Overview of prostate cancer imaging

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Disclosures

- Clovis Oncology: grant support
- Philips: grant support
- Novartis/AAA: trial participation
- ITM: consultant
- Curium: consultant
- RayzeBio: consultant
- Blue Earth Diagnostics: advisory board
- Ipsen: advisory board

1. Review of CT/MRI
2. Introduce PSMA PET
3. Review the impact of PSMA

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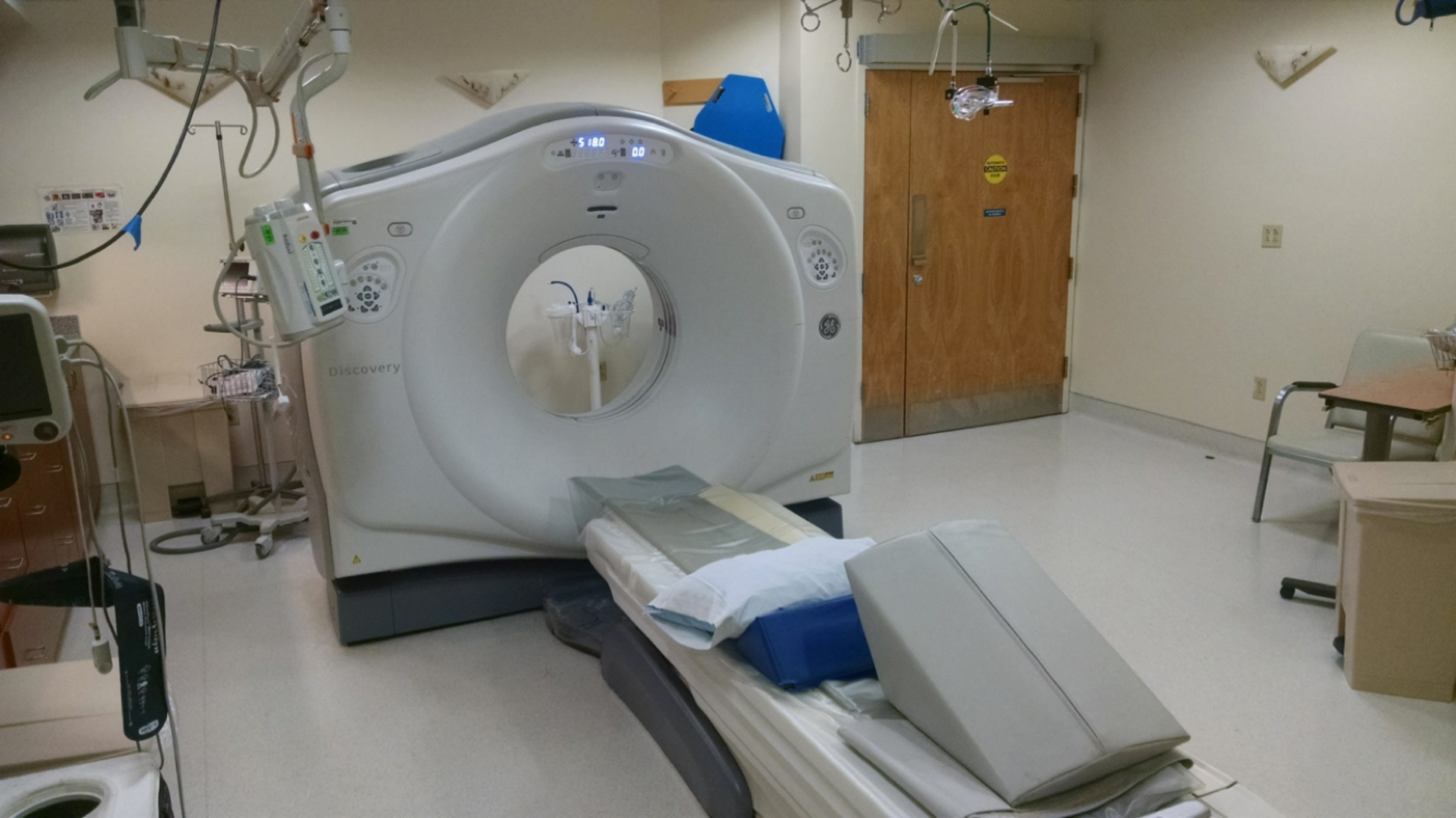
Discovery

CT: computed tomography

- Is a measurement of density
- Intravenous contrast helps in evaluation of solid organs and soft tissues
- Also allows for imaging of bone and lung

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Bone windows

CT: computed tomography

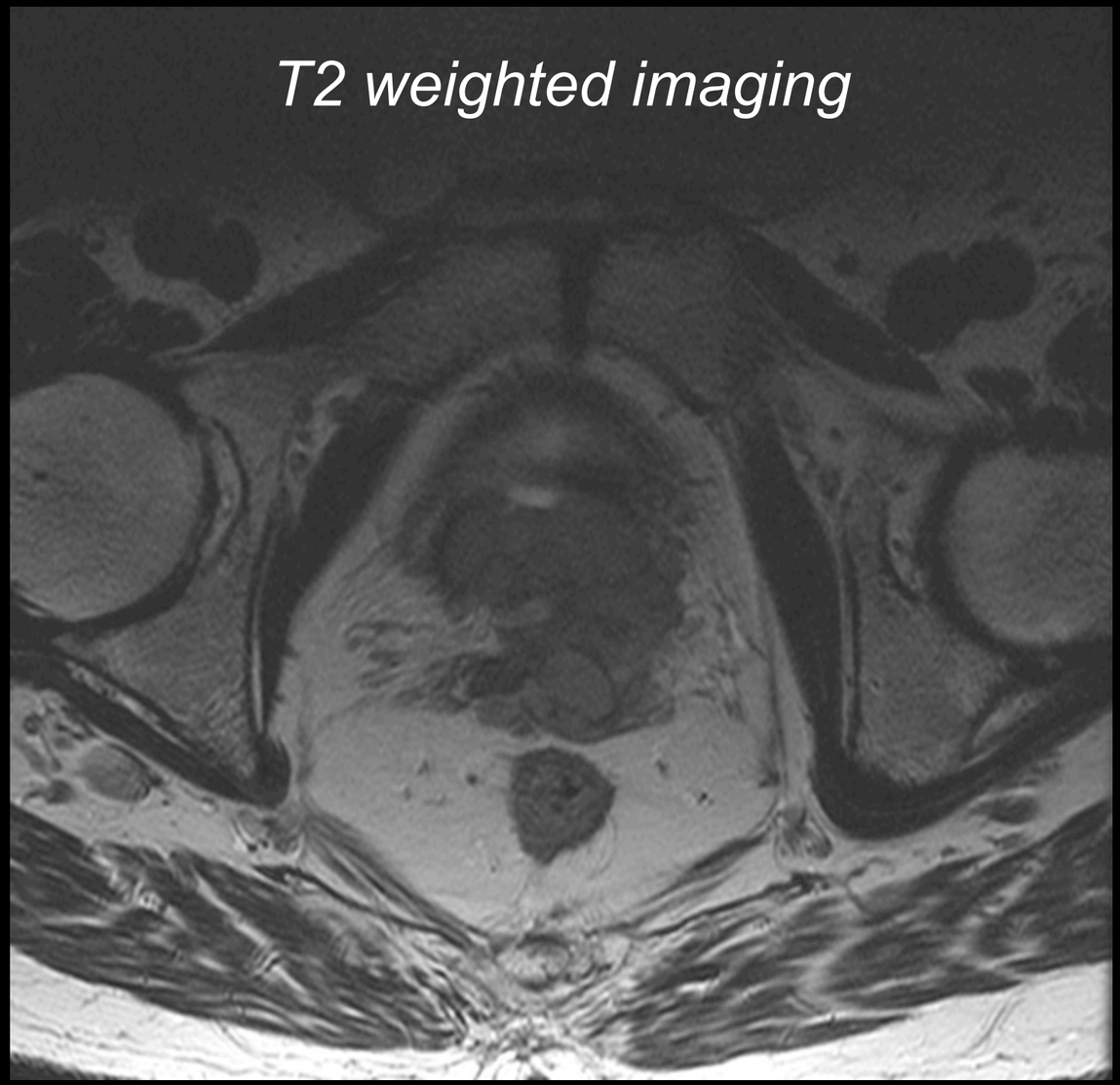
- Is a measurement of density
- Intravenous contrast helps in evaluation of solid organs and soft tissues
- Also allows for imaging of bone and lung

Lung windows


SIGNA
PET/MR

MRI: magnetic resonance imaging

- Standard for evaluation of primary tumor
- Use in biochemical recurrence is more heterogeneous



MRI: magnetic resonance imaging

- Standard for evaluation of primary tumor
- Use in biochemical recurrence is more heterogeneous

T1 post-contrast imaging

MRI: magnetic resonance imaging

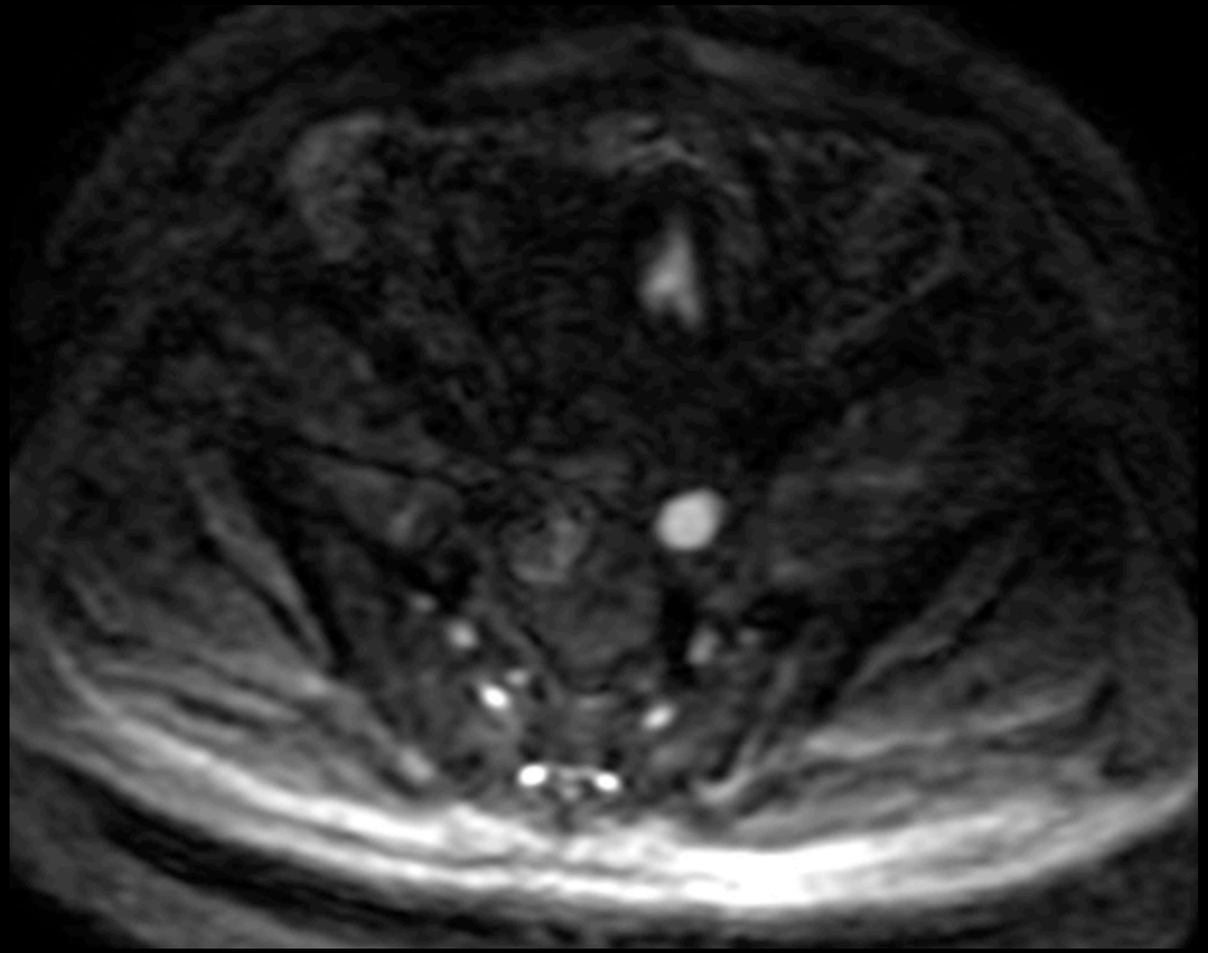
- Standard for evaluation of primary tumor
- Use in biochemical recurrence is more heterogeneous

Dynamic contrast enhanced imaging

MRI: magnetic resonance imaging

- Standard for evaluation of primary tumor
- Use in biochemical recurrence is more heterogeneous

Diffusion weighted imaging



Bone scintigraphy

- Study takes four hours
  - three hours of uptake after injection
- Can perform an associated SPECT/CT, but increases time and costs
- Limited by low sensitivity and specificity

“Conventional Imaging”

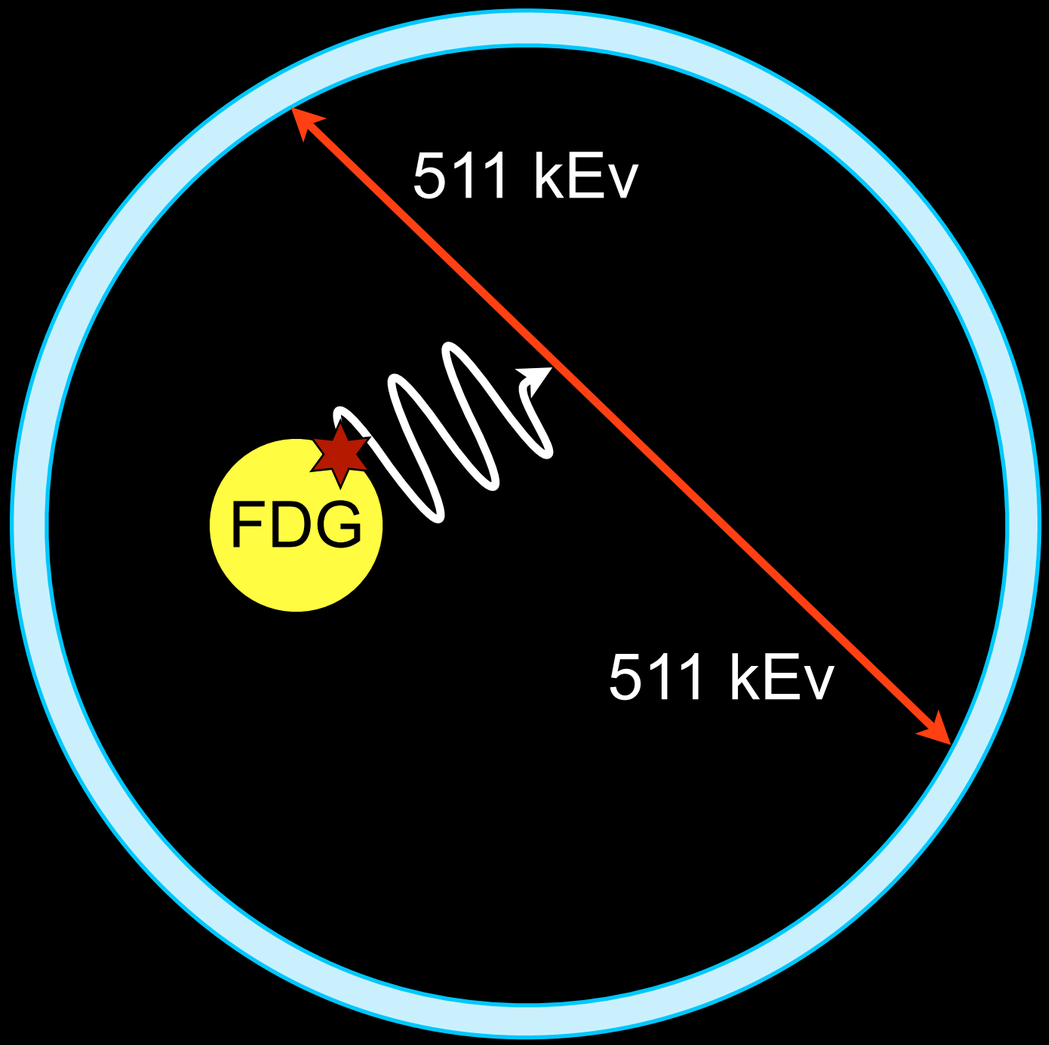
CT	MRI	Bone Scan
• Widely available • Fast, easy • Full coverage (chest/abdomen/ pelvis)	• Usually limited to imaging the pelvis • Uncomfortable (endorectal coil, long, loud, claustrophobic)	• Fast, easy • Cheap, no issues with reimbursement • In all existing guidelines and used in all trials

Overall, all have a low specificity


PHILIPS

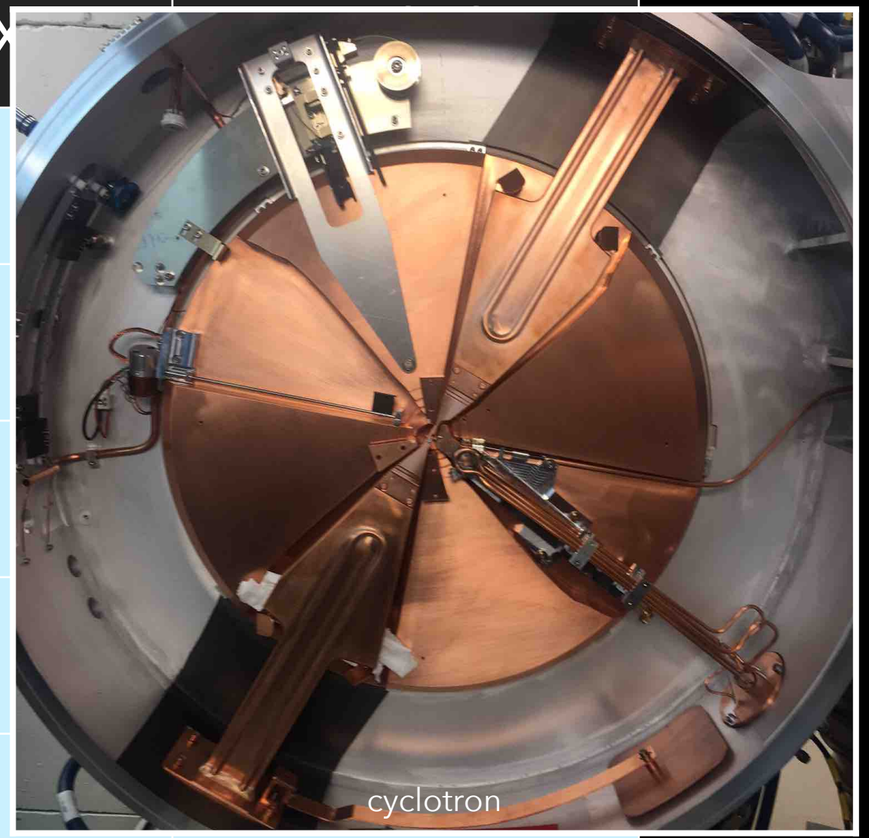
PET/CT

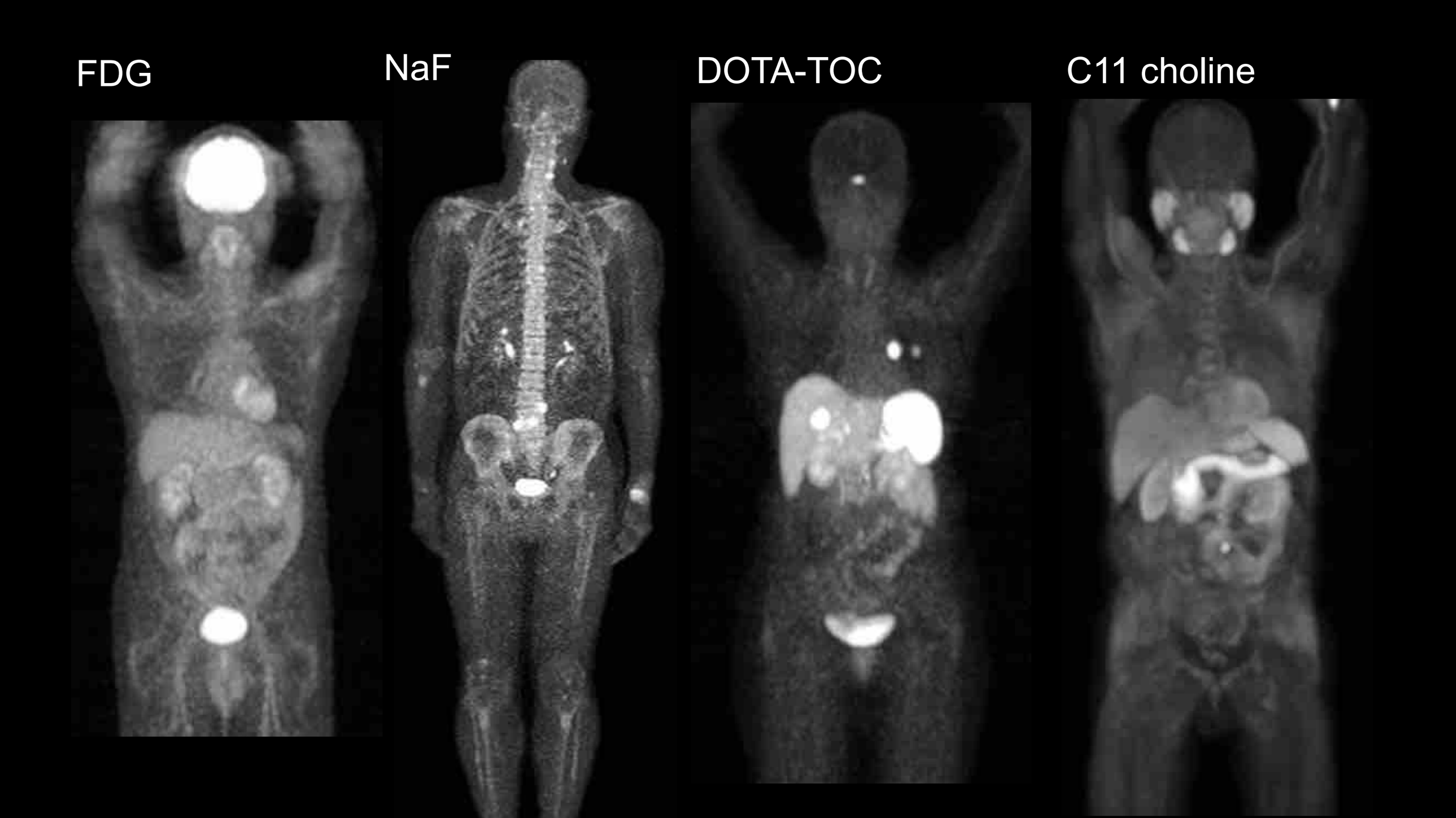
- Radiolabeled compound
  - typically 18F-FDG
  - also Ga68, C11, Cu64…
- Decays by releasing a positron
- Positron then travels a finite distance and decays into two photons
  - positron range of F18 is roughly 2 mm



