ARC
Advanced Radiology Center

UNIVERSITÀ CATTOLICA del Sacro Cuore

Controversy: Should Molecular Imaging Fully Replace Conventional Imaging?

(staging of intermediate and high-risk prostate cancer)

Against

Evis Sala, MD, PhD, FRCR, FRCP

EANM Focus Meeting Disclosure Statement (COI)

UNIVERSITÀ CATTOLICA del Sacro Cuore

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	GE Healthcare
Receipt of honoraria or consultation fees:	GE Healthcare
Participation in a company sponsored speaker's bureau:	GE Healthcare, Canon
Co-founder and stock shareholder:	Lucida Medical

NGI for unfavorable intermediate and high-risk - limitations

Multiple NGI tracers: varying sensitivity even within the PSMA family (polymetastatic invisible disease concept)

False +ve lesions: non-malignant conditions, higher for PSMA-1007 tracer

False -ve disease: 5-10% of patients

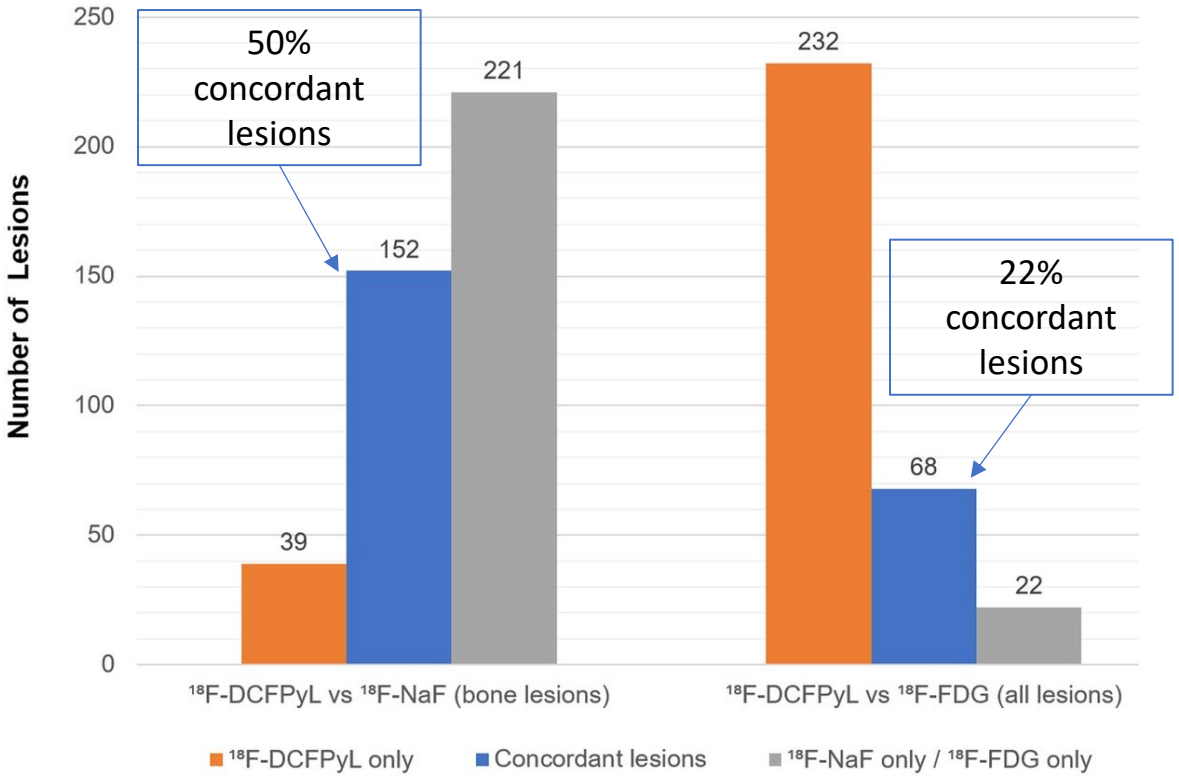
Biases: Will-Rogers effect, stage migration, lead-time and length time bias

