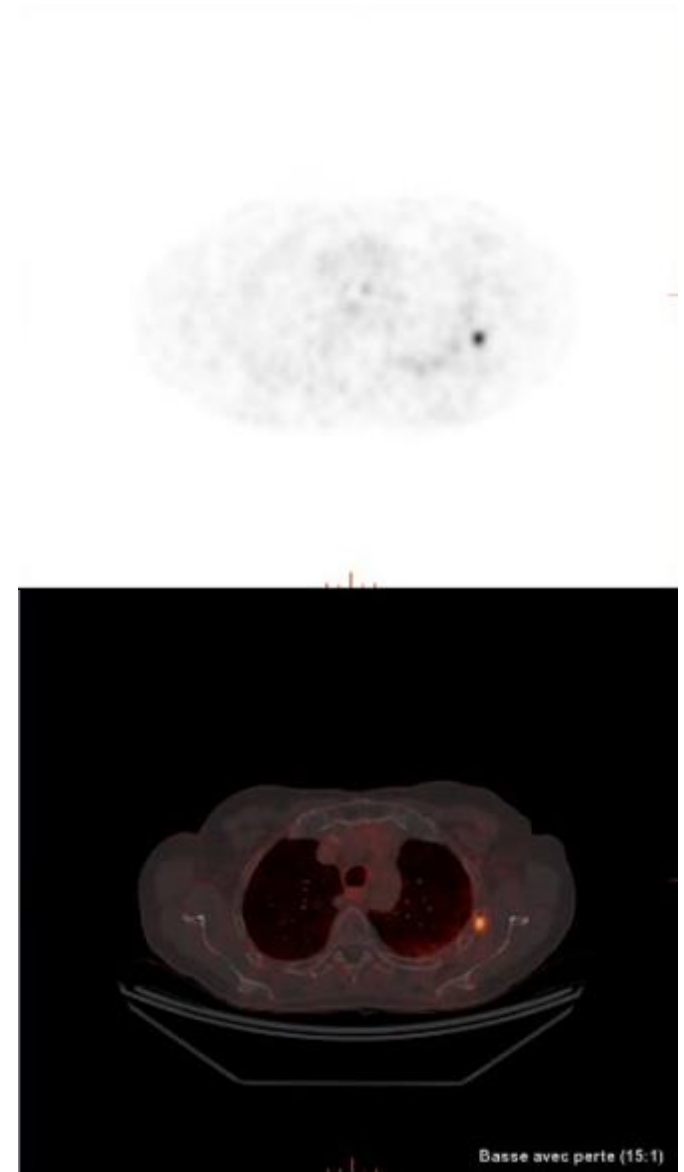
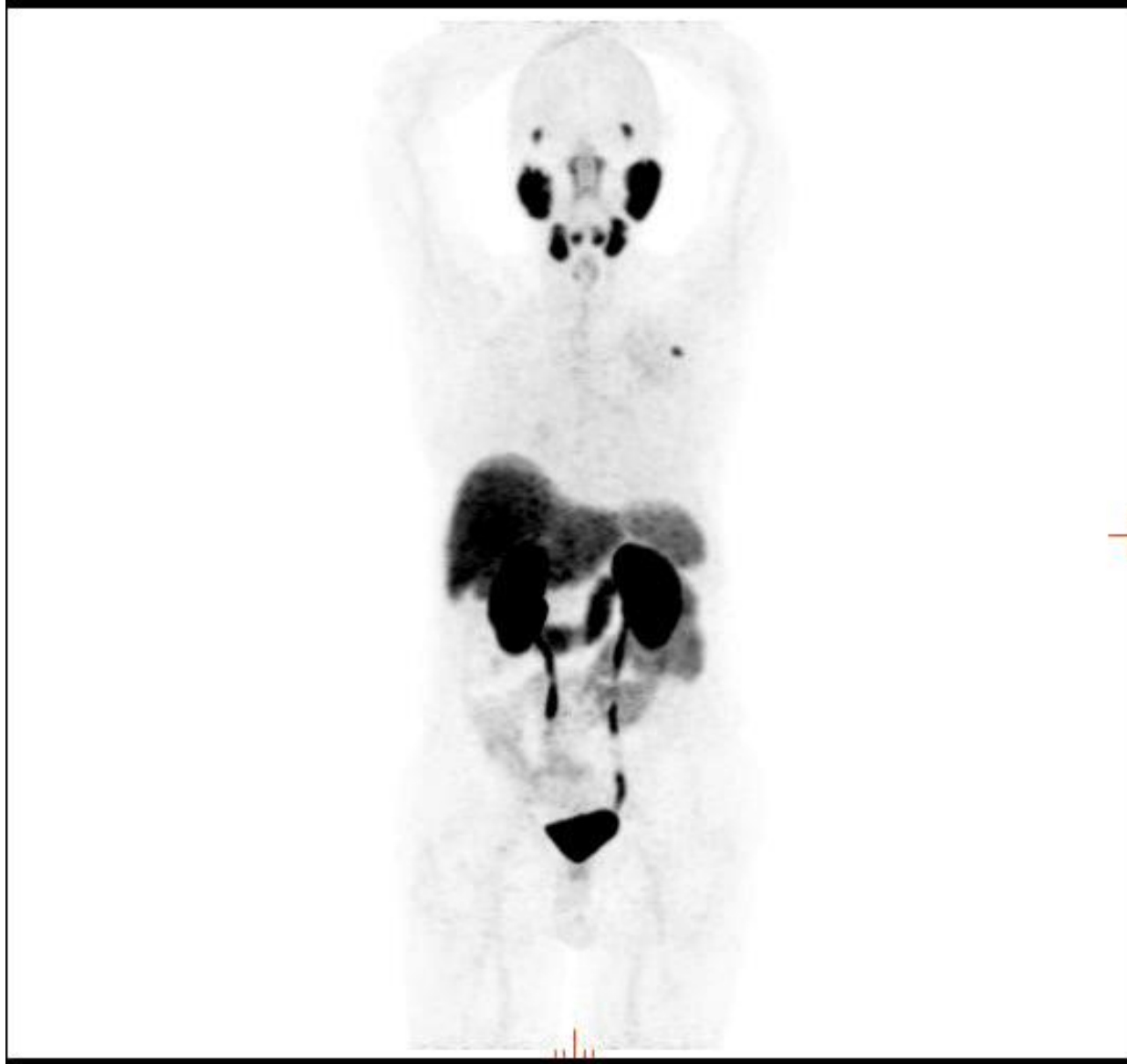
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La RNM de juillet 2016 ne montre pas de lésion suggestive de récidence locorégionale. Taux de PSA fin juillet 2016: 0.26 ng/ml.