PET/CT: various radioisotopes

Isotope	Emax	Rmax
Ga-68	1.9	8.2
O-15	1.7	7.3
N-13	1.2	5.1
C-11	0.97	4.1
F-18	0.64	2.4



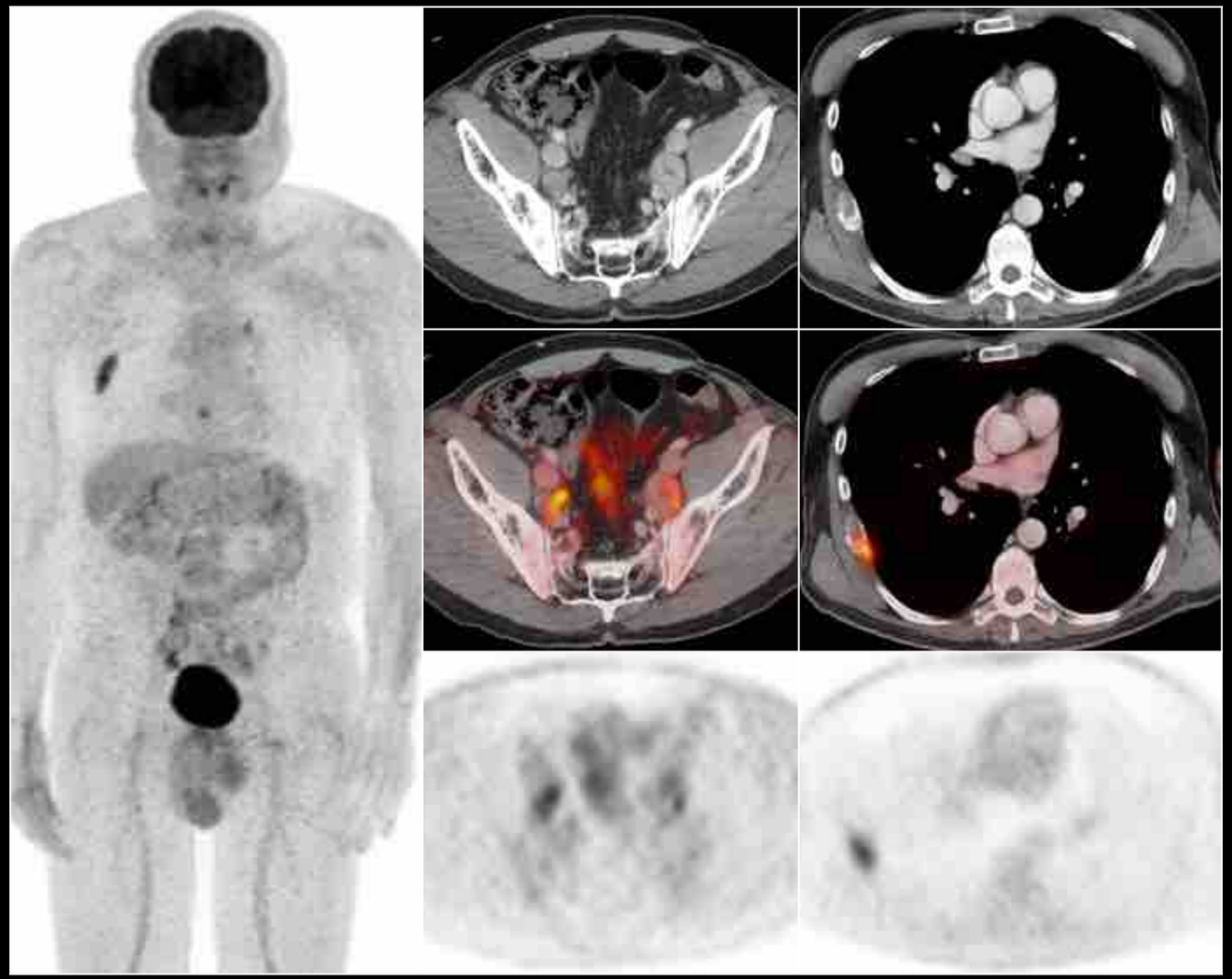

FDG
NaF
DOTA-TOC
C11 choline

NaF PET/CT

- Better spatial resolution
- High signal to background
- CT available for correlation
- Shorter time from injection to imaging
  - imaging is done 60 minutes after injection compared to three hours with bone scans

FDG PET/CT

- No value in detection
- Uptake is correlated with aggressiveness
- Infrequently used, and role is mainly in castrate resistant patients



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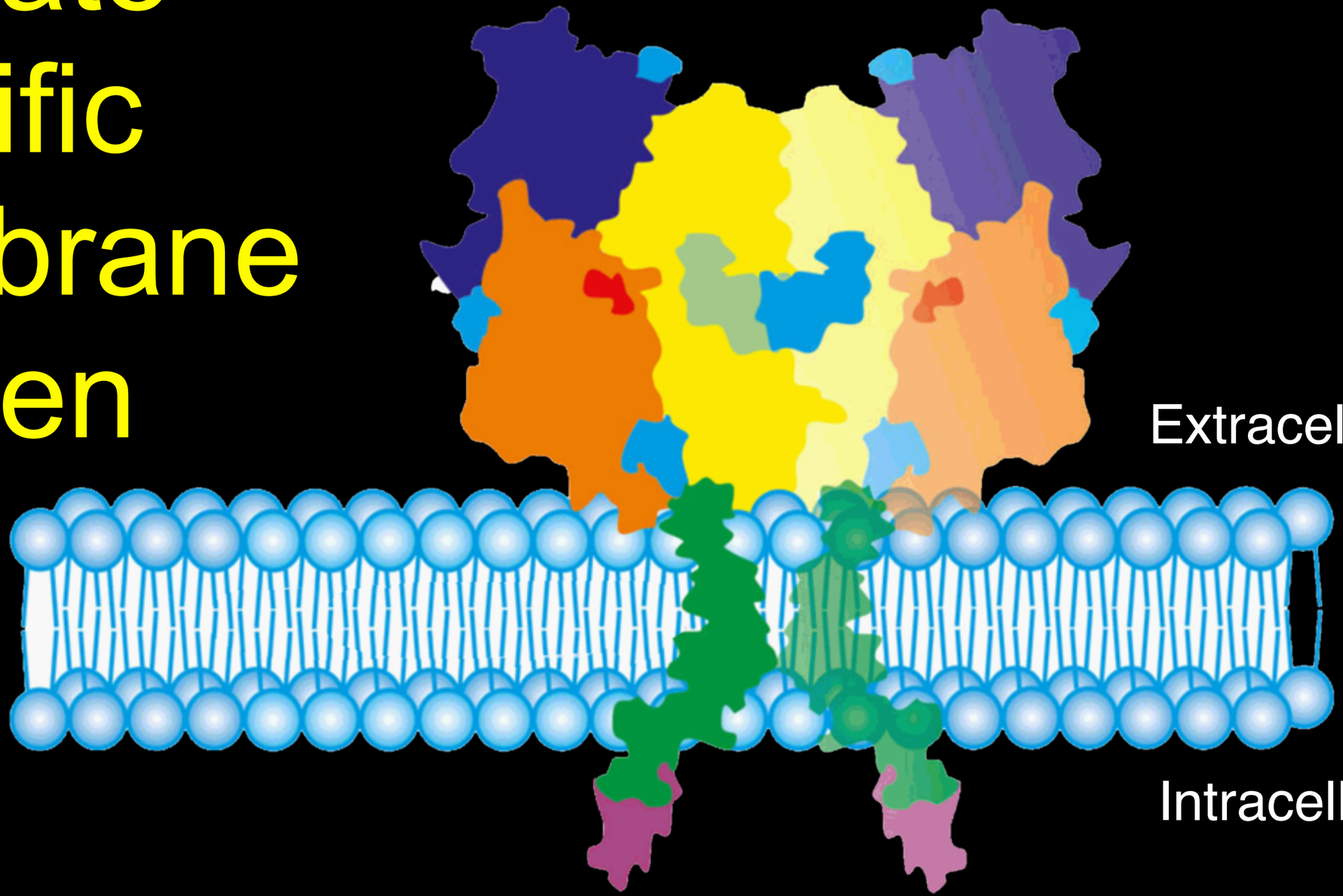
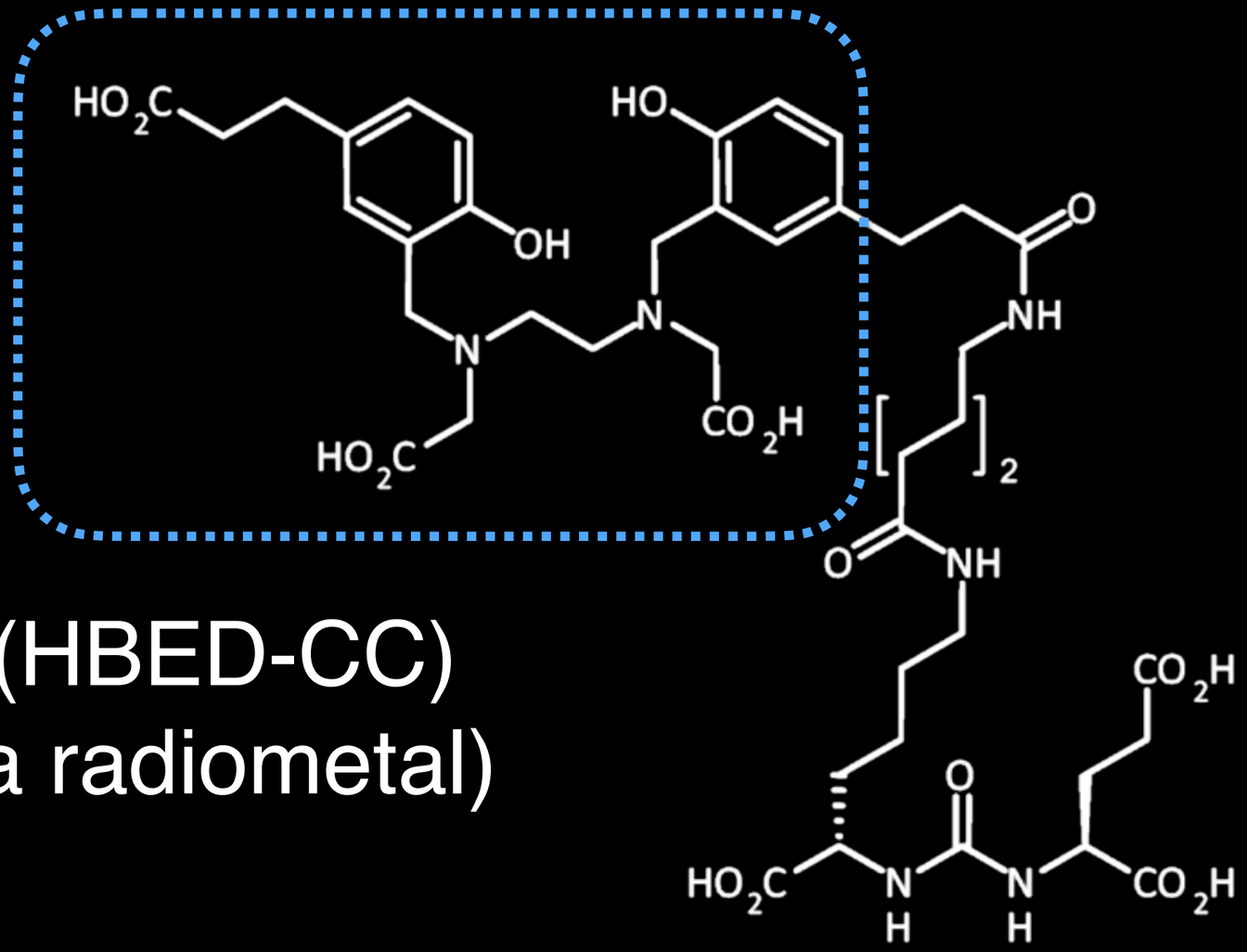
Prostate Specific Membrane Antigen

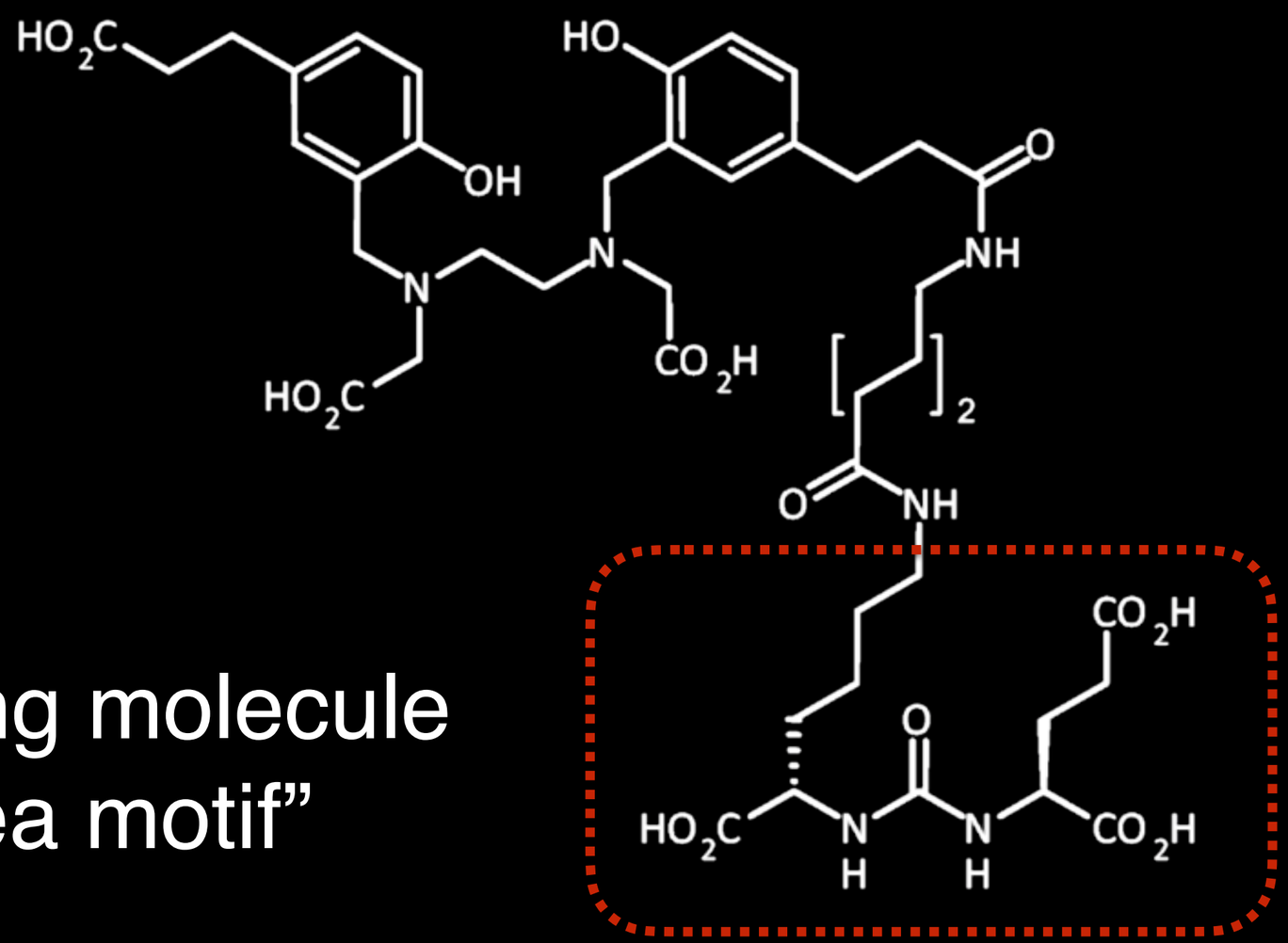


68Ga-PSMA-11



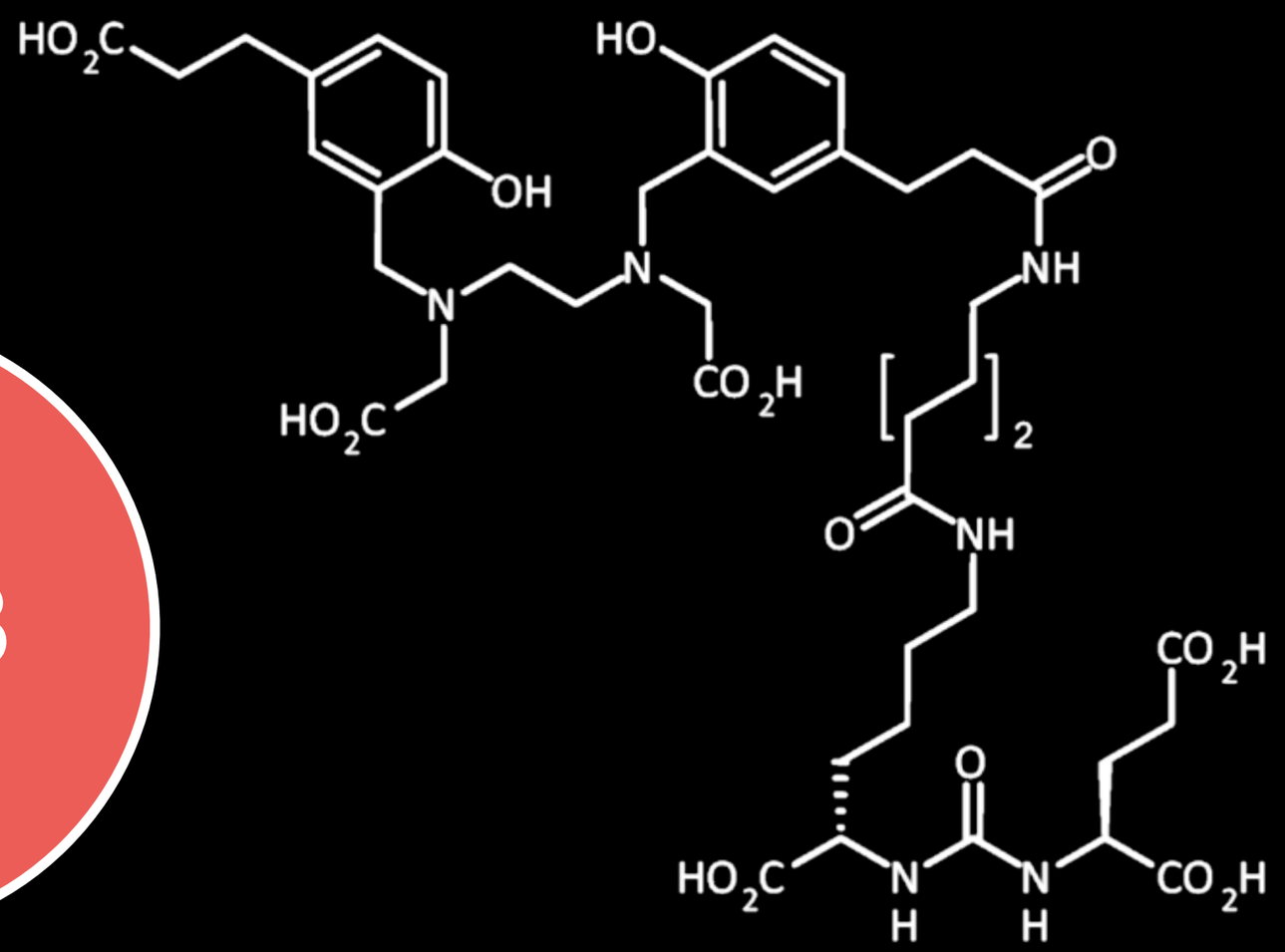
chelator (HBED-CC)
(binds to a radiometal)

68Ga-PSMA-11



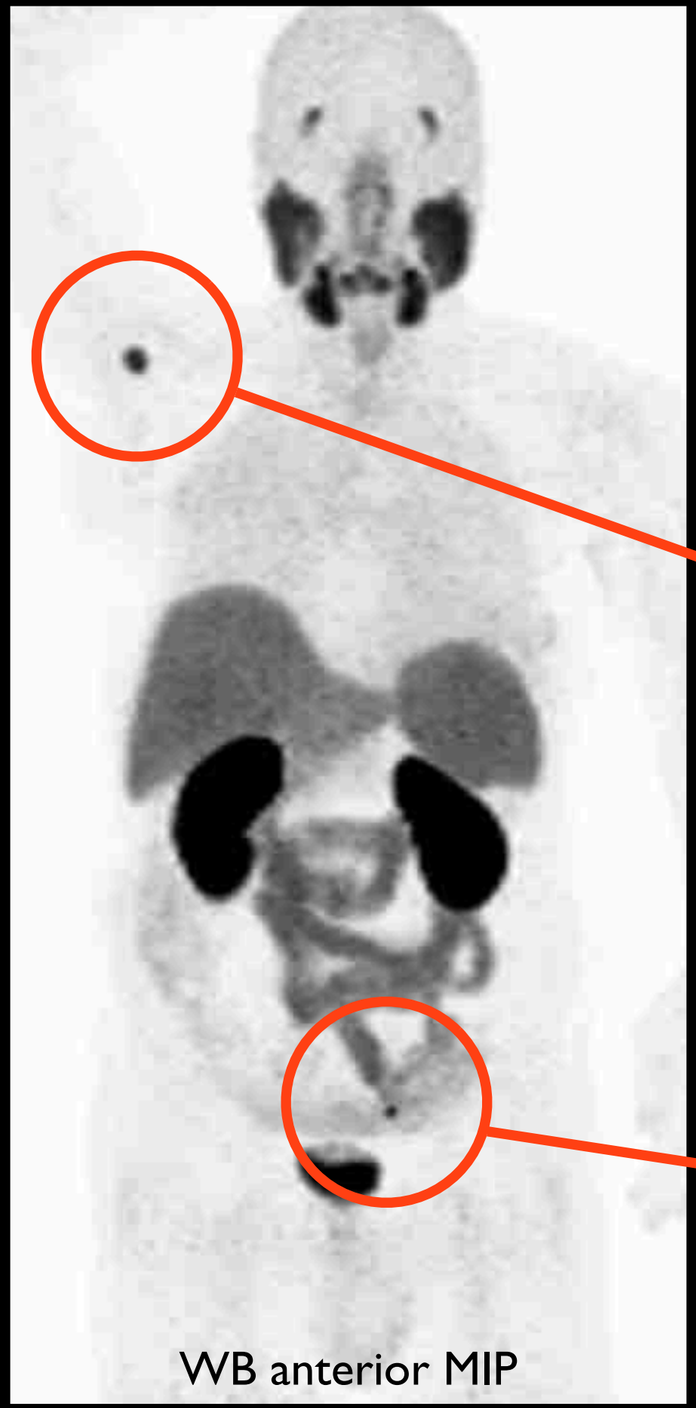
targeting molecule
“urea motif”