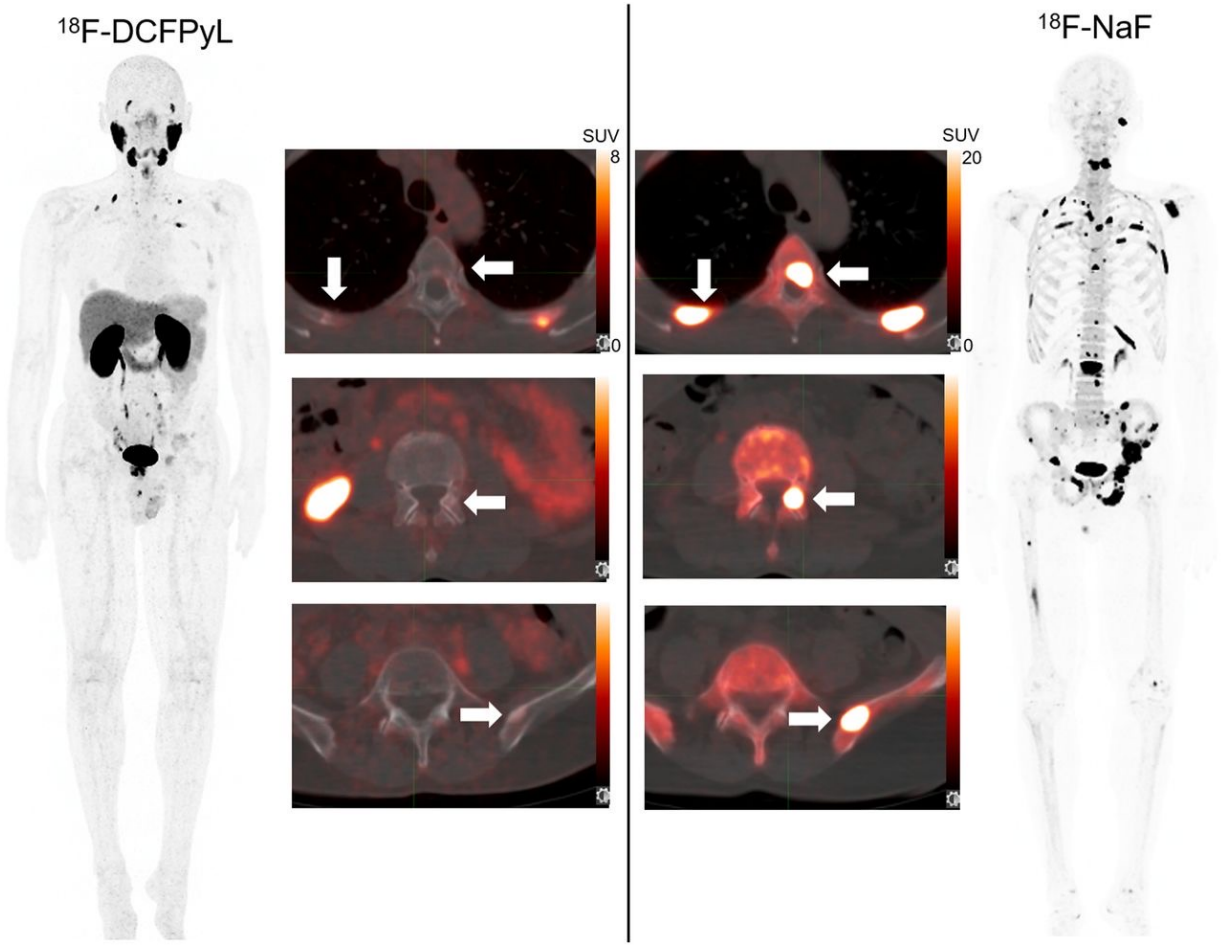
Outcome impacts: Do management impacts ‘really’ change net patient outcomes?

Changing metastasis numbers by PET tracer type

Highly unlikely that a single tracer will all lesions given the heterogenous nature of metastatic prostate cancer

Multiple phenotypes of metastases exist even in the same person, especially in mCRPC





Fourquet A, et al. A Comparison of ^{18}F-DCFPyL, ^{18}F-NaF, and ^{18}F-FDG PET/CT in a Prospective Cohort of Men with Metastatic Prostate Cancer. J Nucl Med. 2022 May;63(5):735-741.