Le Ga68 PSMA –PET/CT a montré une meilleure sensibilité pour la détection des lésions à faible taux de PSMA (>0.2 ng/ml) que la Choline PET/CT

Cas clinique



Cas clinique

Homme de 80 ans. Prostatectomie radicale à l'âge de 68 ans pour un adenocarcinome T2N0, Gleason 8 (4+4)
Déprivation hormonale avec taux de testostérone très faibles.

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En 7 ans post prostatectomie, augmentation du PSA allant de <0.01 ng/ml en janvier 2016, 0.12 en avril 2016 et 0.22 ng/ml en juin 2016.

Traitement par radiothérapie de la lésion costale avec réduction du PSA à niveaux indetectables <0.01 ng/ml 6 mois après traitement.

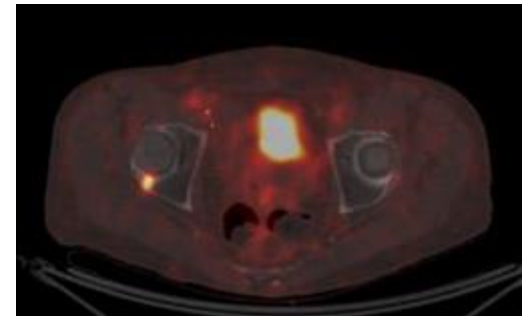
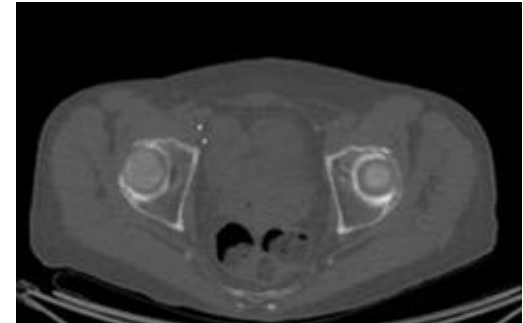
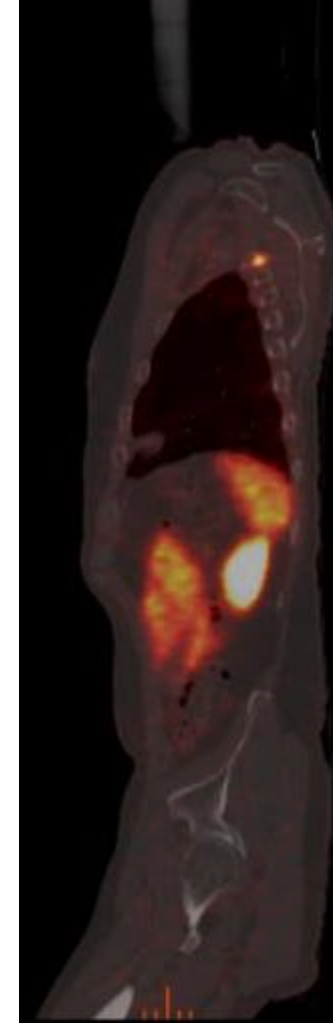
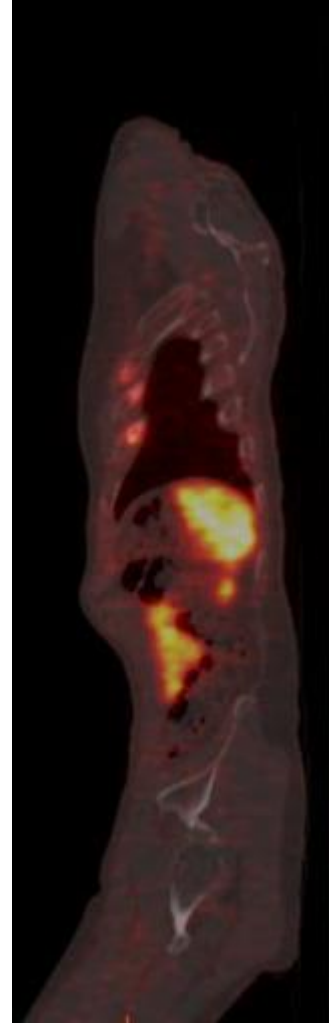
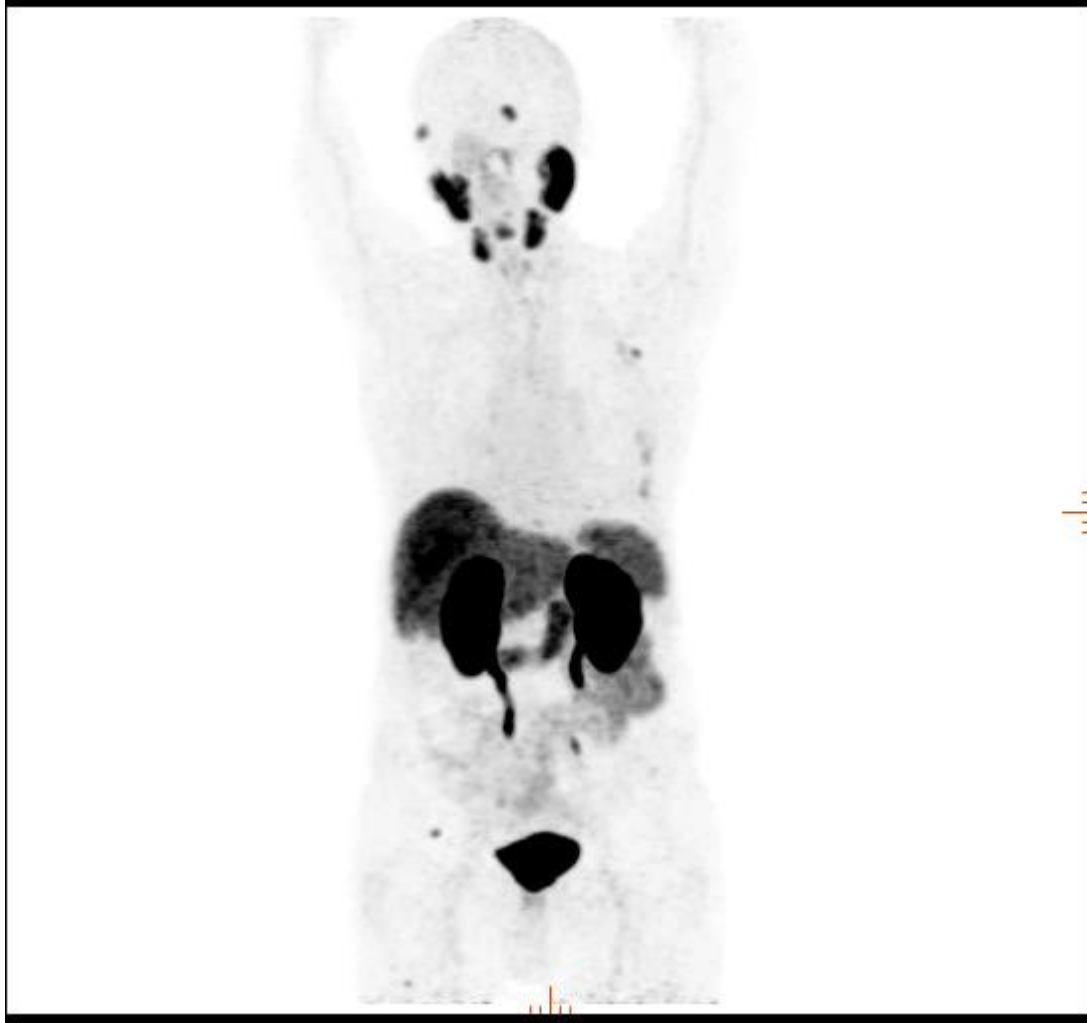
Ré augmentation du PSA en octobre 2018, à 0.12 ng/ml puis à 0.22 en février 2019.