68Ga-PSMA-11

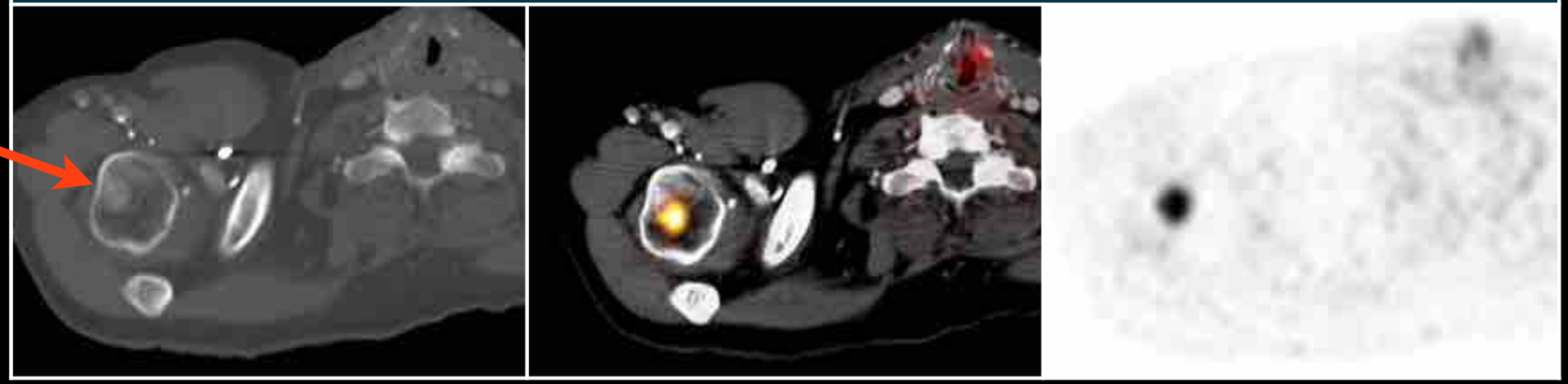


Ga-68

69 year old man status post RP
PSA = 0.67



Disease site 1: right humerus



Disease site 2: left internal iliac node

UCSF/UCLA BCR clinical data

- 635 patients in total, split between UCSF and UCLA
- Median PSA of 2.1
- Three blinc
  - Actually 9
- Composite
  - 223 patien validation
  - 93 with his
- PPV:
  - Composite endpoint: 0.92
  - Histopathology: 0.84

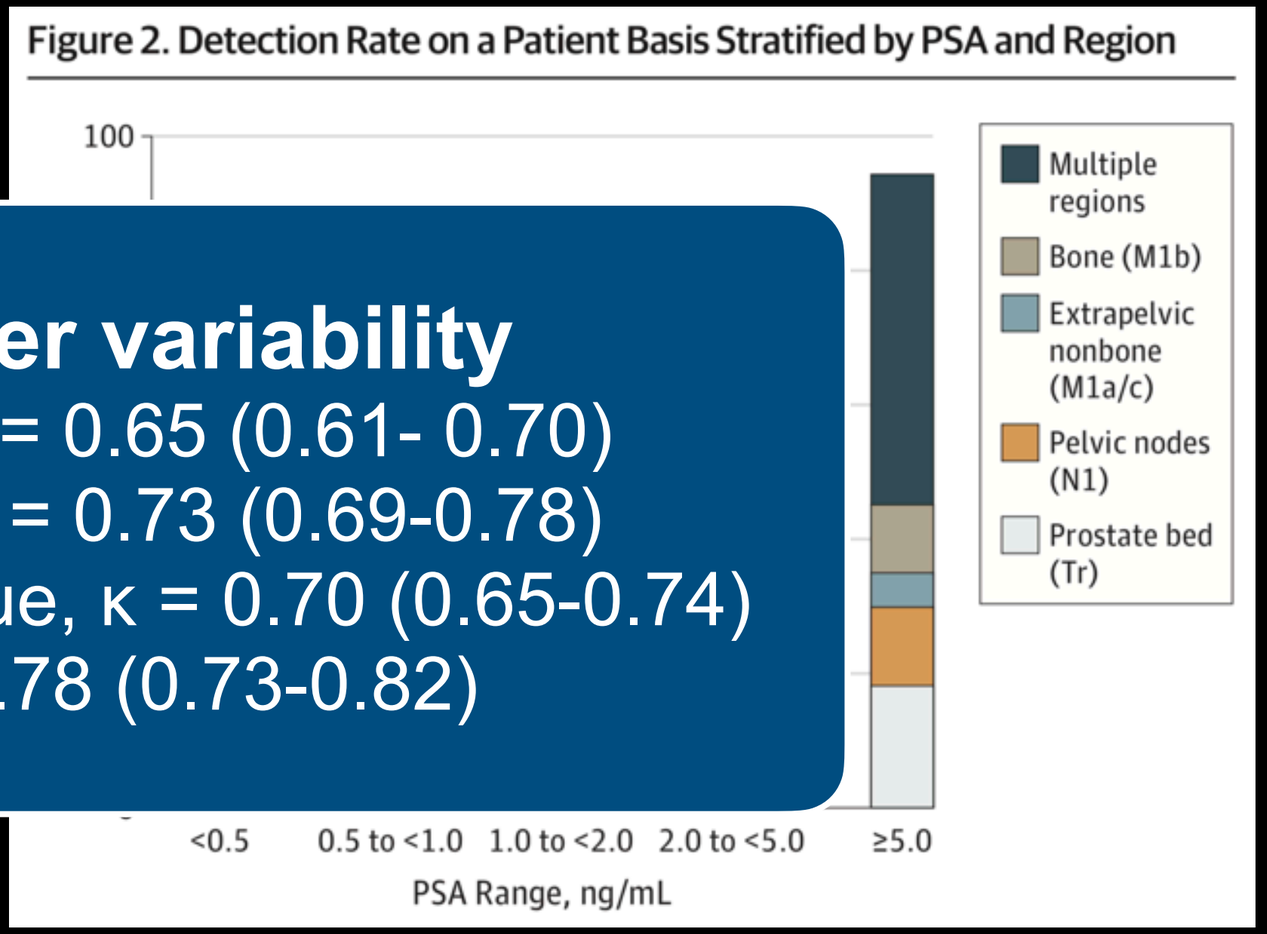
Inter-reader variability

prostate bed, κ = 0.65 (0.61- 0.70)

pelvic nodes, κ = 0.73 (0.69-0.78)

extrapelvic soft tissue, κ = 0.70 (0.65-0.74)

bone, κ = 0.78 (0.73-0.82)



Fendler, JAMA Oncology (2019)

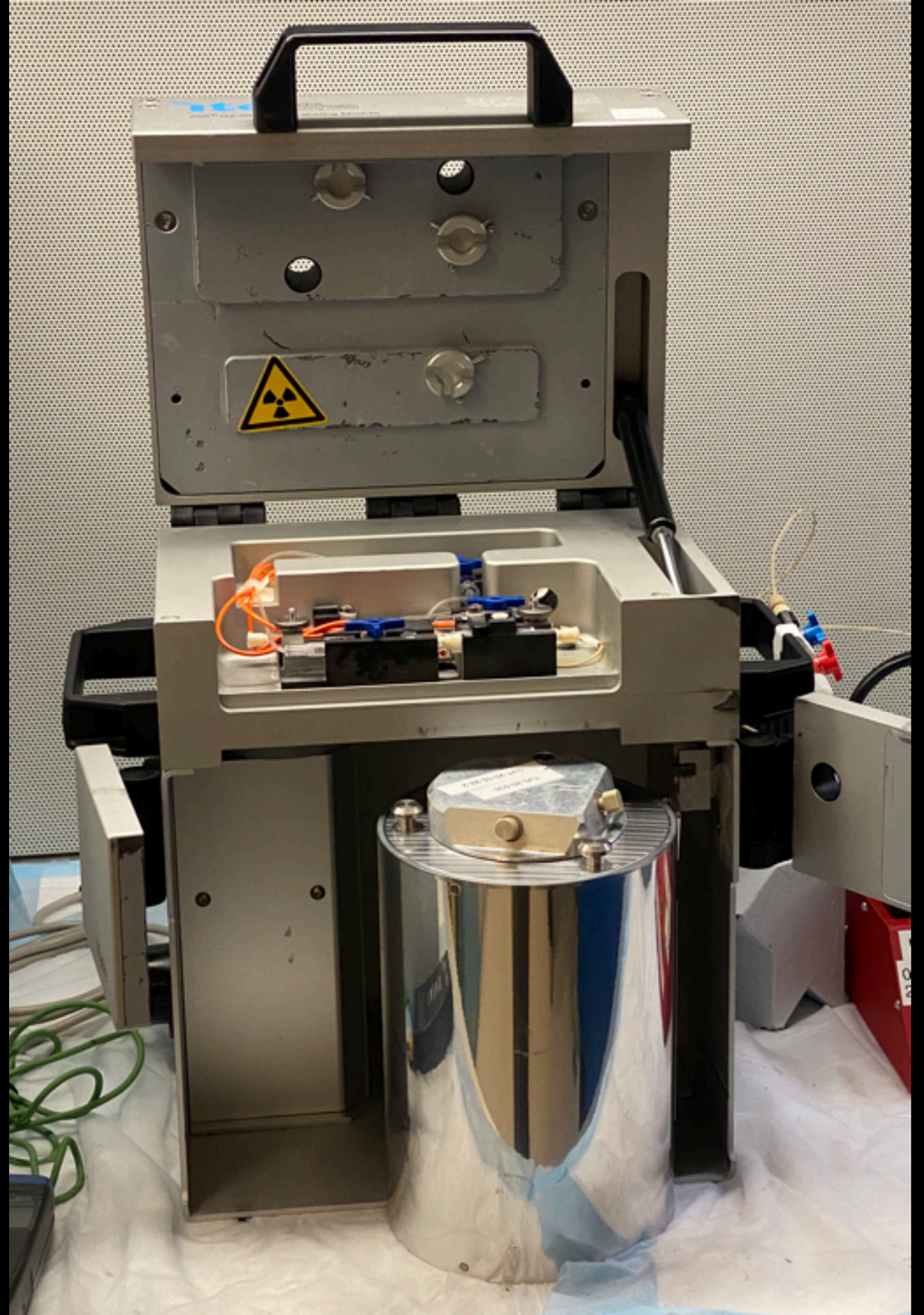
Ga 68 PSMA-11 PET FDA Approval

- Ga 68 PSMA-11 Injection is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:
  - with suspected metastasis who are candidates for initial definitive therapy.
  - with suspected recurrence based on elevated serum prostate- specific antigen (PSA) level.

Approved December 2020

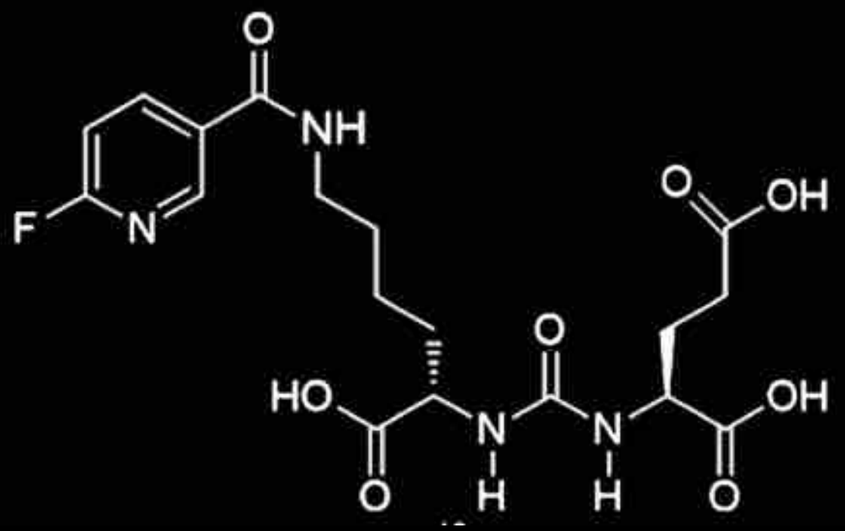
Gallium-68

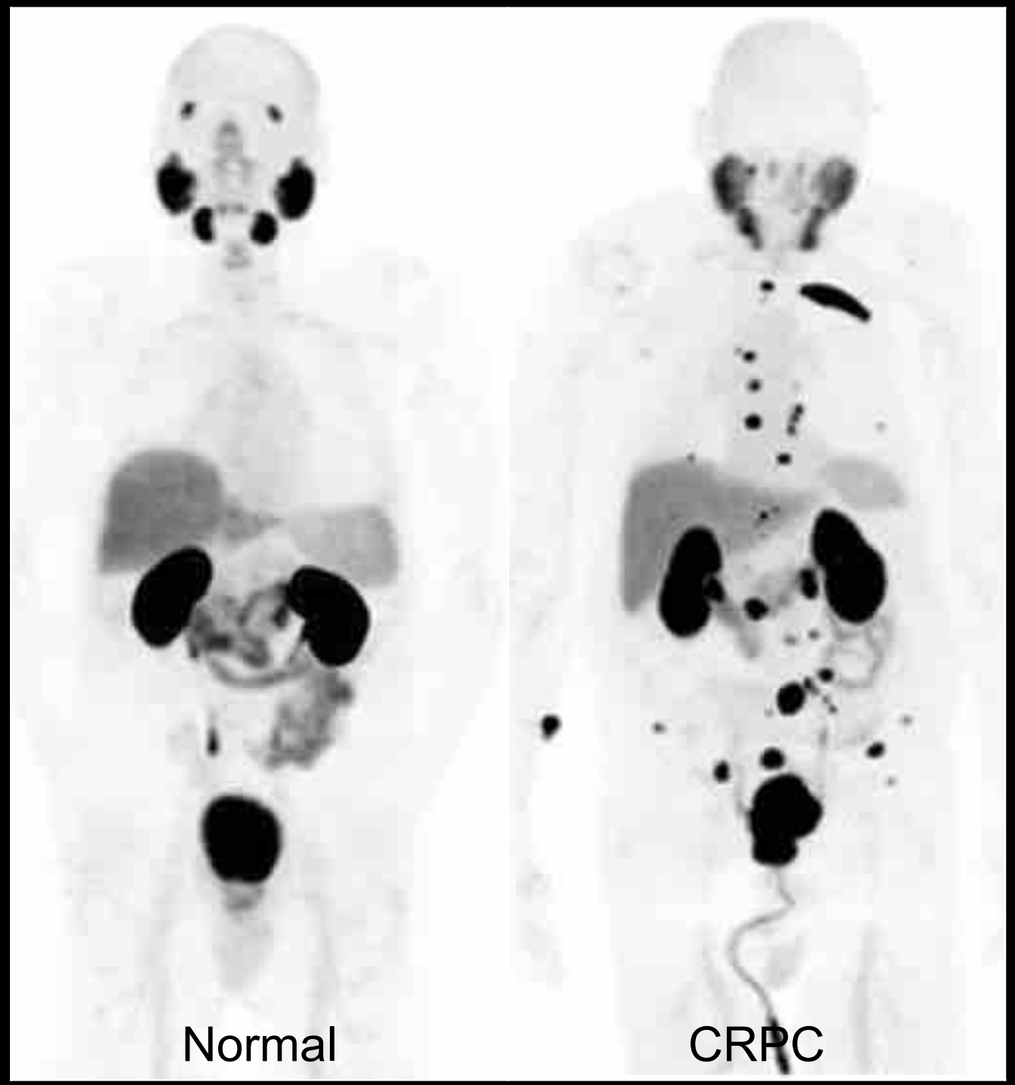
- 68 minute half-life
- Generator produced
  - Usually can only make 2-3 doses per synthesis
- PET emitter (91%)
  - 8 mm positron range
- Metal chemistry
  - simple synthesis using modules



^{18}F-DCFPyL

- Termed the “PyL” compound
- Much lower blood pool activity
- Completed Phase III trials awaiting NDA approval!





Rowe JNM (2015)

DCFPyL: OSPREY and CONDOR trials

OSPREY	CONDOR

• Cohort A: initial staging (n=252)
  • Specificity 98%, sensitivity 40%
• Cohort B: biochemical recurrence (n=93)
  • Inclusion criteria required disease on conventional imaging
  • Sensitivity 96% and PPV 82%
  • Median PSA of 11.3
	• Biochemical recurrence only
	• n=208
	• Did not require biopsiable lesions
	• Baseline PSA of 0.8
	• Correct localization rate: 85-87%
	  • CLR: % of patients with a one-to-one correspondence between 18F-DCFPyL by the ce
	  the composite SO
	• Detection rate 59-6

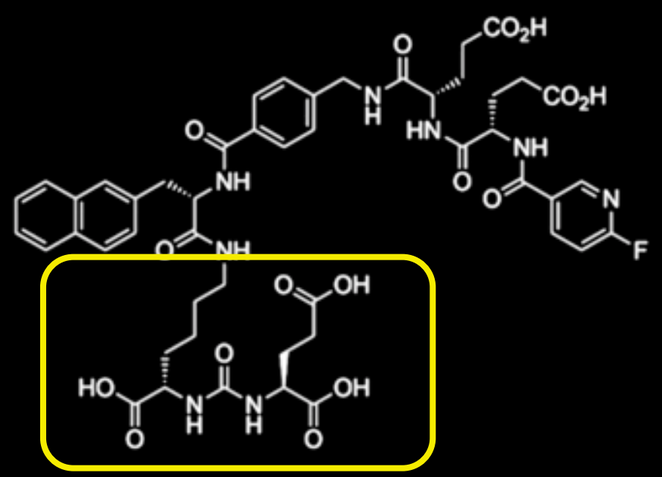
Pienta J Urol 2021	Morris Clin Cancer Res 2021

PYLARIFY or piflufolostat

Piflufolastat F 18 PET FDA Approval

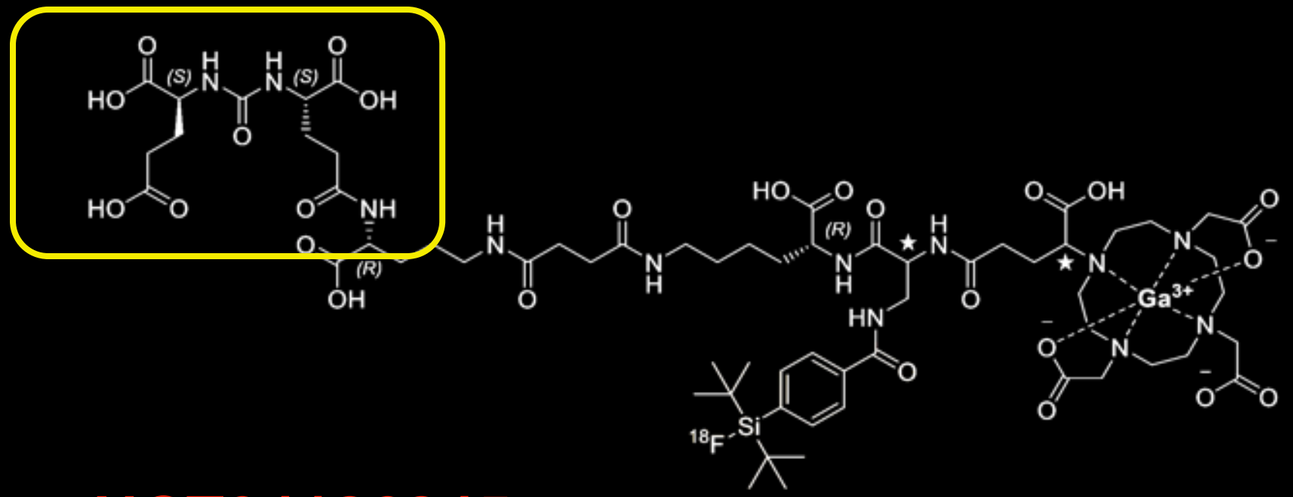
- PYLARIFY Injection is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:
  - with suspected metastasis who are candidates for initial definitive therapy.
  - with suspected recurrence based on elevated serum prostate- specific antigen (PSA) level.