NGI for unfavorable intermediate and high-risk - limitations

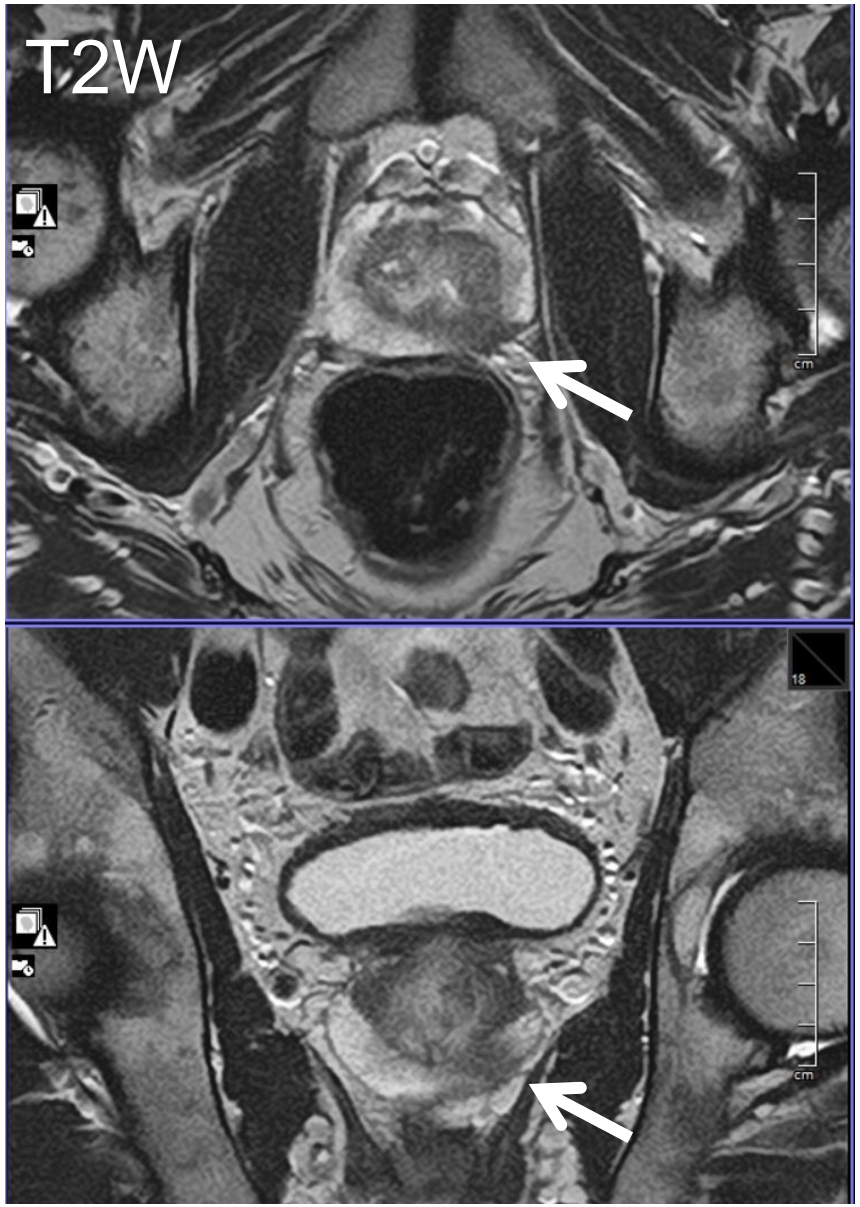
Multiple NGI tracers: varying sensitivity even within the PSMA family (polymetastatic invisible disease concept)

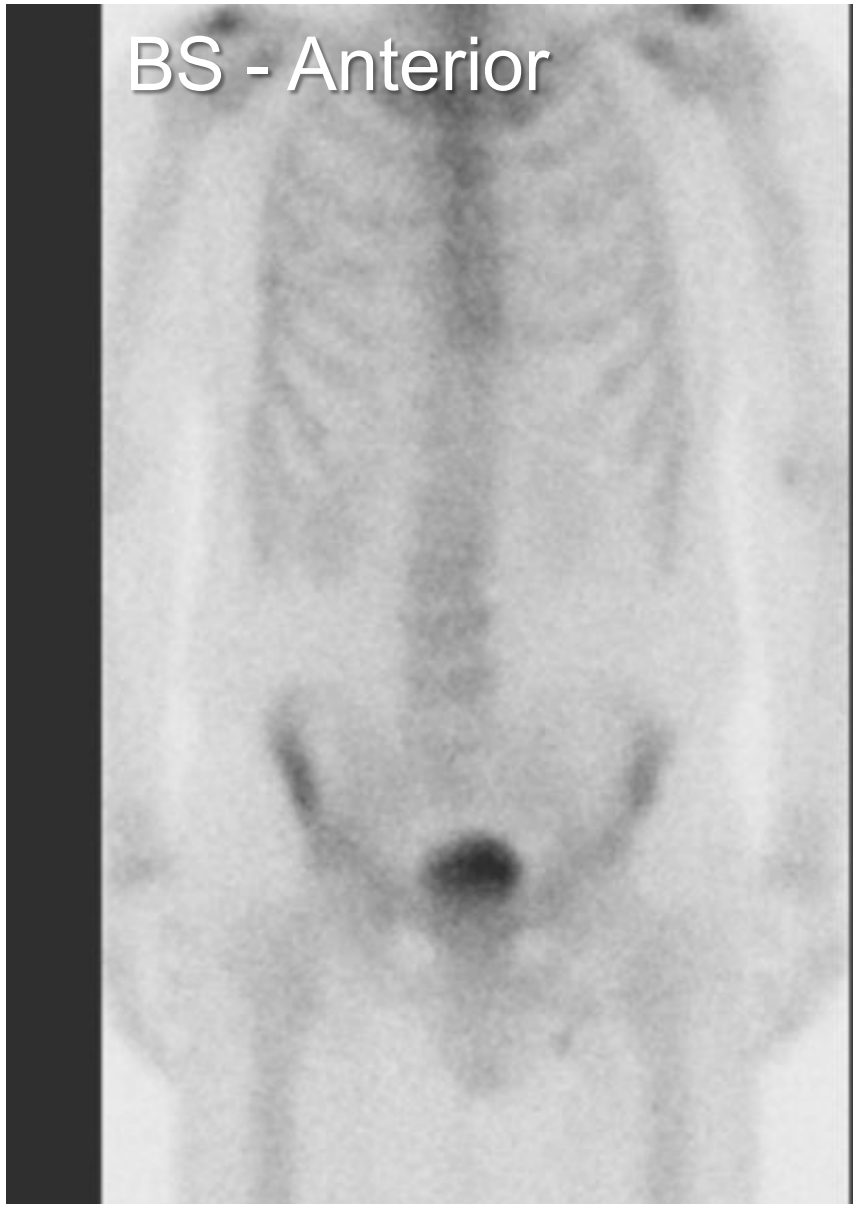
False +ve lesions: non-malignant conditions, higher for PSMA-1007 tracer