En votre opinion

A- On pourrait proposer réaliser une nouvelle tomographie par émission de positons au Ga68 PSMA

B- On devrait attendre un taux de PSA >2 ng/ml.

Cas clinique



Cas clinique

Homme de 80 ans. Prostatectomie radicale à l'âge de 68 ans pour un adénocarcinome T2N0, Gleason 8 (4+4)
Déprivation hormonale avec taux de testostérone très faibles.

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Ré augmentation du PSA en octobre 2018, à 0.12 ng/ml puis à 0.22 en février 2019.

Ga68 PSMA PET CT de juin 2019:

- Persistance d'une lésion avide pour le PSMA sur la 4^e côte gauche. Lésion viable?
- Fractures costales avides pour le PSMA!! Sur les arcs costaux gauches 7^e, 8^e et 9^e.
- Lésion avide pour le PSMA sur le sourcil postérieur de l'acetabulum de la coxofémorale droite.

En votre opinion

A- Vu qu'il n'y a pas de réaction ostéoblastique sur les images CT, la lésion avide pour le PSMA sur le sourcil postérieur de l'acetabulum de la coxofémorale droite est un faux positif

B- La lésion avide pour le PSMA sur le sourcil postérieur de l'acetabulum de la coxofémorale droite est une nouvelle lésion métastatique et un nouveau traitement local pourrait être proposé.

Take-Home messages

- PSMA « is not only ^{68}Ga -PSMA », ^{99}Tc -PSMA could be an alternative if PET technology is not easily available
- ^{68}Ga PSMA PET/CT is not « yet » recommended in initial staging in patient with moderate/High risk prostate cancer
- ^{68}Ga PSMA PET/CT is a promising tool in therapy planning including, lymph node Radiotherapy planning
- ^{68}Ga PSMA PET/CT is Highly recommended in case of biochemical recurrence order to plan salvage radiotherapy/surgery or multimodality treatments
- ^{68}Ga PSMA PET/CT is a major tool in the field of theragnostic's, if it possible to propose to patients, clinical trials using ^{177}Lu PSMA or ^{225}Ac -PSMA

MERCI POUR VOTRE ATTENTION