Approved May 2021



PSMA-1007

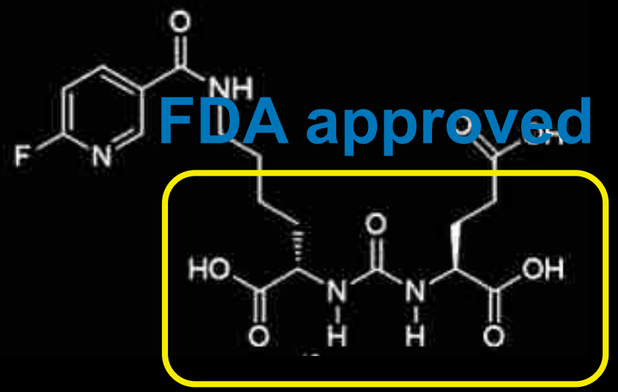
NCT04742361



NCT04186845

NCT04186819

rh-PSMA-7

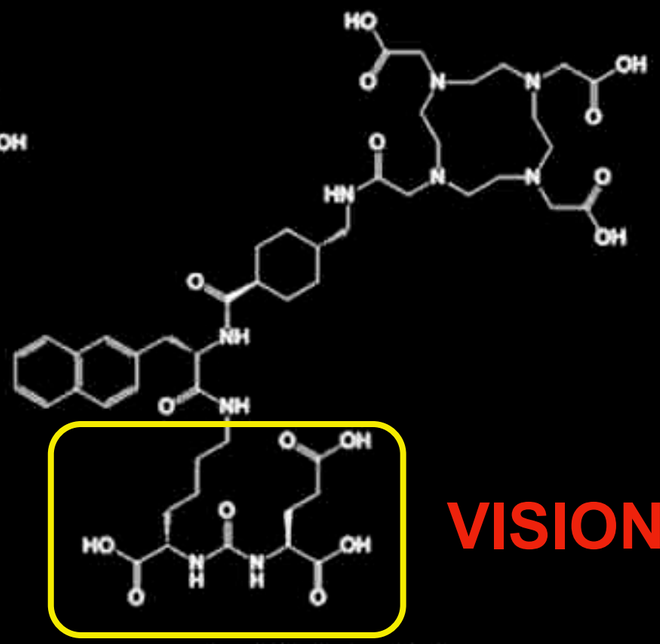


FDA approved

DCFPyL

FDA approved

PSMA-11



VISION trial

PSMA-617

Ga 68 gozetotide PET FDA Approval

- ILLUCCIX, after radiolabeling with Ga 68, is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:
  - with suspected metastasis who are candidates for initial definitive therapy.
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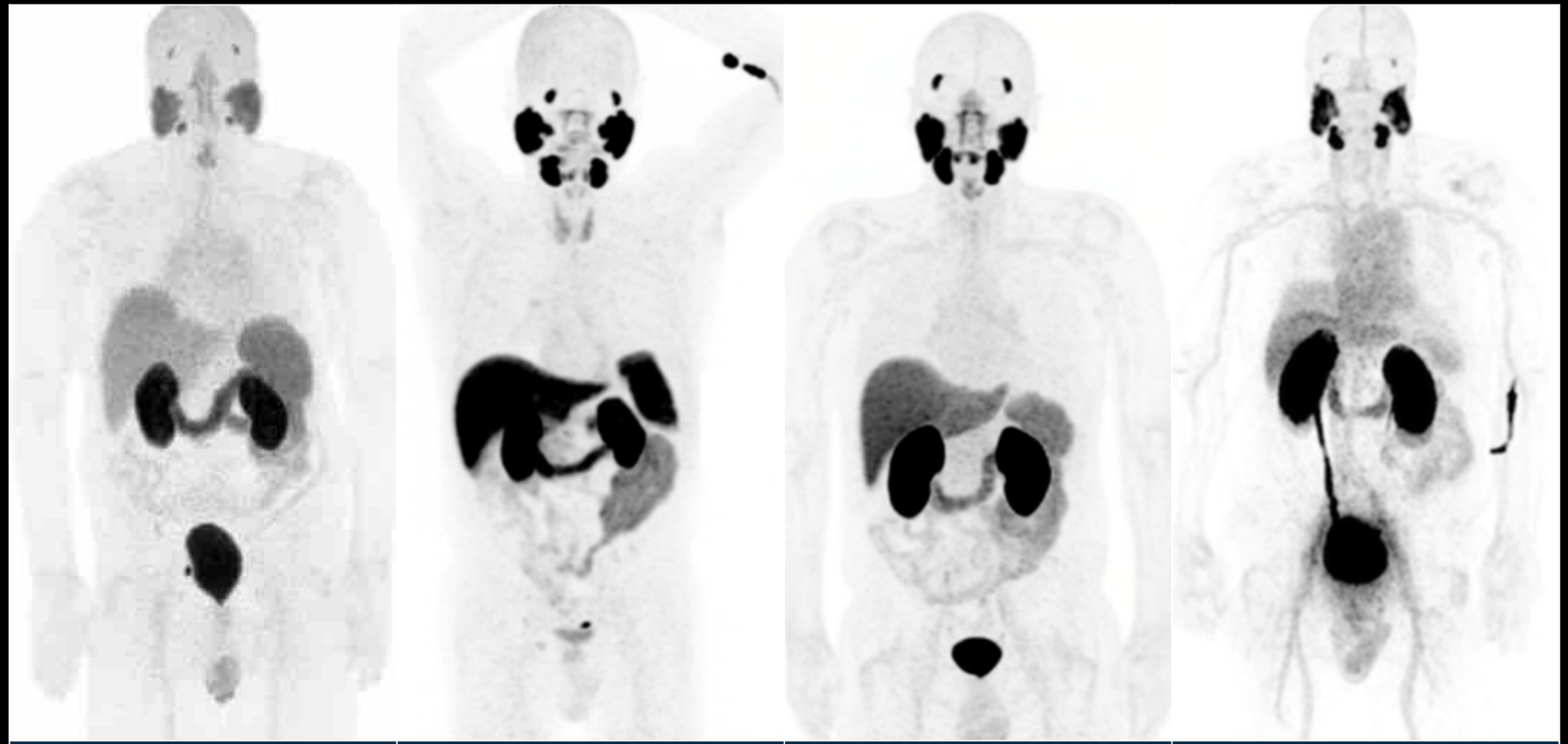
Approved December 2021

Variations in biodistribution…



PSMA-11	PSMA-1007	DCFPyL	CTT1057

NCCN guidelines: *updated 9/10/2021*

- Initial staging (PROS-2)
  - Indicated in unfavorable intermediate, high and very high risk patients
- Biochemical recurrence (PROS-9, PROS-10 and PROS-11)
  - No PSA cutoff provided
- Progression for CSPC systemic therapy (PROS-12)
  - Includes patients with castration resistant disease
- Progression with M0CRPC (PROS-13)

NCCN guidelines: *updated 9/10/2021*

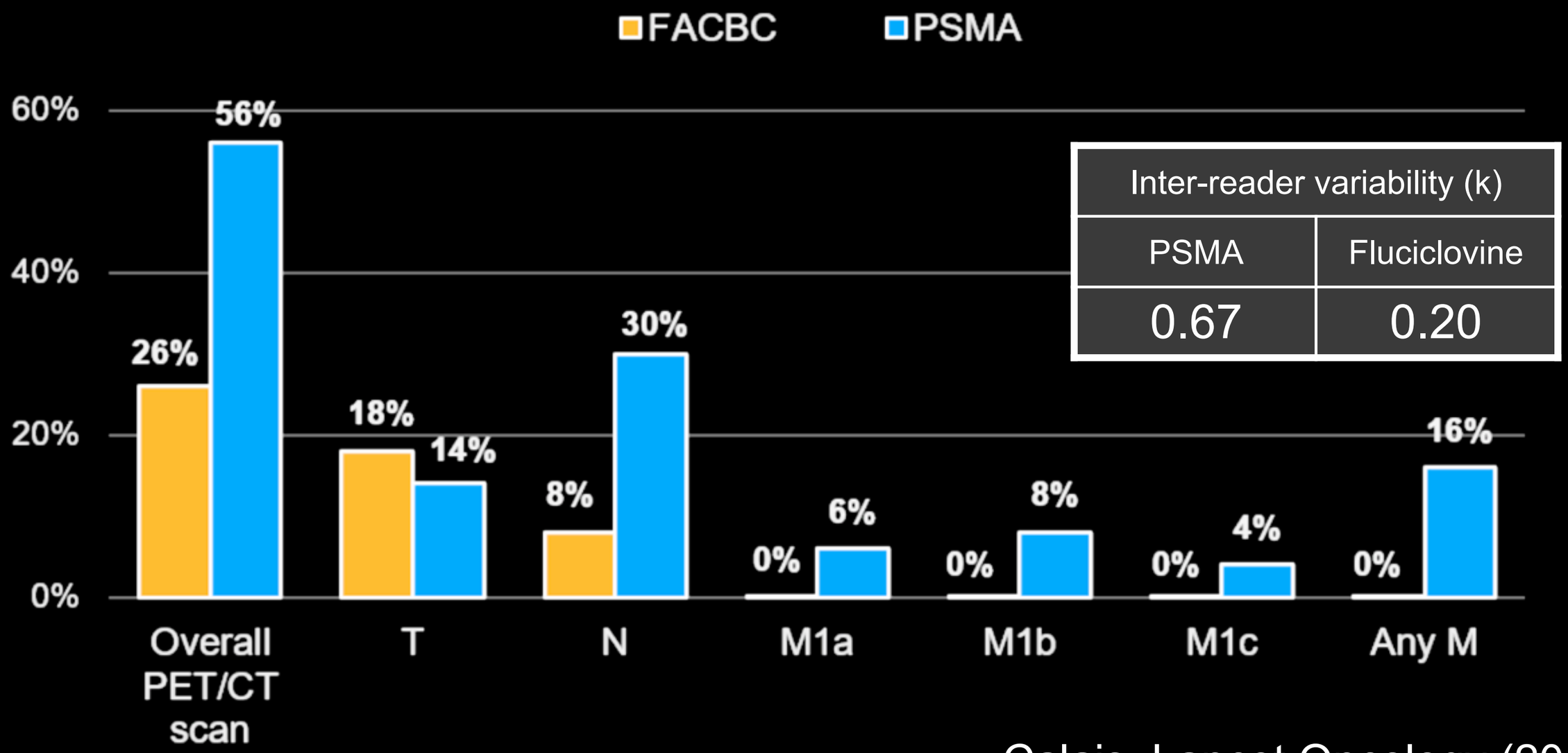
- Ga-68 PSMA-11, or F-18 piflufolastat PSMA can be considered for equivocal results on initial bone imaging.
- Ga-68 PSMA-11 or F-18 piflufolastat PSMA PET/CT or PET/MRI can be considered for bone and soft tissue (full body) imaging.
- Studies suggest that F-18 piflufolastat PSMA or Ga-68 PSMA-11 PET imaging have a higher sensitivity than C-11 choline or F-18 fluciclovine PET imaging, especially at very low PSA levels.
- Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.

CMS coverage

- The following diagnoses are applicable to piflufolastat F 18 (PYLARIFY®) injections when billed with 78811, 78812, 78813, 78814, 78815 or 78816. Use A9597 to bill for this service effective 5/26/2021. Use the PS modifier.
  - NOTE: Whenever a personal history diagnosis code (Z85.XXX) is on a claim, the claim must also contain a diagnosis code from the list of covered C, D, or R diagnosis codes.
- Effective 09/10/2021, the NCCN Guidelines have been updated to allow PMSA-PET/CT or PMSA-PET/MRI with F 18 piflufolastat PSMA to be considered effective for initial bone imaging with the use of the ‘PI’ modifier.

Code	Description
C61	Malignant neoplasm of prostate
R97.21	Rising PSA following treatment for malignant neoplasm of prostate
Z85.46	Personal history of malignant neoplasm of prostate

PSMA vs Fluciclovine



Inter-reader variability (k)	
PSMA	Fluciclovine
0.67	0.20

Calais, Lancet Oncology (2019)

False positive interpretations

- Benign lesions
  - Rib lesions
  - Pre-sacral ganglia
  - Dorsal root ganglia
  - Hemangiomas
  - Paget’s disease
- Other tumors
  - HCC
  - Thyroid cancer
  - Lung cancer

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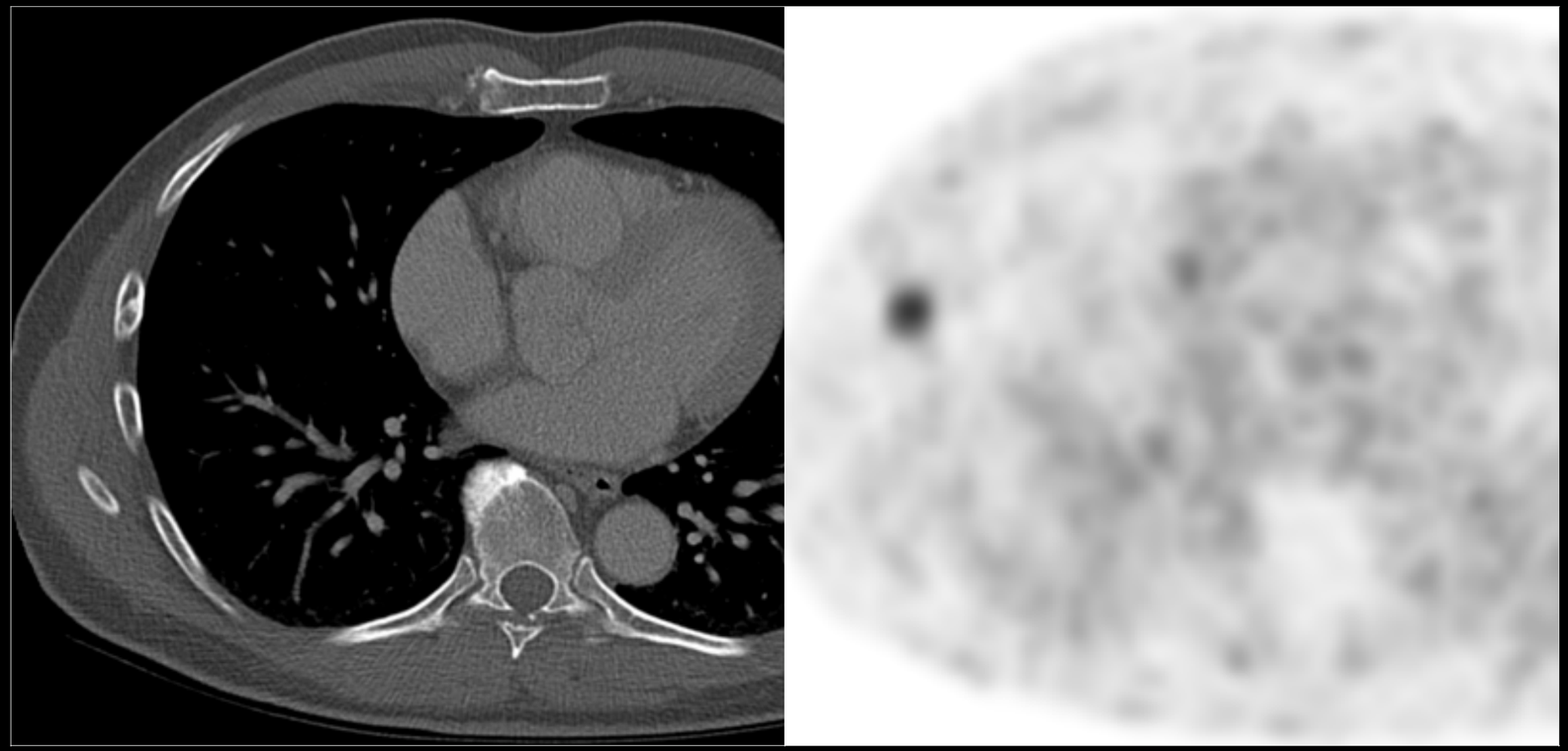

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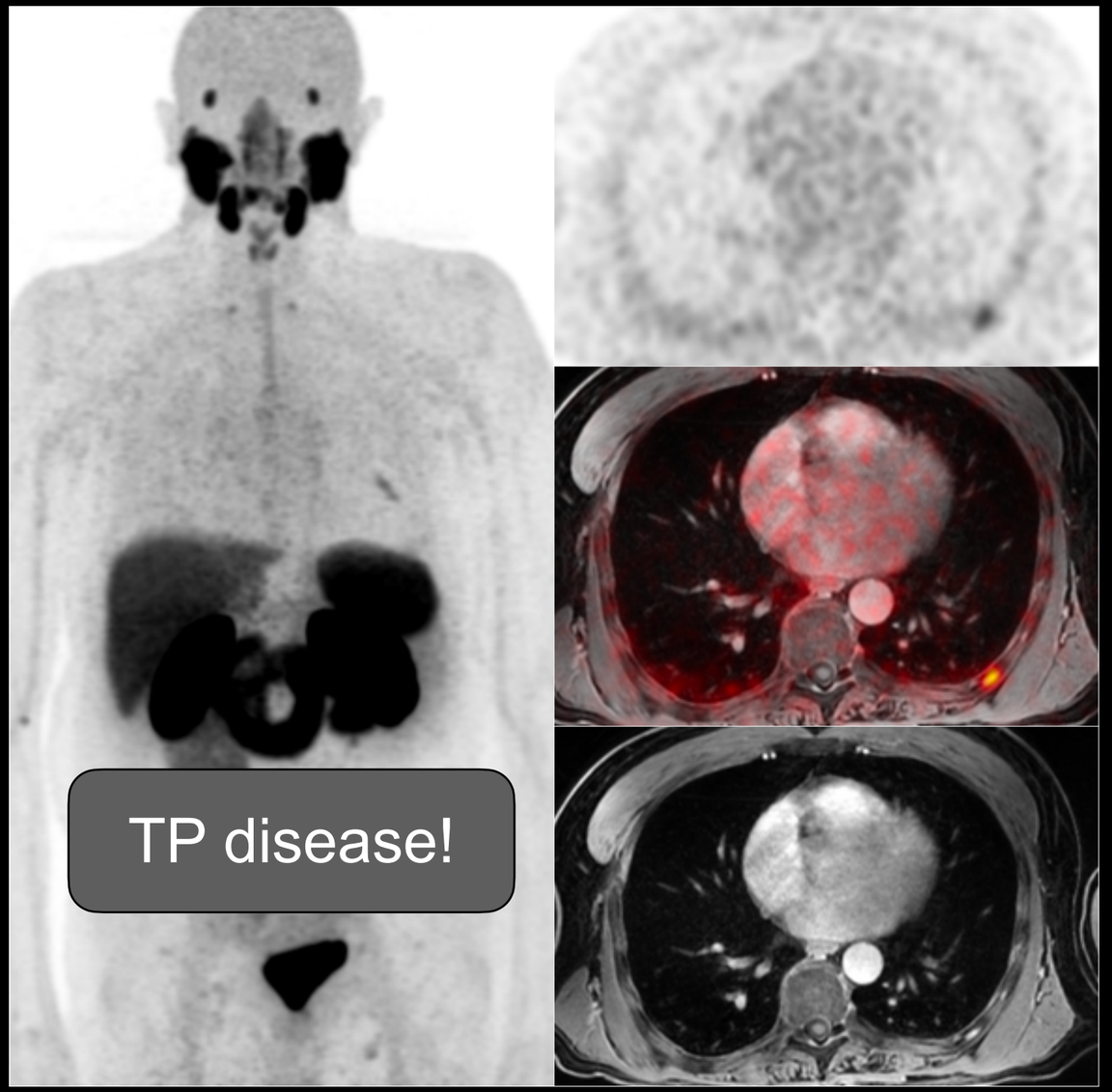

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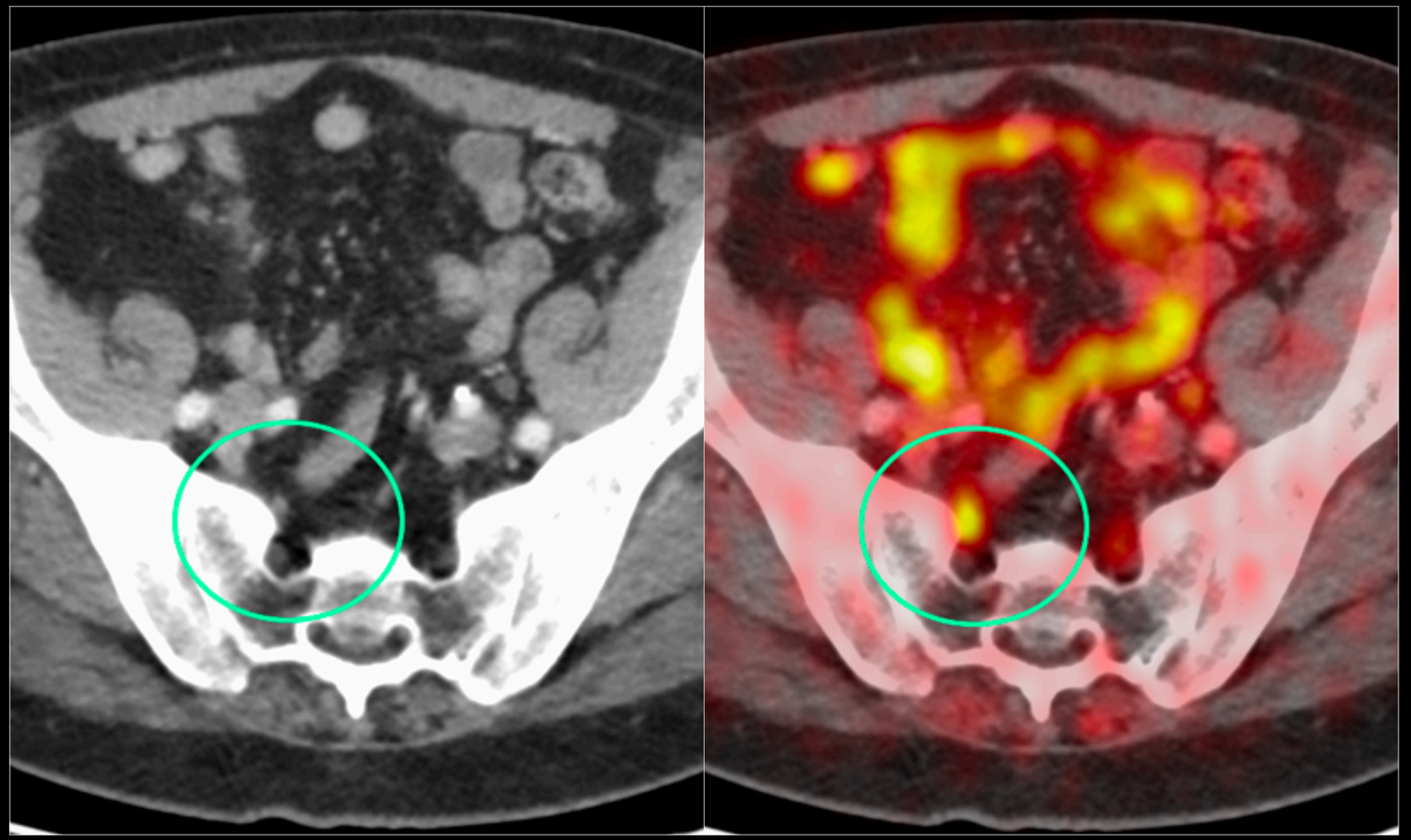

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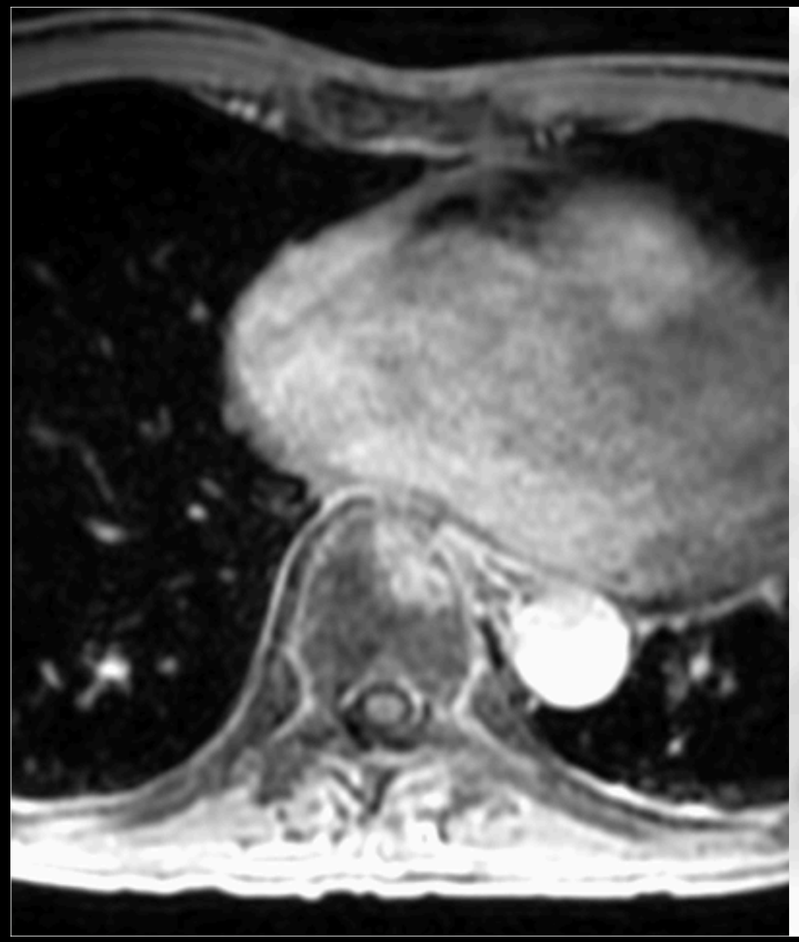