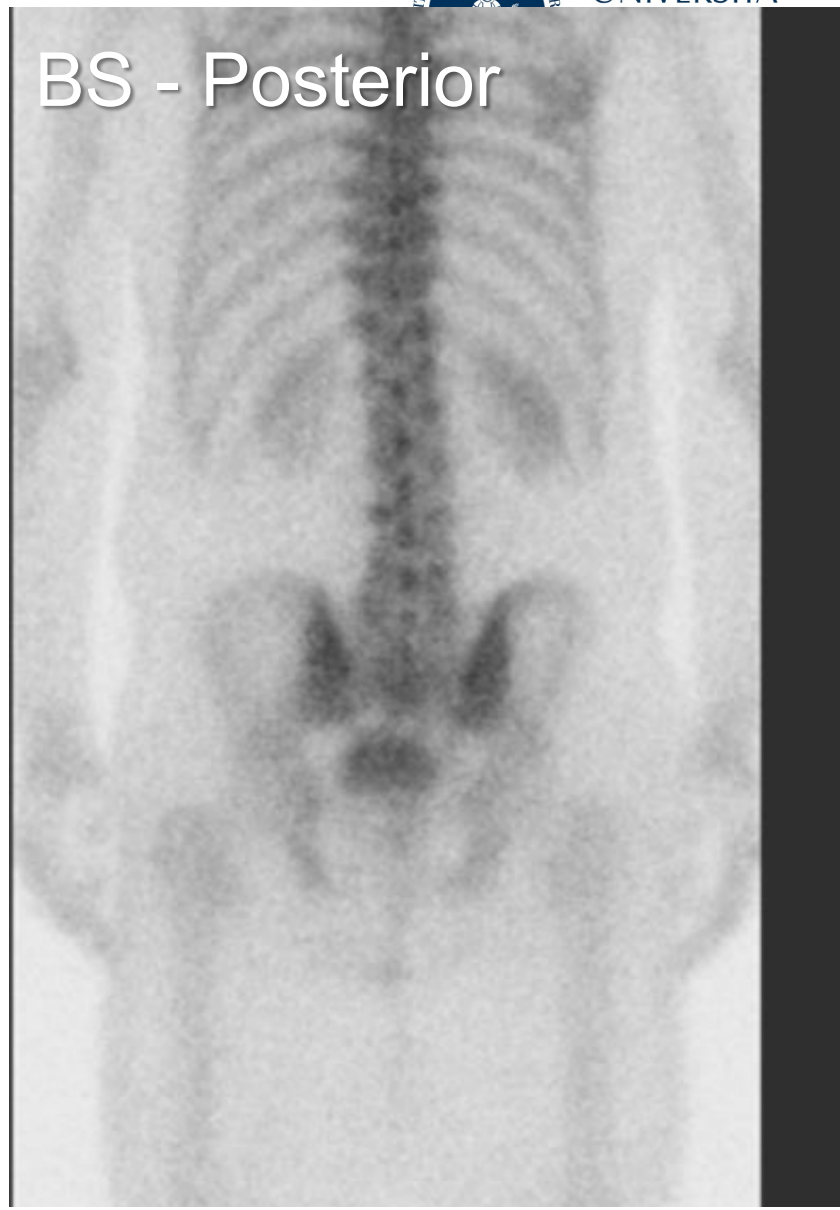
False -ve disease: 5-10% of patients

Biases: Will-Rogers effect, stage migration, lead-time and length time bias

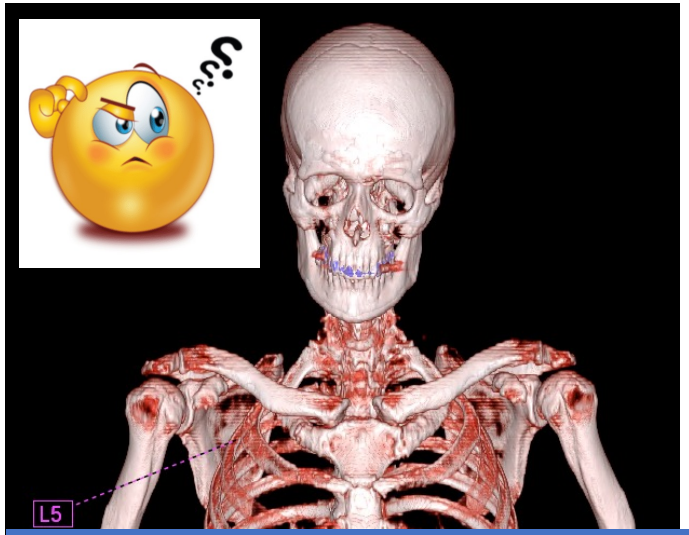
Outcome impacts: Do management impacts ‘really’ change net patient outcomes?

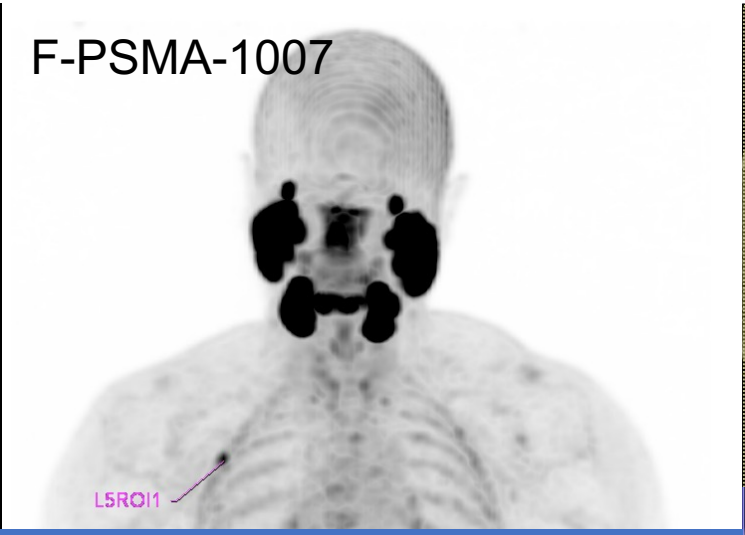


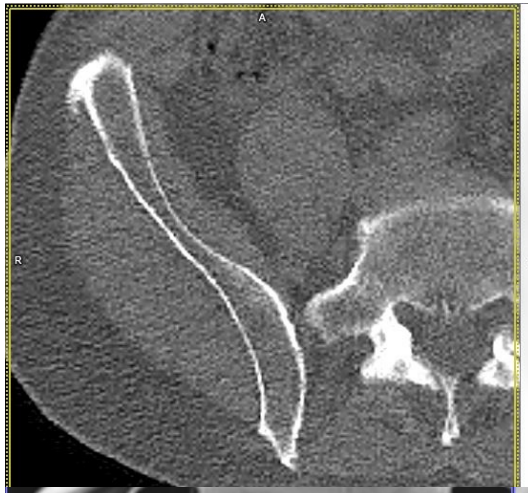


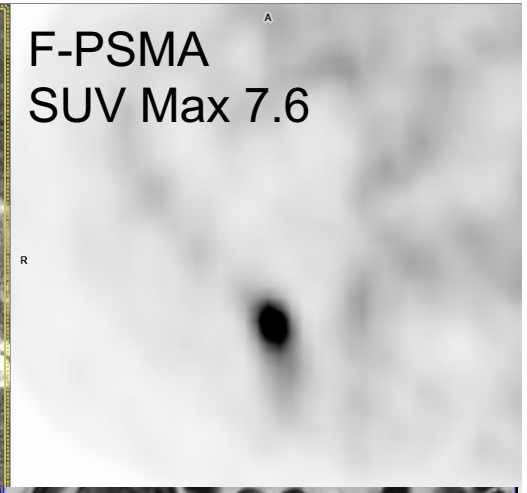


72M PSA 7.2 ng/mL. GS 4+3 (GG3) adenocarcinoma. T3A – microscopic. Bone scan - negative.