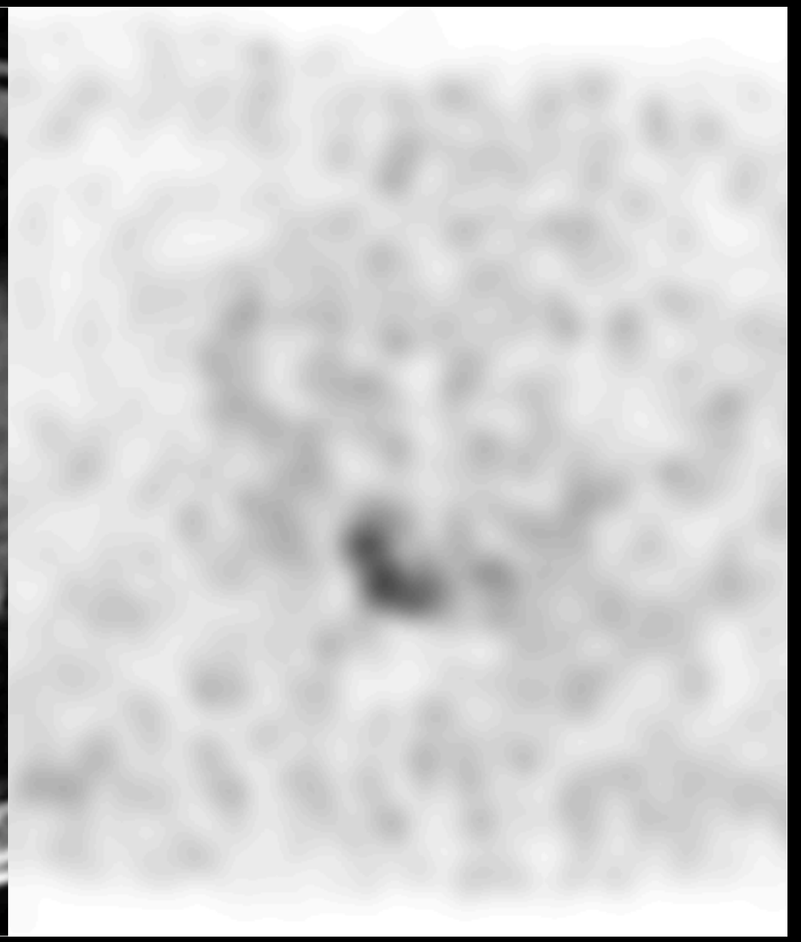

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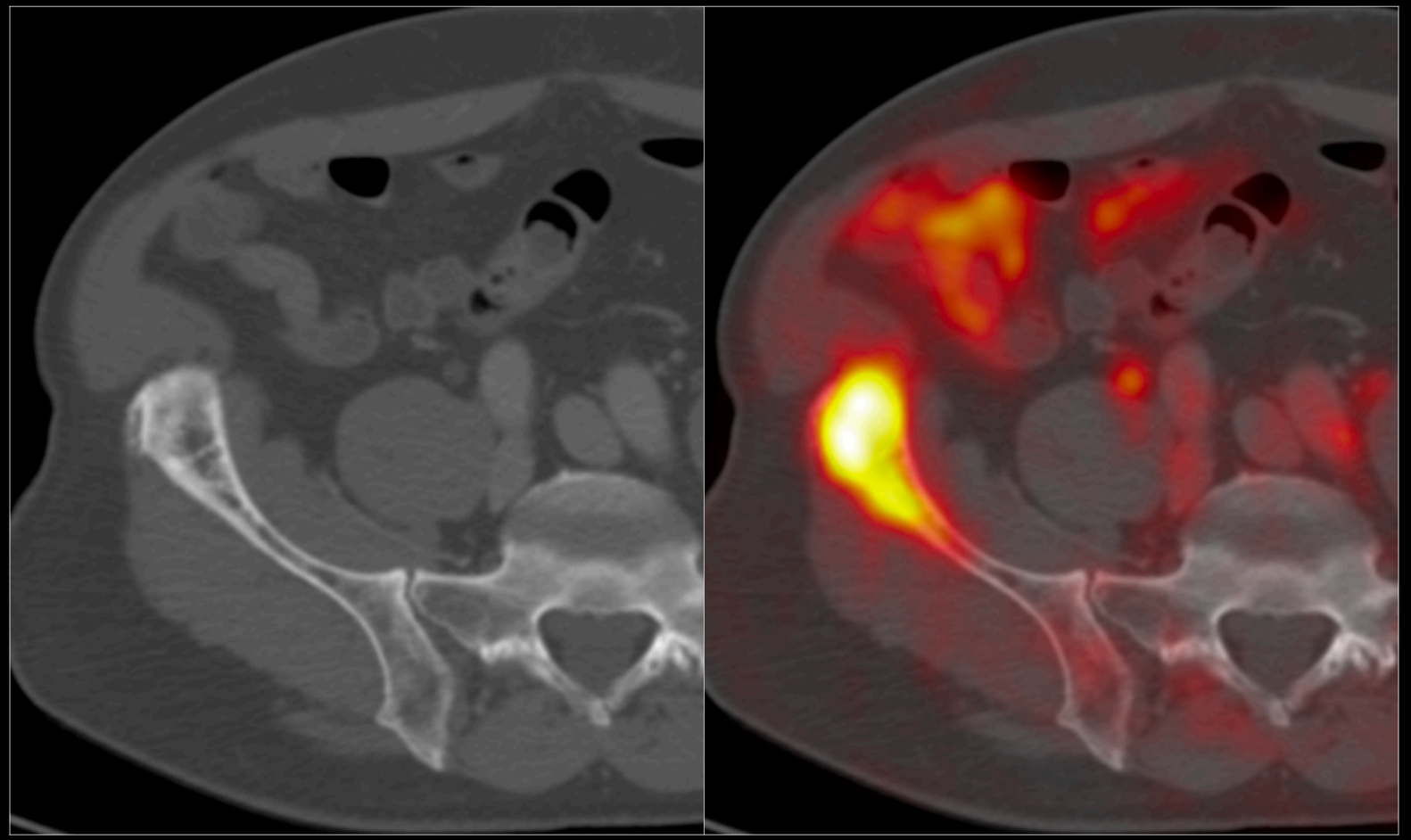

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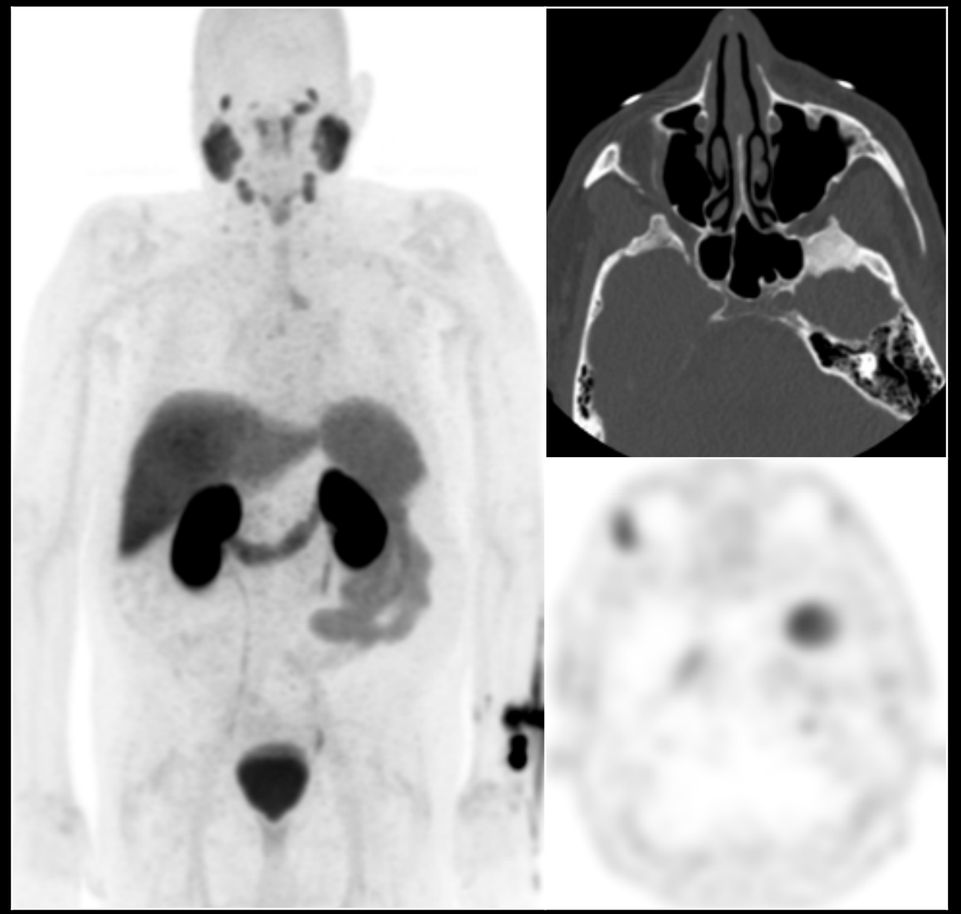
Fibrous dysplasia



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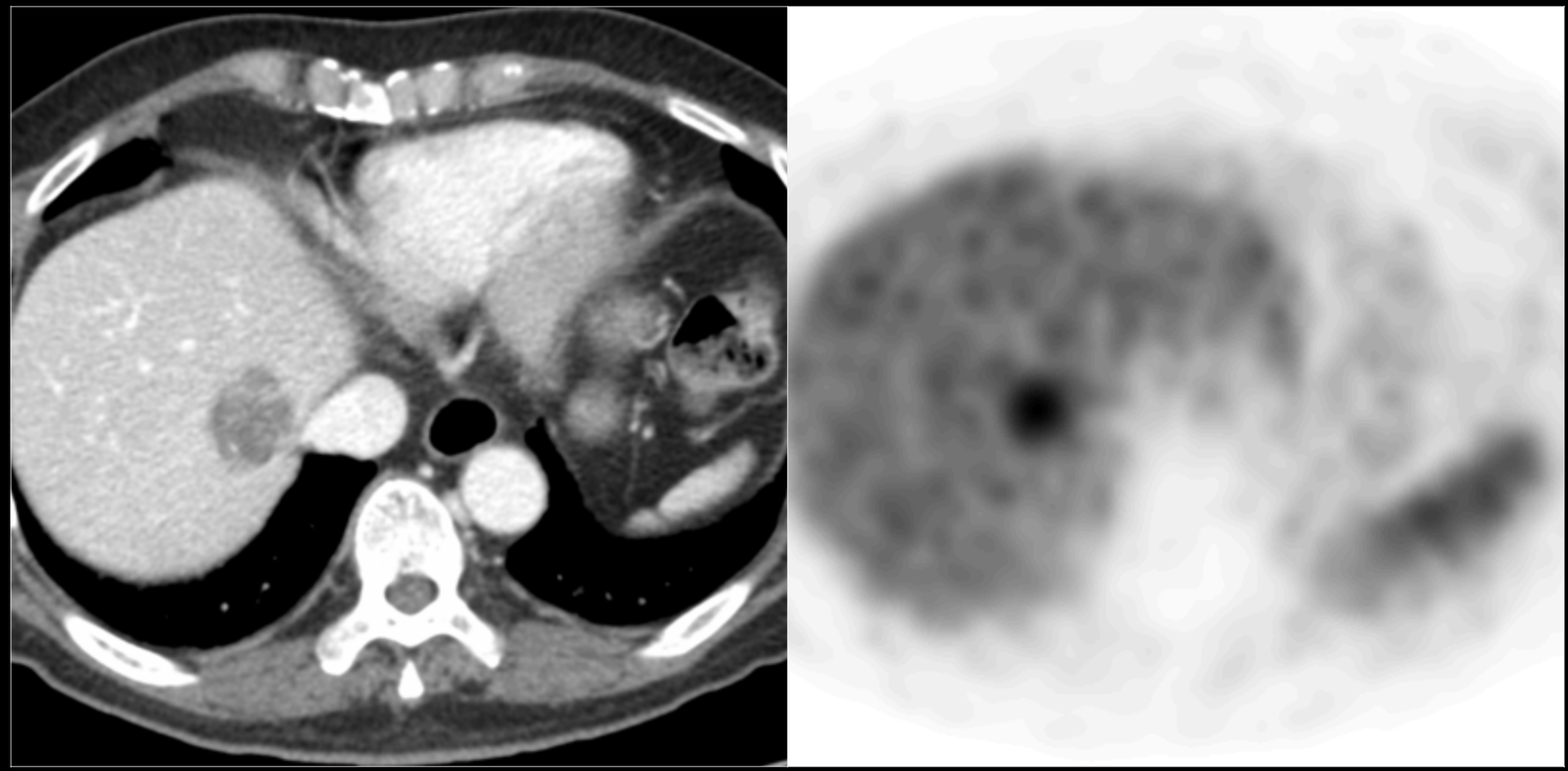

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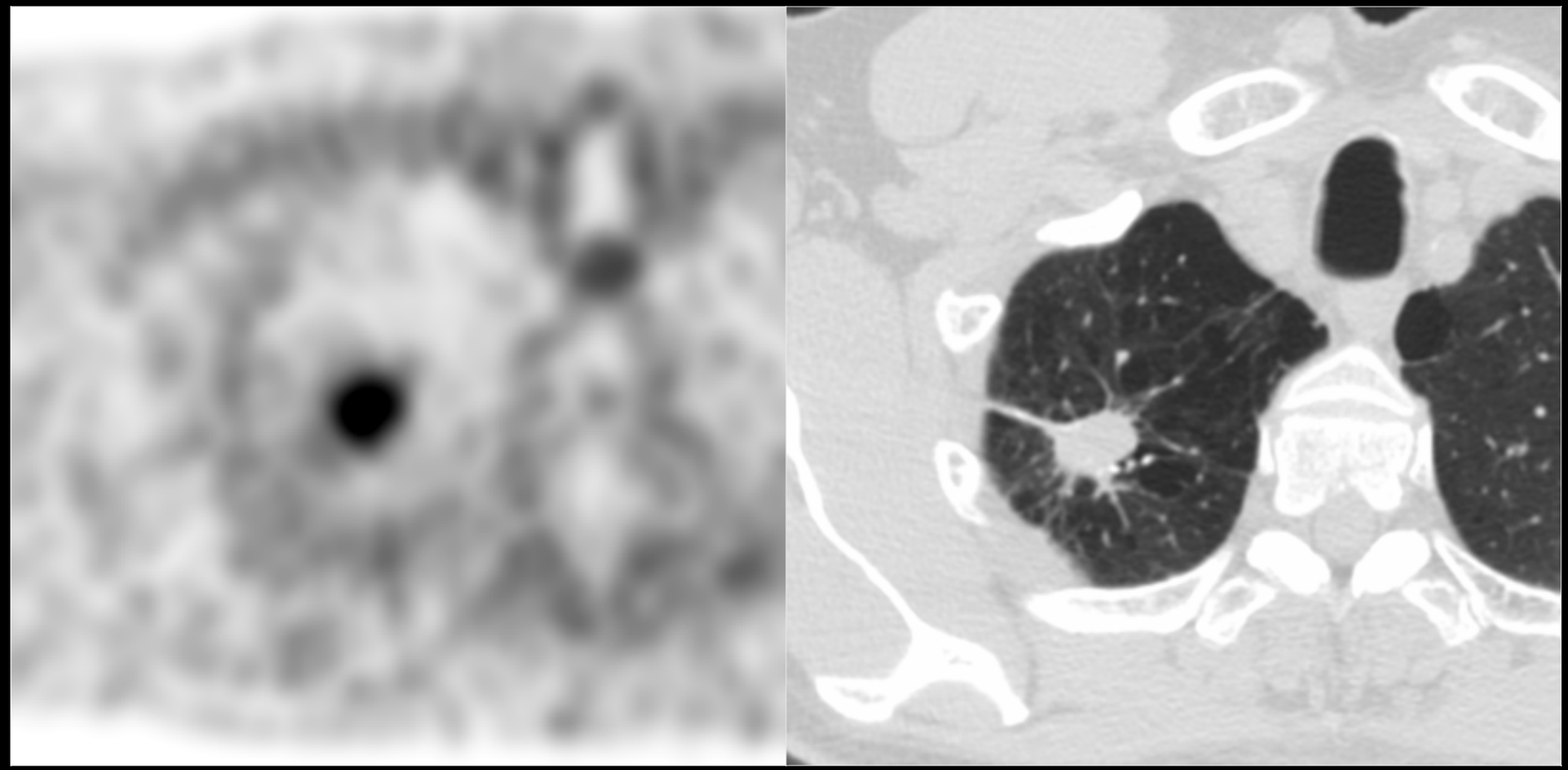

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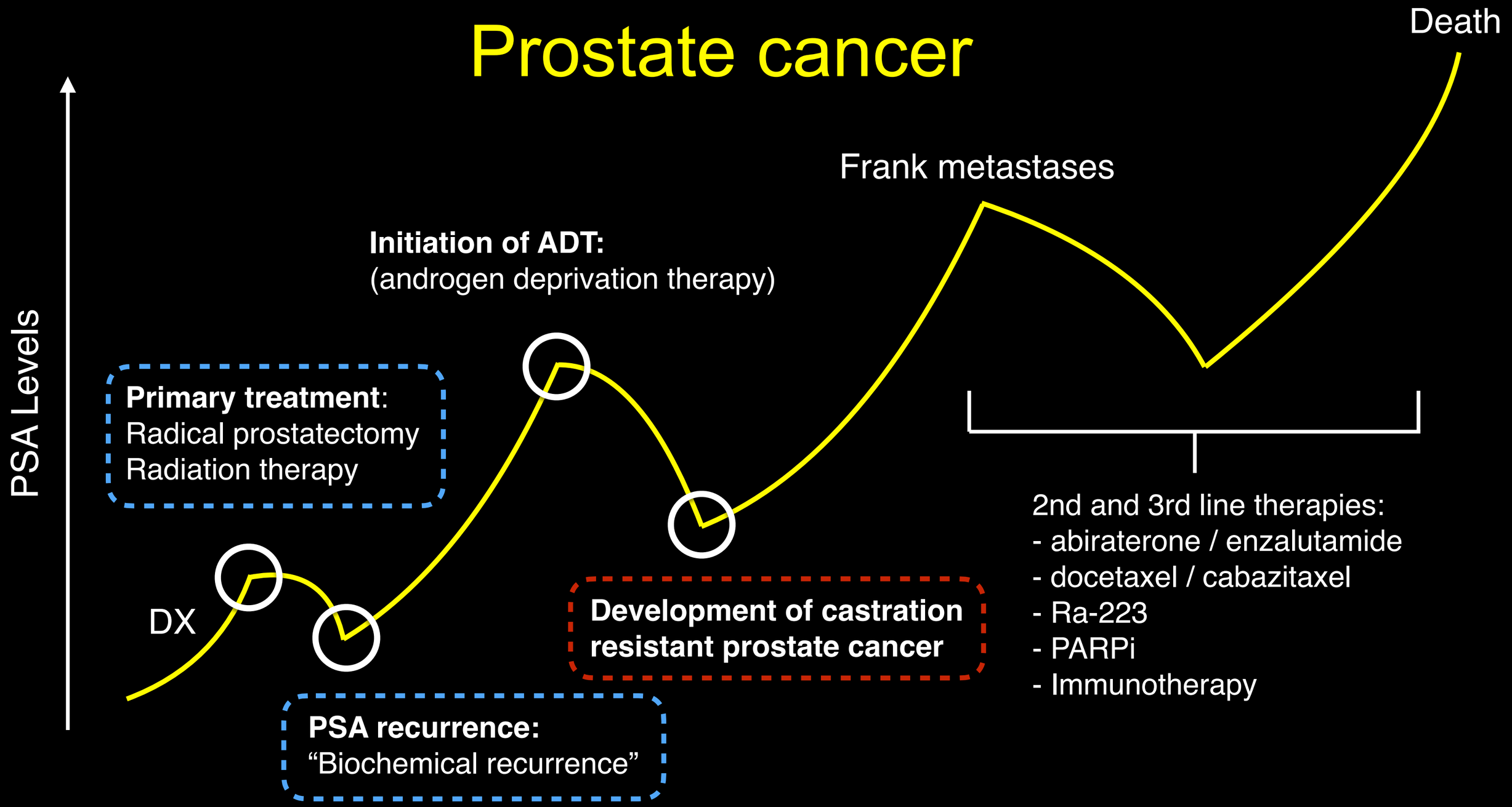
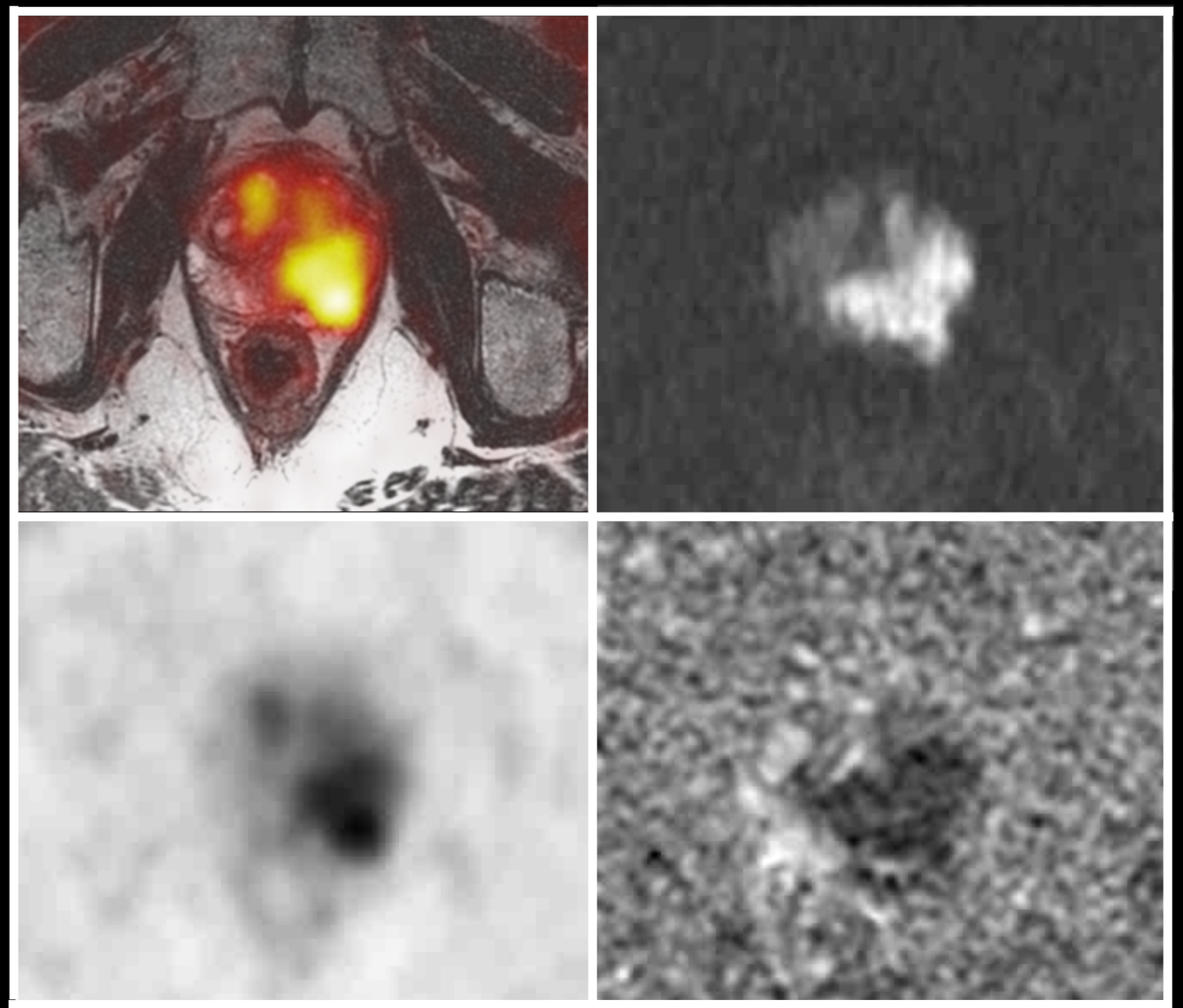
Prostate cancer