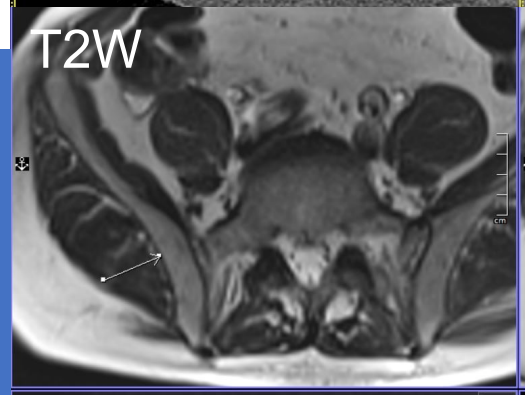


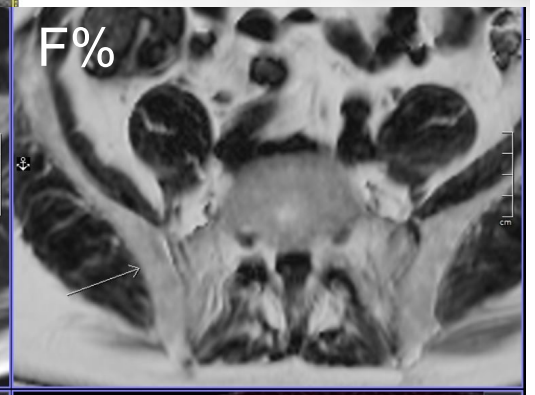


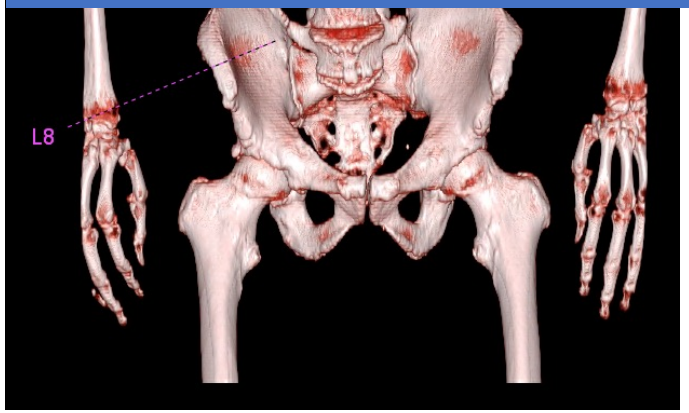


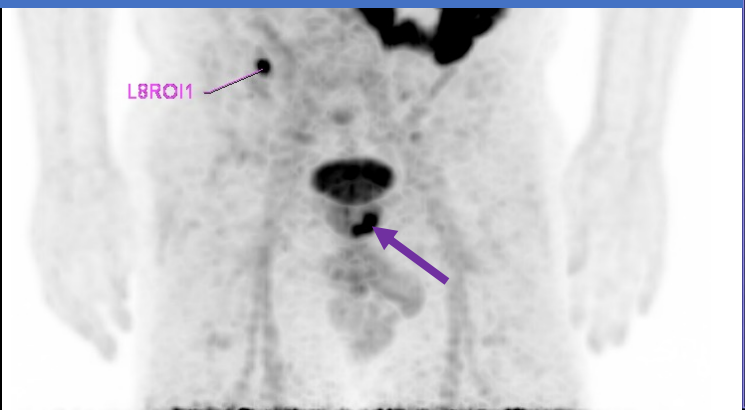


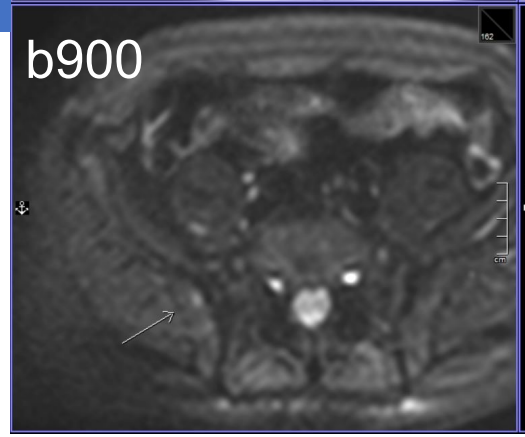
Multimodality or biopsy confirmation & MDT review are needed before Rx decisions