72 year old man with Gleason 4+4



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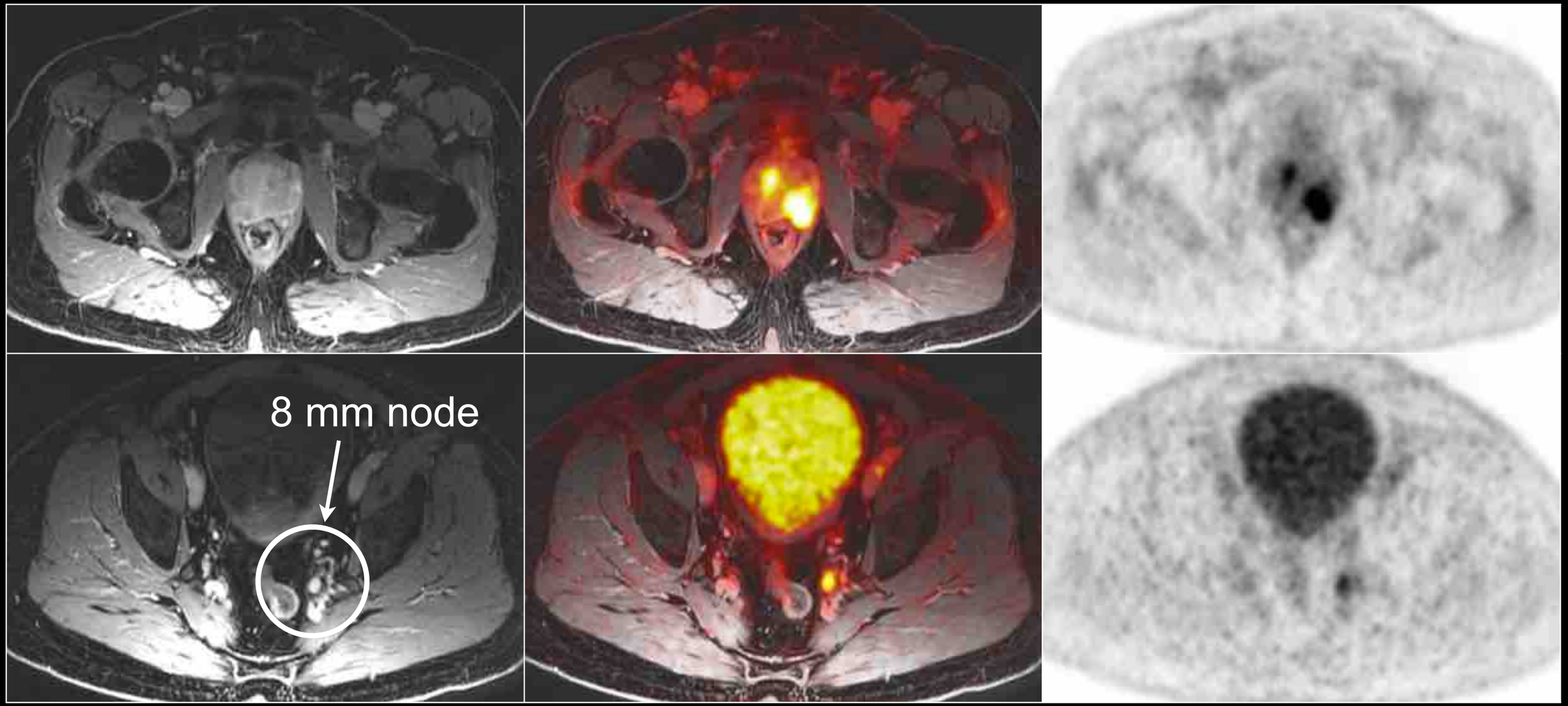


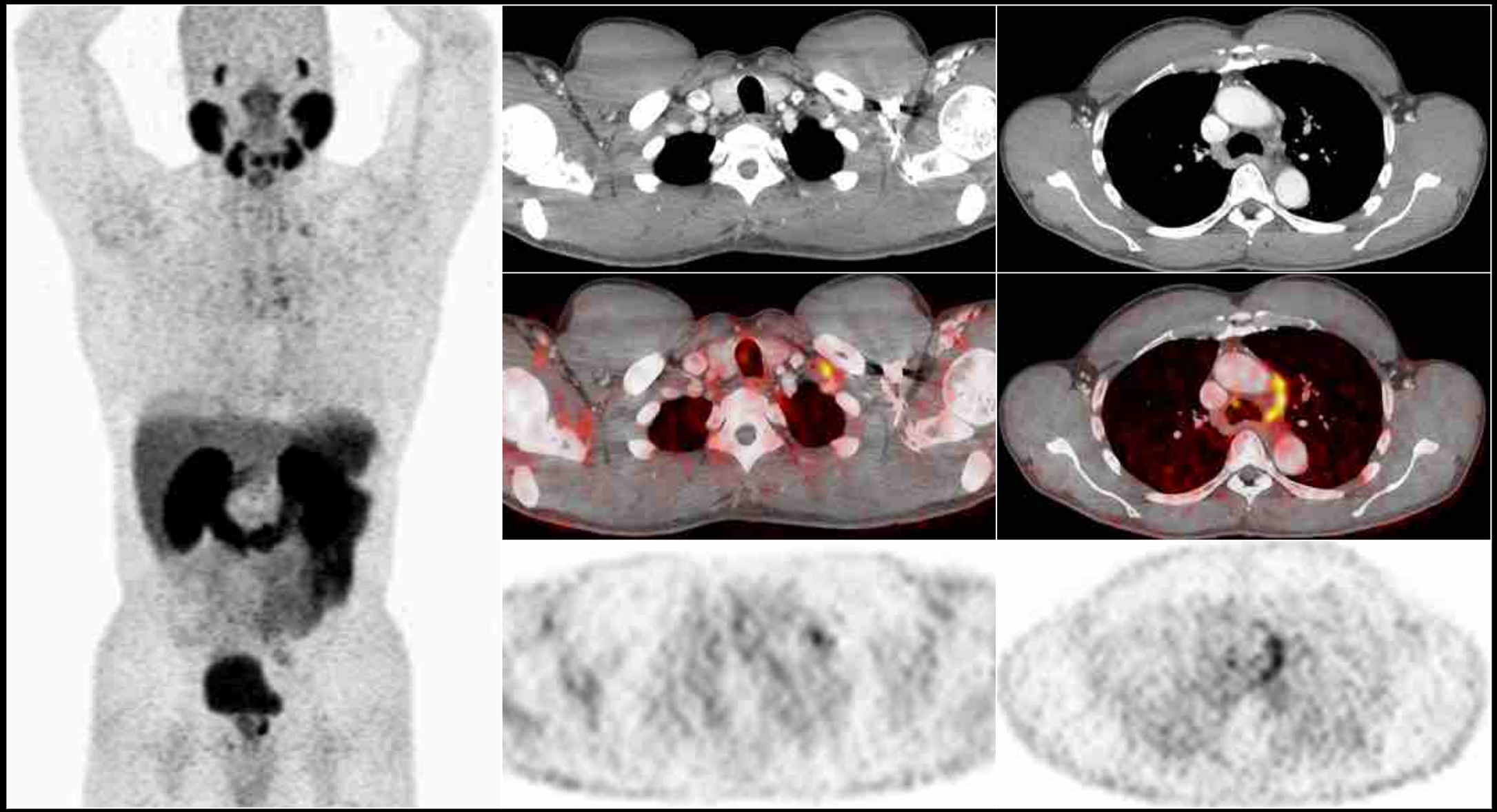
Role in initial staging: PSMA PET versus pathology at time of prostatectomy (n=277)

75 patients were positive on pathology (27%)

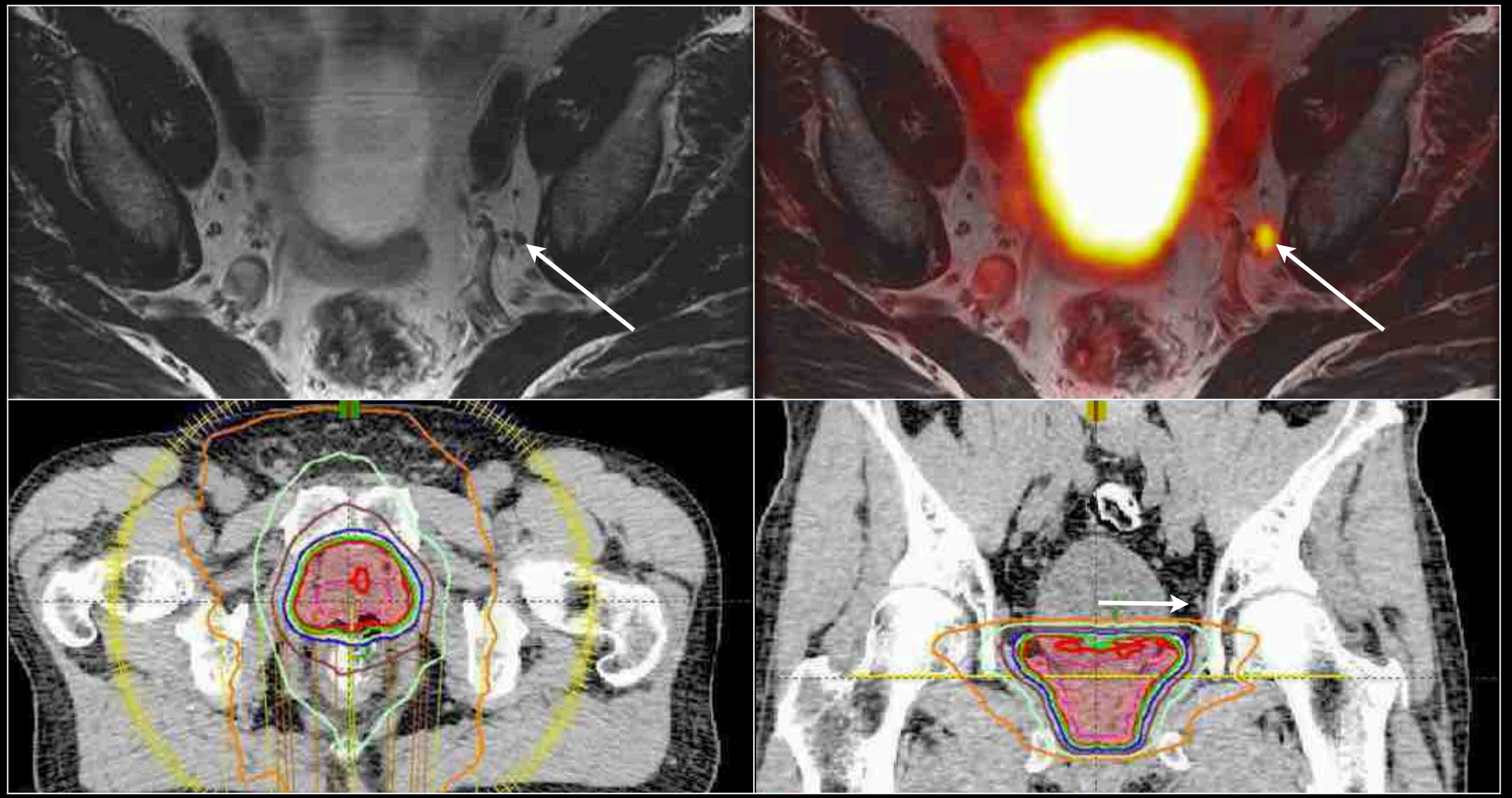
	+ LN on path	- LN on path
+ LN on PSMA	30	10
- LN on PSMA	45	192

- Sensitivity ➡40%
- Specificity ➡95%

PSA of 23.7, Gleason 4+3



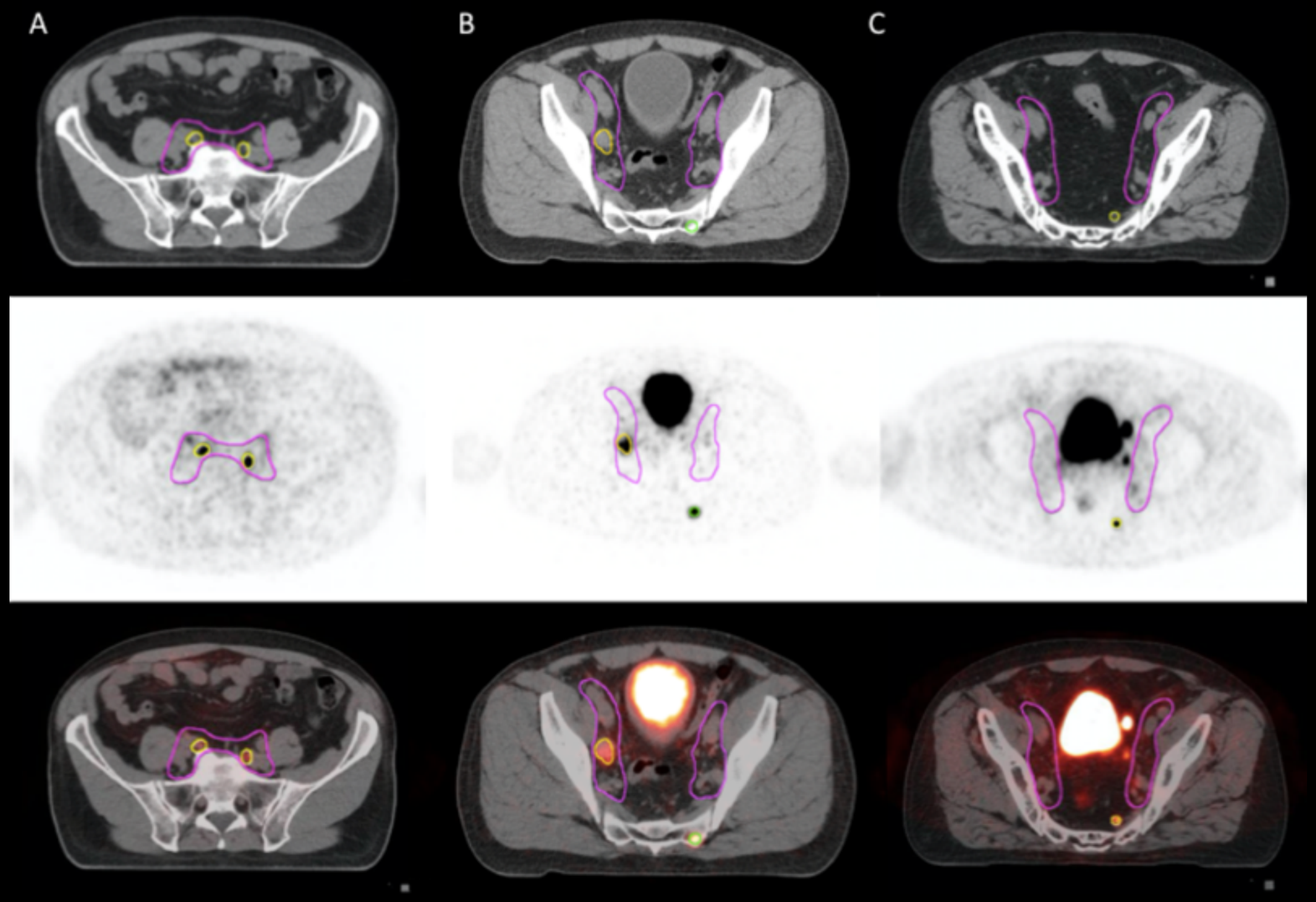
Recurrence after radiation therapy



Effect of PSMA PET on RT planning

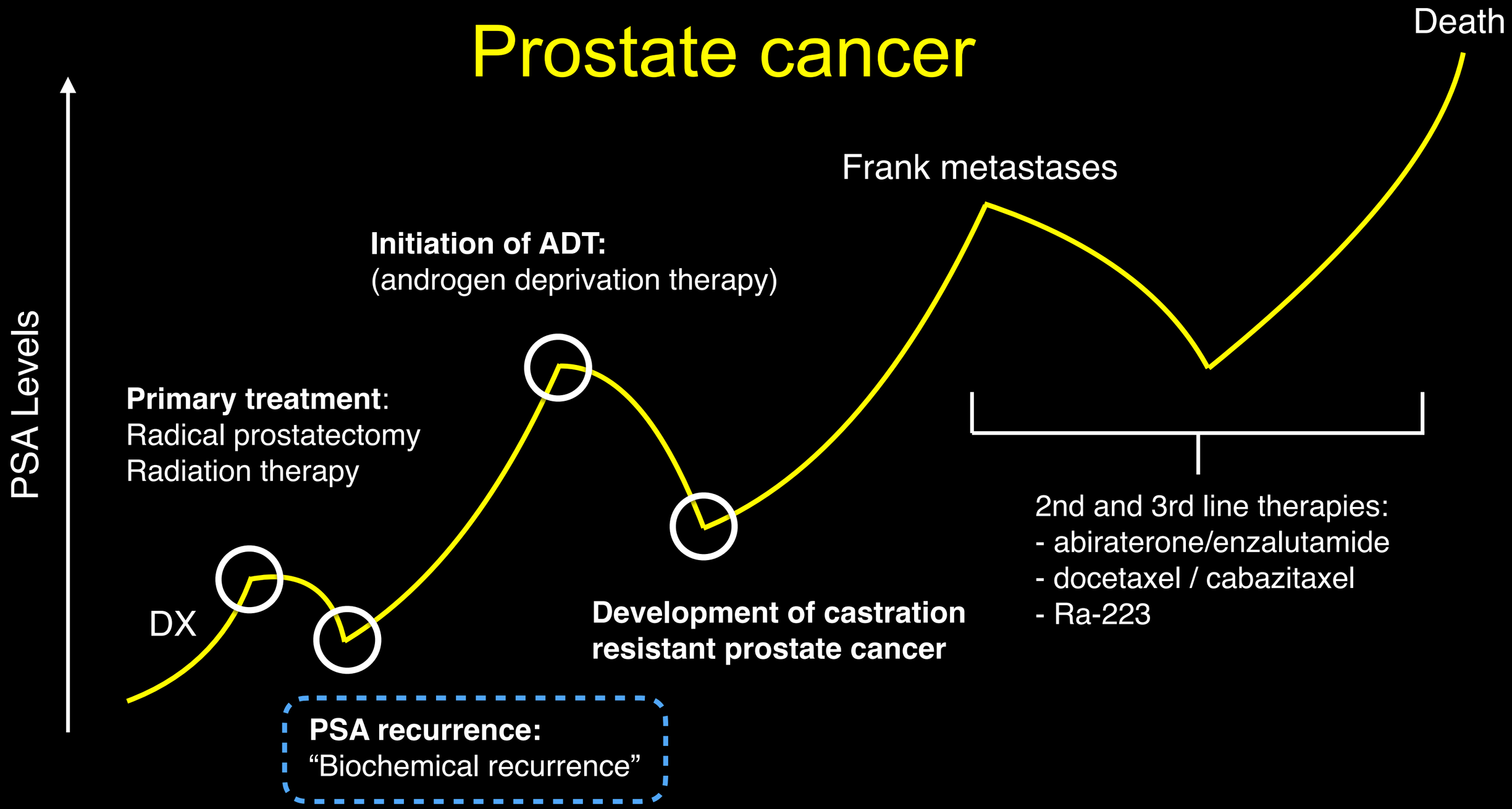
- 45 patients with high risk at staging
  - 12 received boost to nodes
  - 6 had RT to bone metastases
  - 8 had nodes outside of consensus CTV

53% had change in RT plans



Wu, Urology (2019)