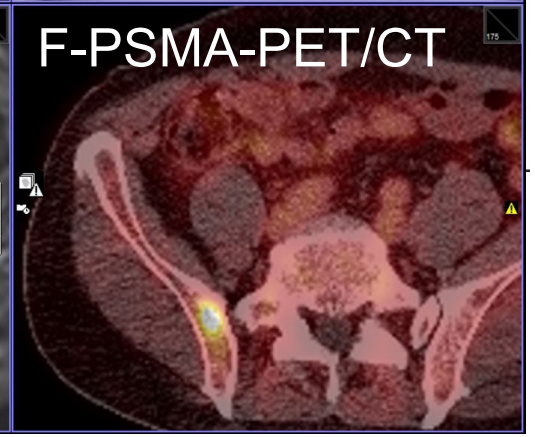








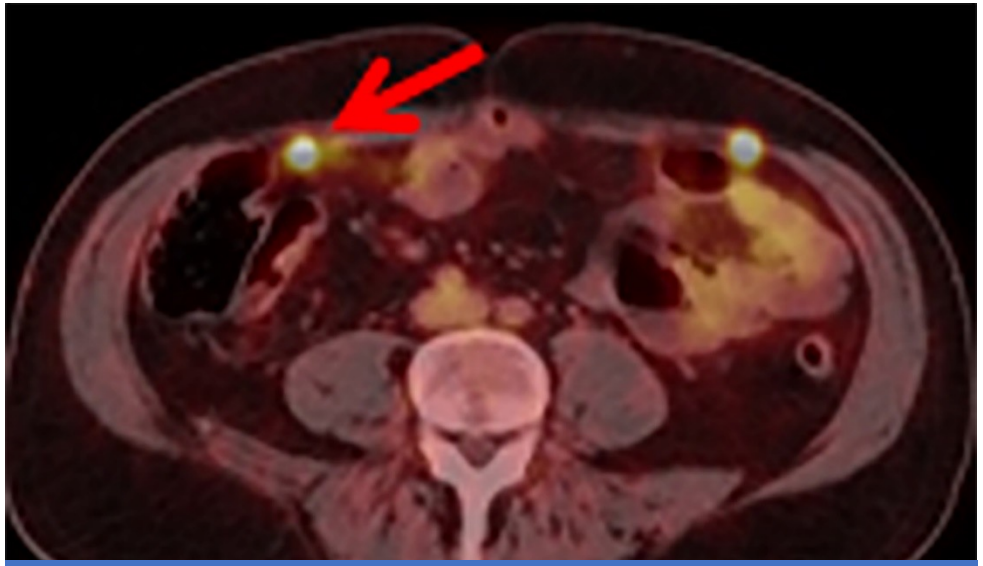




72M PSA 7.2 ng/mL. GS 4+3 (GG3) adenocarcinoma. T3A – microscopic. Bone scan - negative.

18F-DCFPyL PSMA-PET/CT for Initially Diagnosed and Biochemically Recurrent Prostate Cancer: Prospective Trial with Pathologic Confirmation

UNIVERSITÀ CATTOLICA del Sacro Cuore



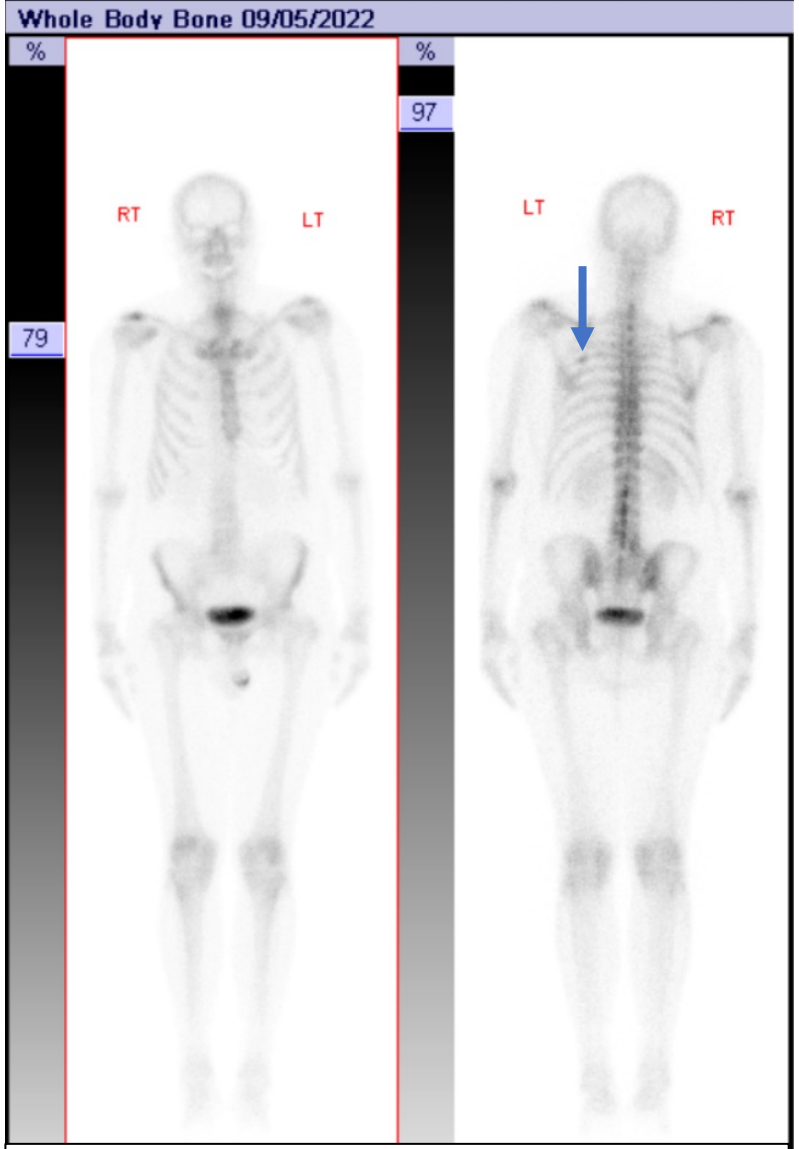
One of out of 4 lesions is not cancer in a biopsy proven study!