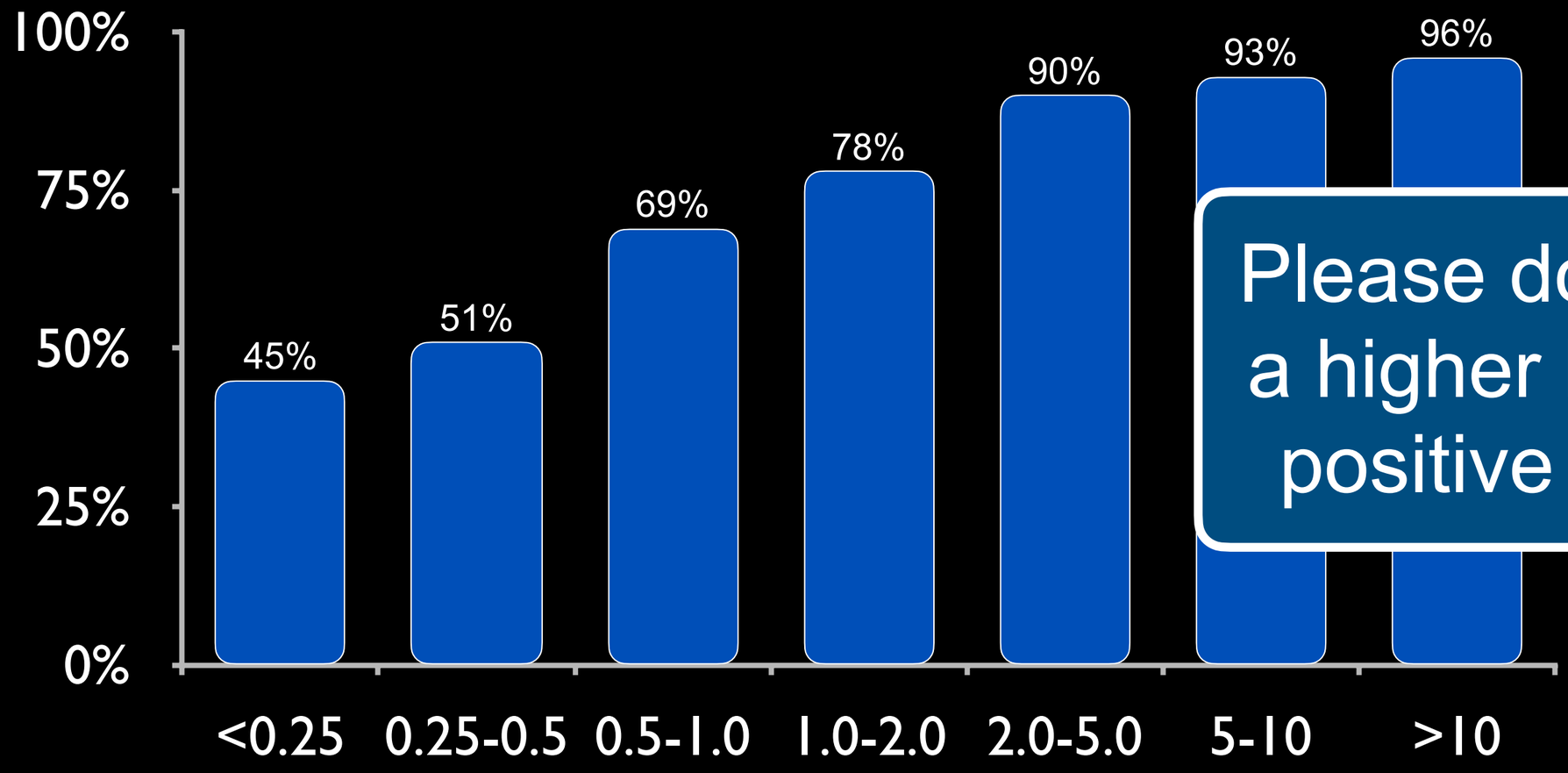
Prostate cancer



Biochemical Recurrence

Post-RP	Post-Radiation
AUA guidelines: • PSA > 0.2 ng/dL 6-12 weeks after prostatectomy • Confirmed on repeated PSA	ASTRO-Phoenix: • PSA rise over post-radiation nadir of at least 2.0 ng/dL

Detection rate on PSMA PET directly related to the PSA at time of imaging

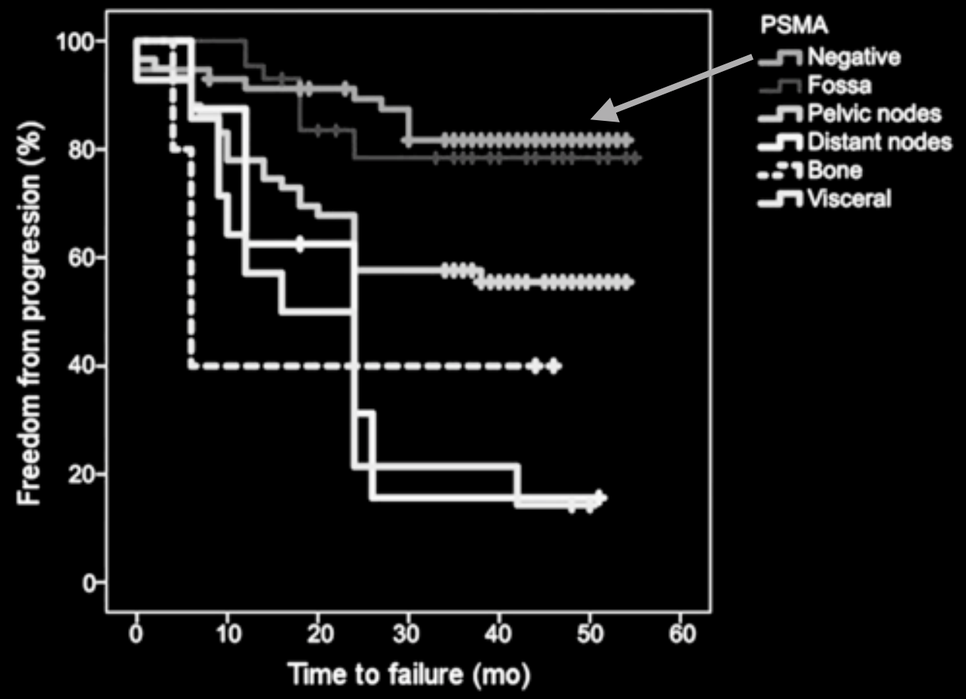


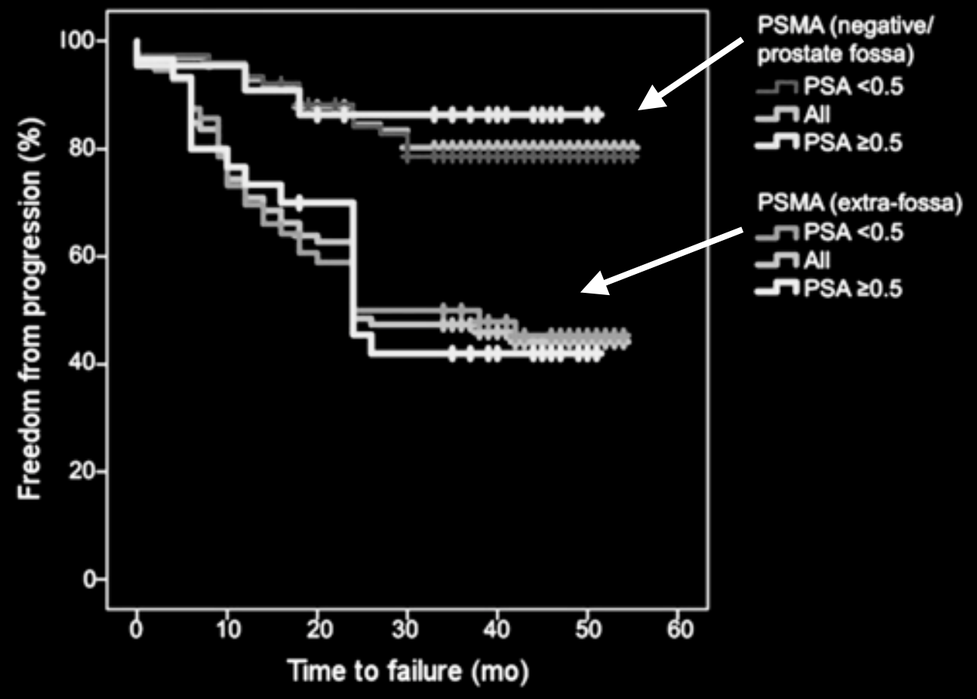
Please don't "wait" for a higher PSA to get a positive PSMA PET

Abghari-Gerst JNM 2021

PSMA “negative” tumors

Outcomes in patients treated with SRT after PSMA PET (median PSA 0.26)



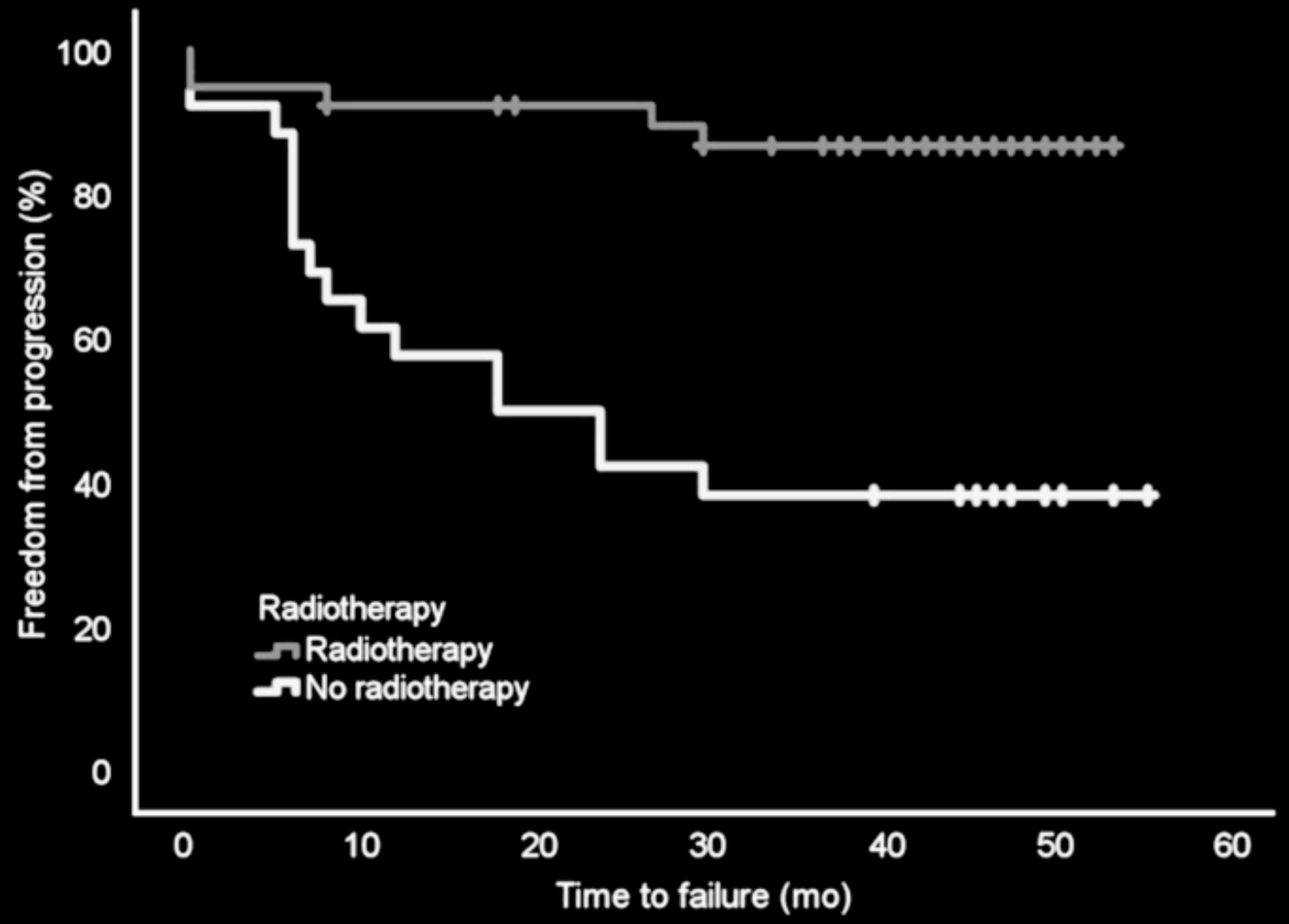


Freedom from Progression (FFP): PSA rise of 0.2 over nadir

Emmett JNM 2020

PSMA “negative” tumors

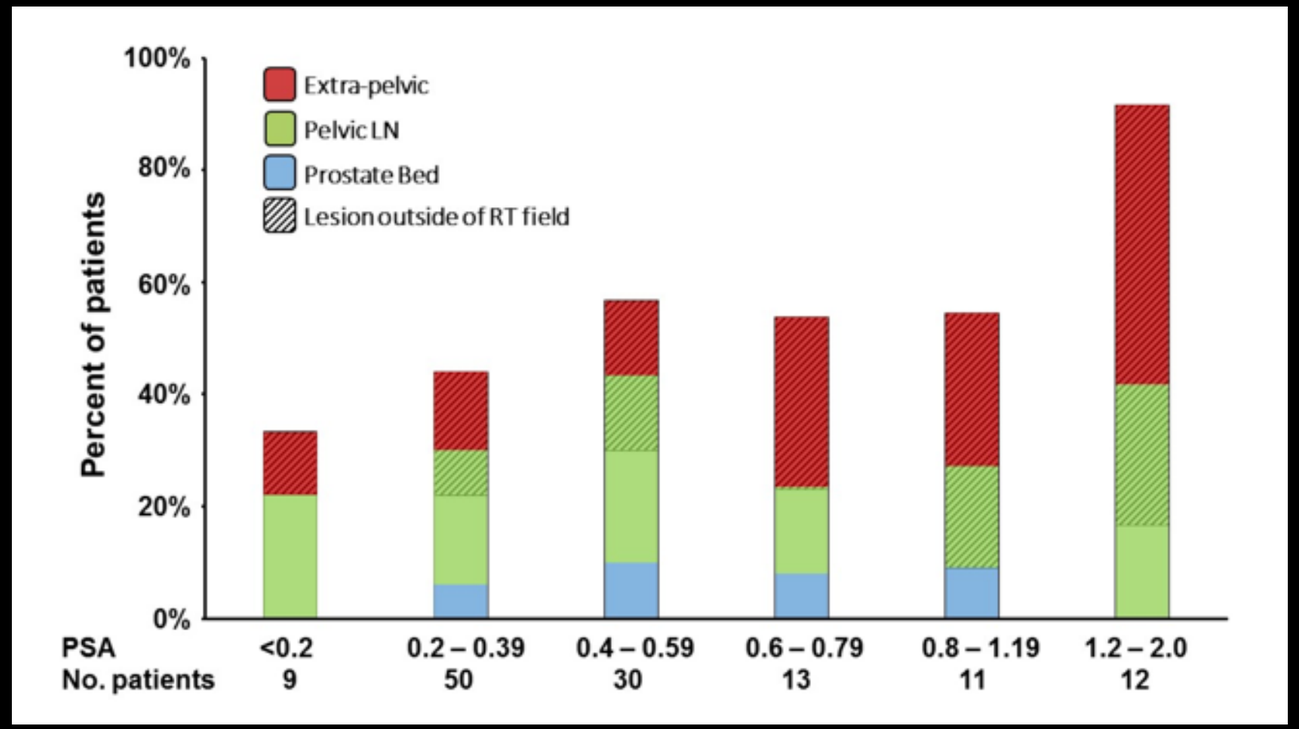
Remember, a negative PSMA PET does not mean that men should be observed…

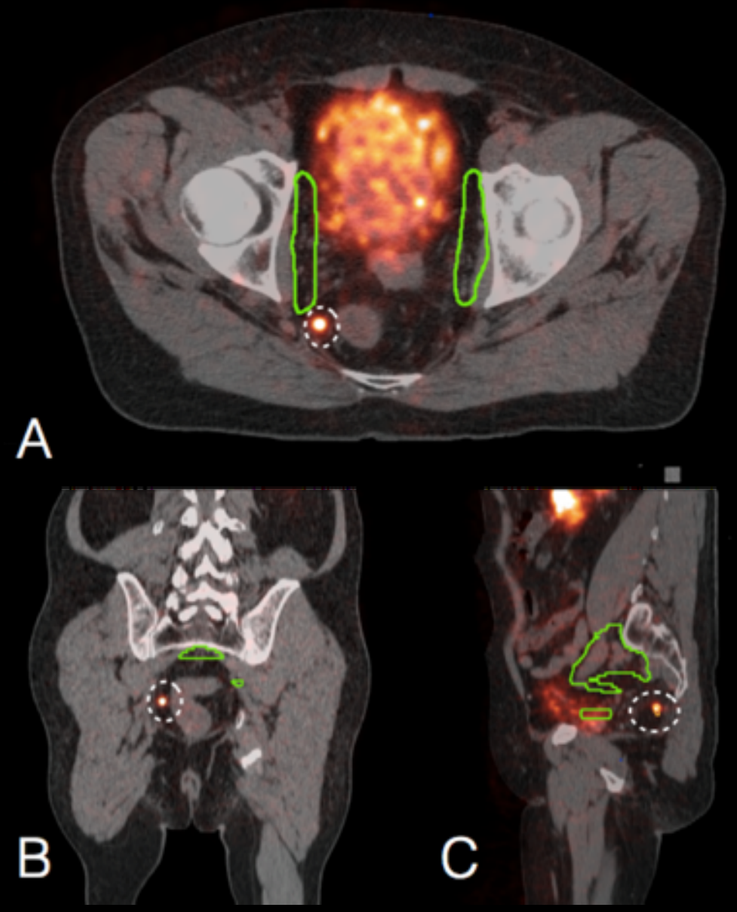


Emmett JNM 2020

Location of recurrence

- 125 patients with PSA < 2.0 after RP
- 53% with PSMA+ disease
- 30% had disease missed by standard RT

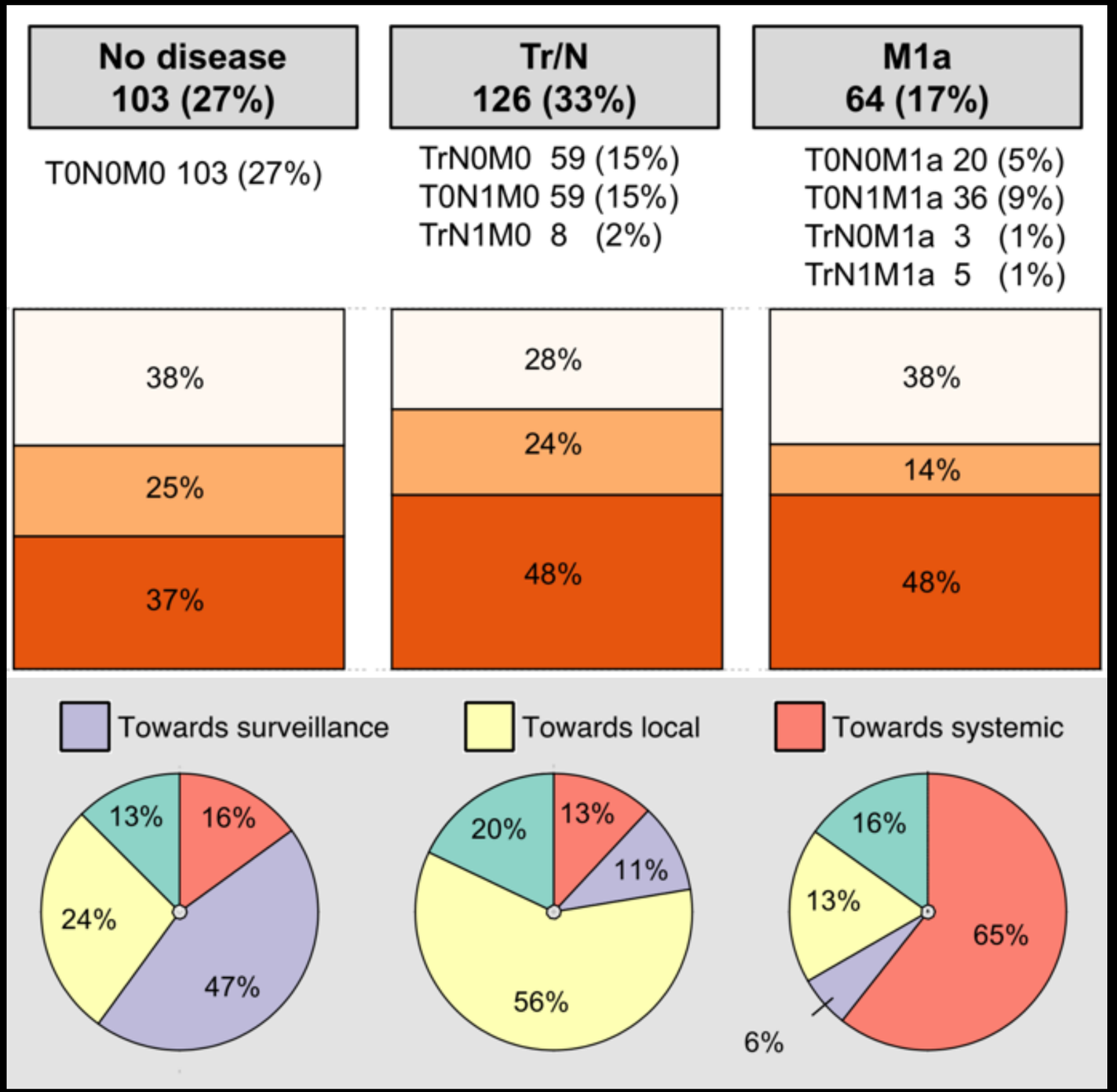




Boreta Urology 2019

Management changes depends on location of disease

- Neg > surveillance
- Pelvic nodes > RT
- Mets > systemic



Fendler 2019 JNM

Biochemical recurrence

Post RP: PSA increase from 0.5 to 0.9

WB anterior MIP

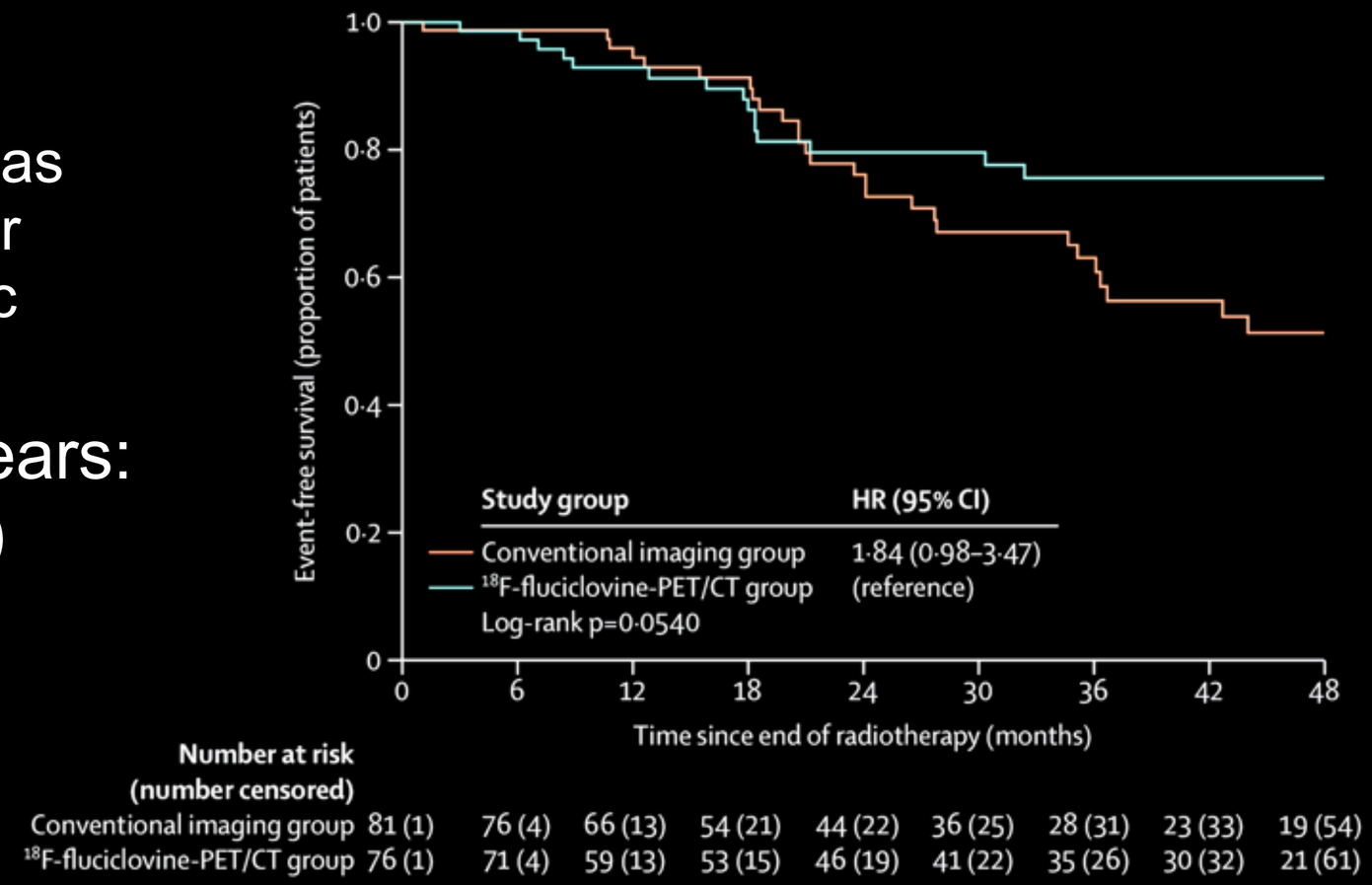
Disease site 1: right pelvic side wall node 1

Disease site 2: right pelvic side wall node 2

EMPIRE-1: Fluciclovine vs CI

- Post-RP BCR patients
- Primary endpoint:
  - Event free survival (events defined as biochemical or clinical recurrence or progression, or initiation of systemic therapy)
- Biochemical free survival @ 4 years: 51.2% versus 75.5% (p<0·0001)

	Conventional imaging-guided (n=82)	^{18}F-fluciclovine-PET/CT-guided (n=83)
PSA before radiotherapy, ng/mL	0·34 (0·82)	0·34 (0·92)
Androgen deprivation therapy—long-term use (18–24 months)	8 (10%)	9 (11%)
Androgen deprivation therapy—any use	28 (35%)	30 (38%)



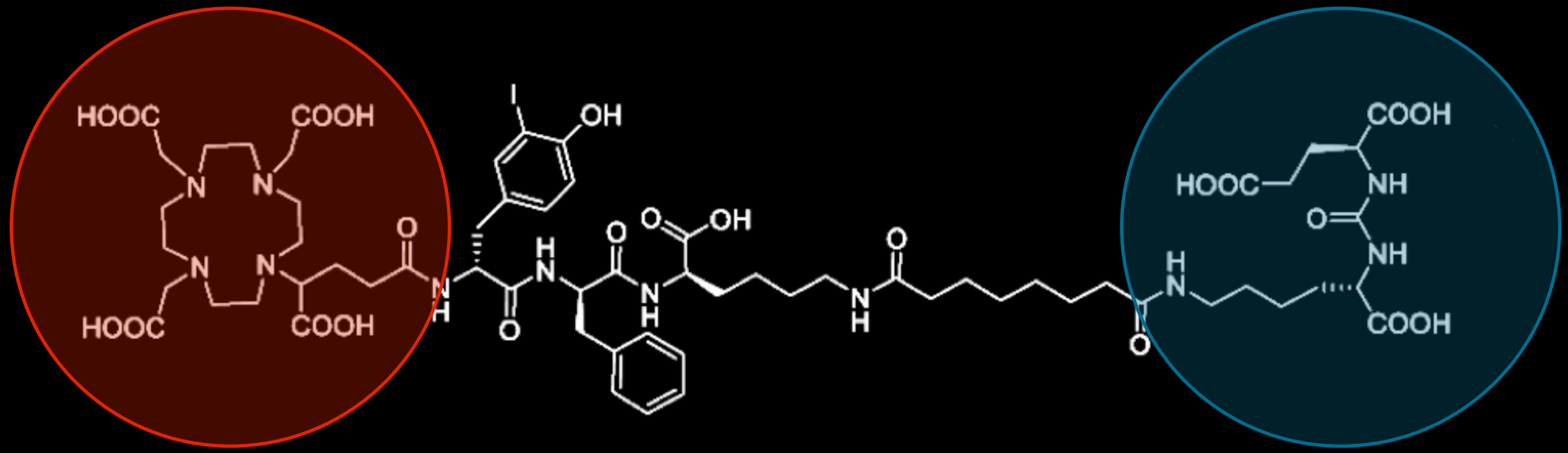
Jani 2021 Lancet

Theranostics

- The use of a compound for both diagnostics and therapeutics

Imaging
Ga-68

Therapy
Lu-177
Y-90

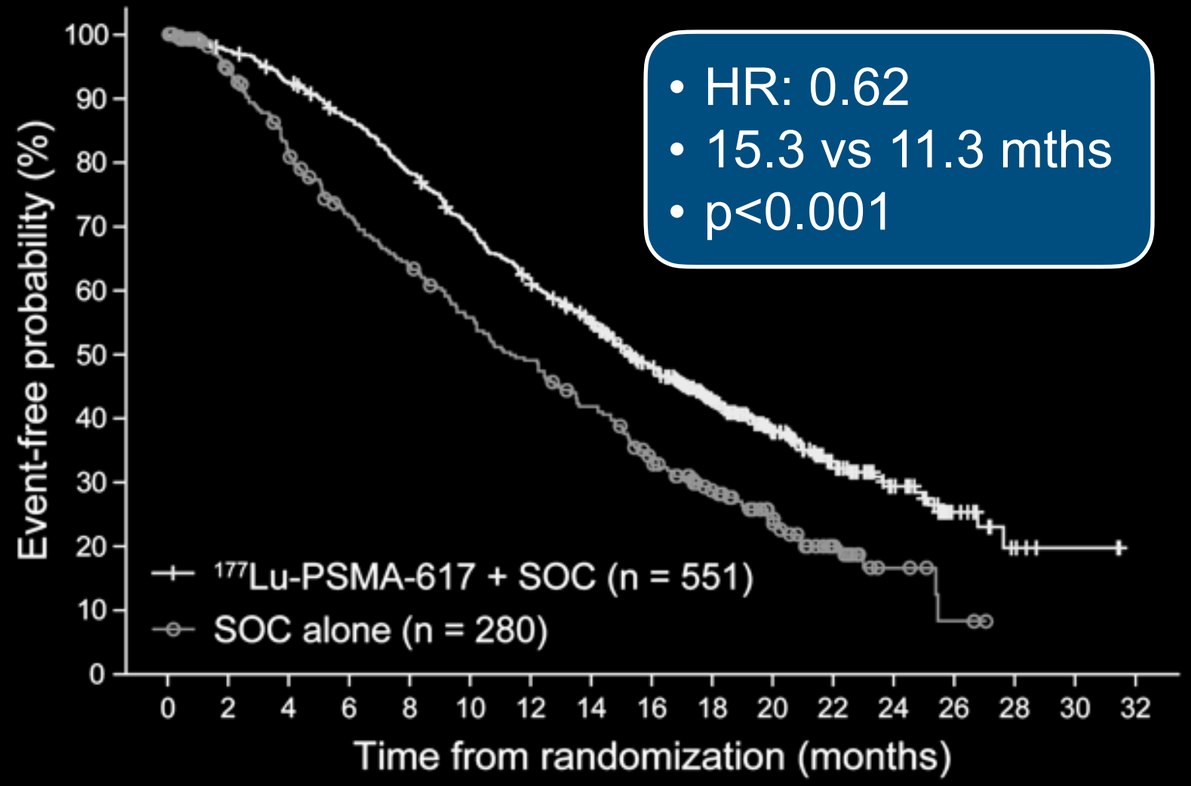


PSMA I&T

Schottelius 2015,
EJNNMI Research

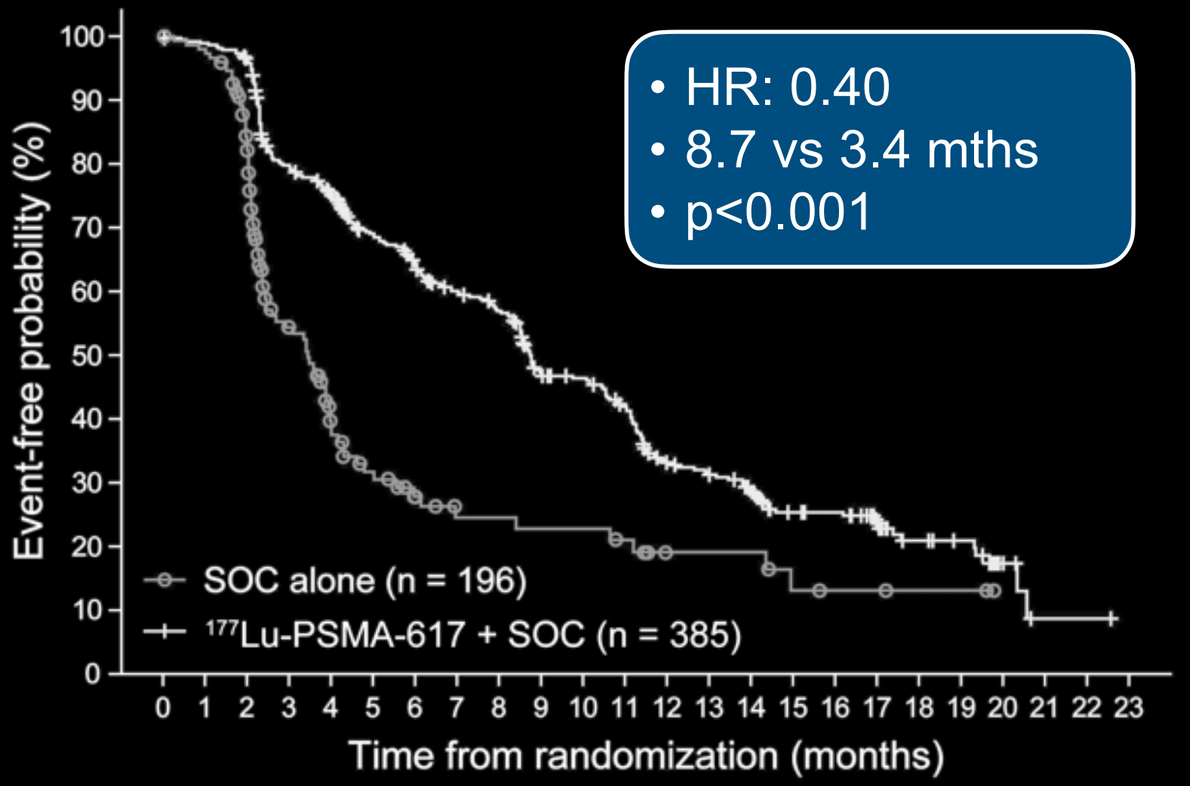
VISION results: 177Lu-PSMA-617

Overall Survival



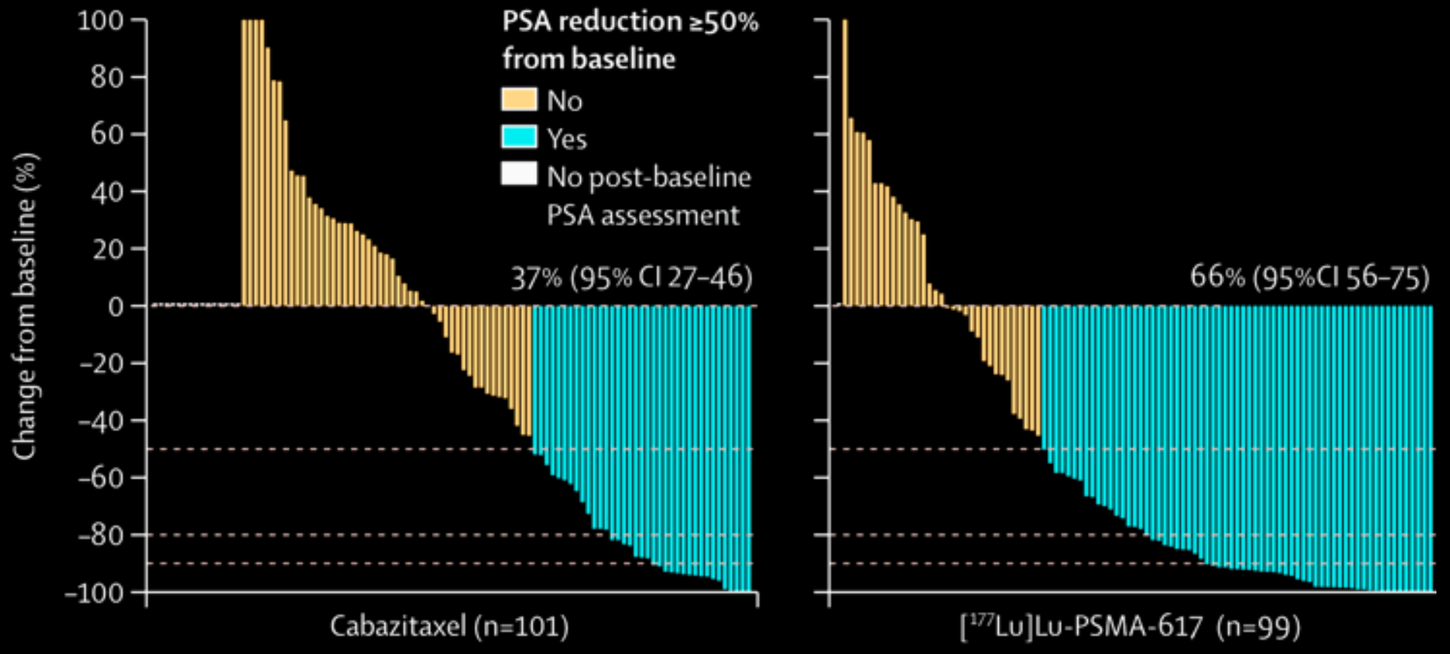
- HR: 0.62
- 15.3 vs 11.3 mths
- p<0.001

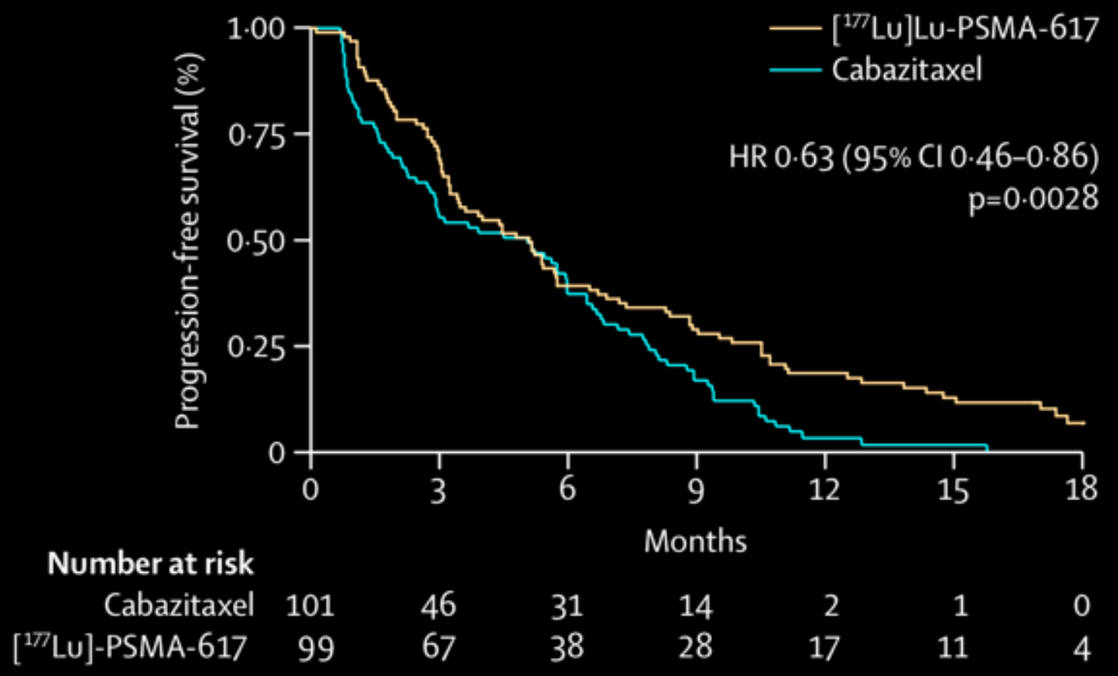
PFS



- HR: 0.40
- 8.7 vs 3.4 mths
- p<0.001

TheraP trial…





Hofman et al Lancet 2021

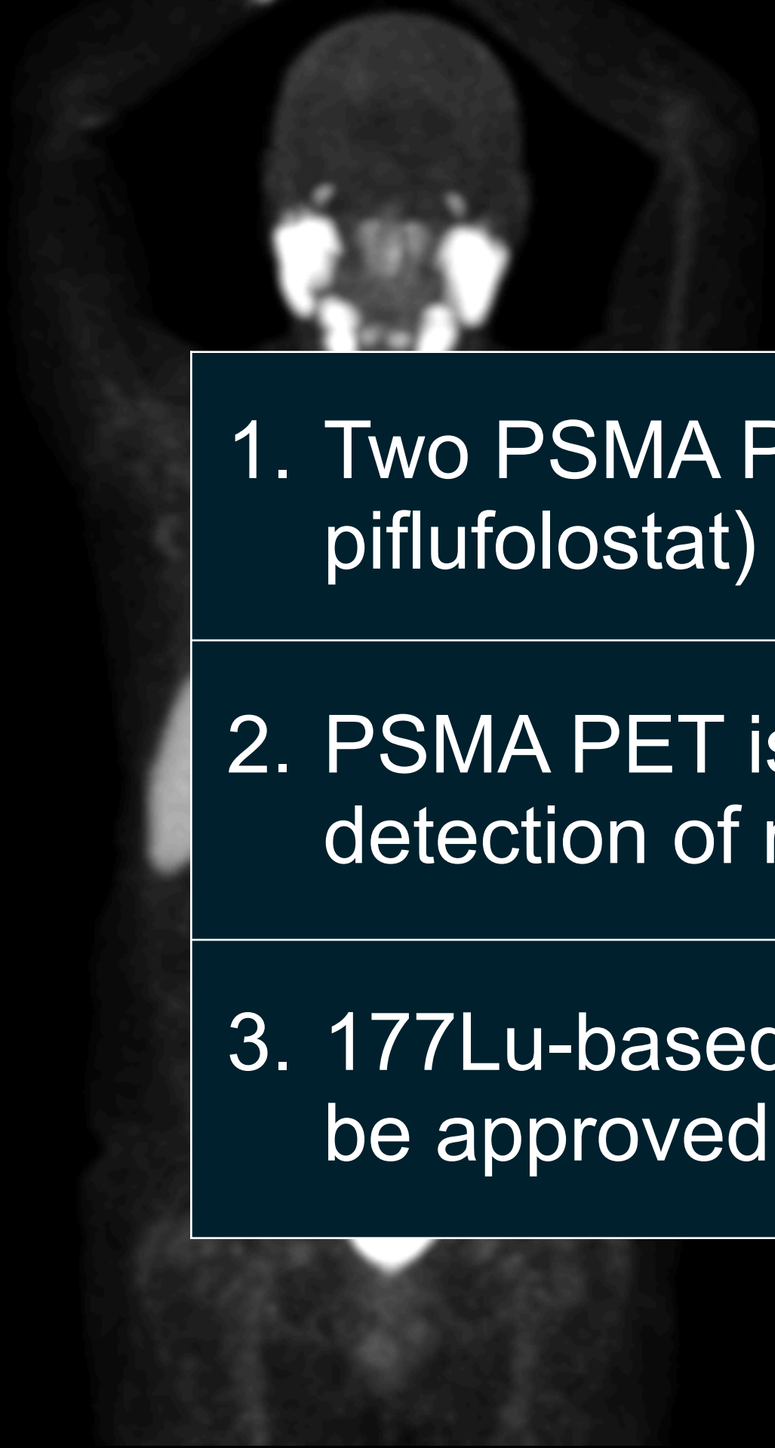
Pending PSMA trials

Company sponsored	Academic trials
PSMAddition (AAA/Novartis); n=750+ 177Lu-PSMA-617+ADT/abi vs ADT/abi Metastatic CSPC	ENZA-P (ANZUP); n=160 177Lu-PSMA-617+enza vs enza First line mCRPC
PSMAfore (AAA/Novartis); n=495 177Lu-PSMA-I&T vs second line abi/enza Pre-chemo mCRPC	LuPARP (Peter Mac); n=52 177Lu-PSMA-617 + olaparib Post-chemo mCRPC
SPLASH (POINT Biopharma); n=415 177Lu-PSMA-I&T vs second line abi/enza Pre-chemo mCRPC	CCTG trial; n=200 177Lu-PSMA-617 vs docetaxel Pre-chemo mCRPC
AcTION (AAA/Novartis); n=30 225Ac-PSMA-617 Phase 1 Pre/post-chemo mCRPC	Bullseye (Radbound); n=58 177Lu-PSMA-617 in oligometastatic patients Pre-hormonal mCSPC

Nuclear Medicine Therapy
@therapynuclear

Targeted Ac225 Alpha Therapy is one of the most effective Treatments for Metastatic Prostate Cancer. For more information on the efficacy of Actinium 225 Therapy do call us at +91 98111 27080, or write to us at info@nuclearmedicinetherapy.in or visit nuclearmedicinetherapy.in

3:44 AM · Sep 27, 2021 · Twitter Web App



Summary

1. Two PSMA PET radiotracers (PSMA-11 and 18F-piflufolostat) are FDA approved and covered by Medicare
2. PSMA PET is superior to existing radiotracers for the detection of metastatic prostate cancer
3. 177Lu-based PSMA-targeted radioligand therapy should be approved by the FDA in the coming months


Thank you!
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