Fused DCFPyL PET/CT scan in a 72-year-old man shows biopsy-proven subcentimeter right anterior abdominal wall metastasis (arrow).

- In a prospective trial of DCFPyL in 184 patients with initially diagnosed and recurrent prostate cancer, 50 of 60 (83%) biopsied DCFPyL-avid lesions were malignant at biopsy.
- The biopsy-proven PPV of DCFPyL PSMA-PET/CT for distant metastases in newly diagnosed high-risk prostate cancer was 74% and that for sites of recurrence in men with biochemical recurrence was 89%.
- Solitary DCFPyL avidity in the ribs and pelvis locations should not be presumed as malignant; biopsy may be needed prior to therapy decisions.
- (Multimodality confirmation is an alternative)

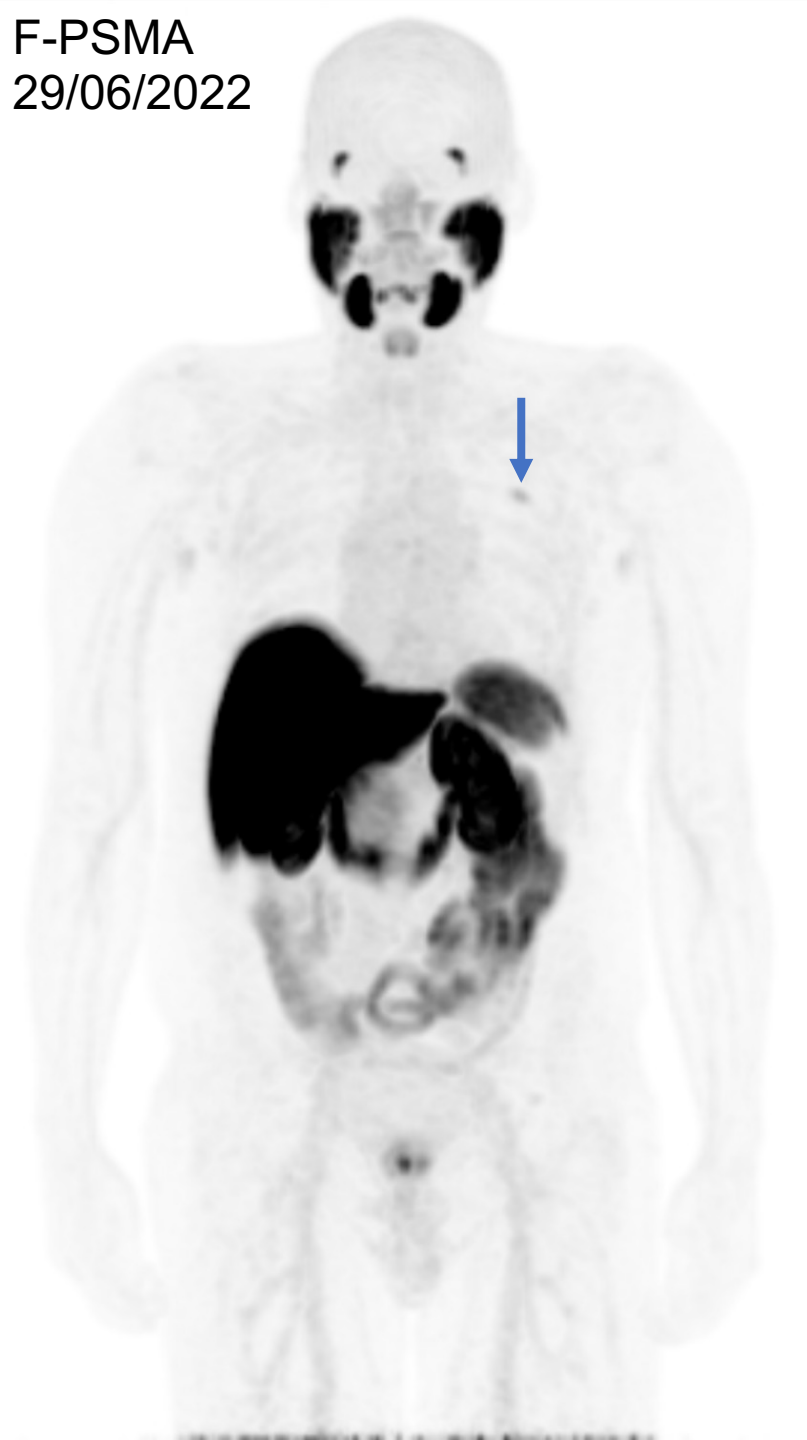
Ulaner GA, et al. ^{18}F-DCFPyL PET/CT for Initially Diagnosed and Biochemically Recurrent Prostate Cancer: Prospective Trial with Pathologic Confirmation. Radiology. https://doi.org/10.1148/radiol.220218

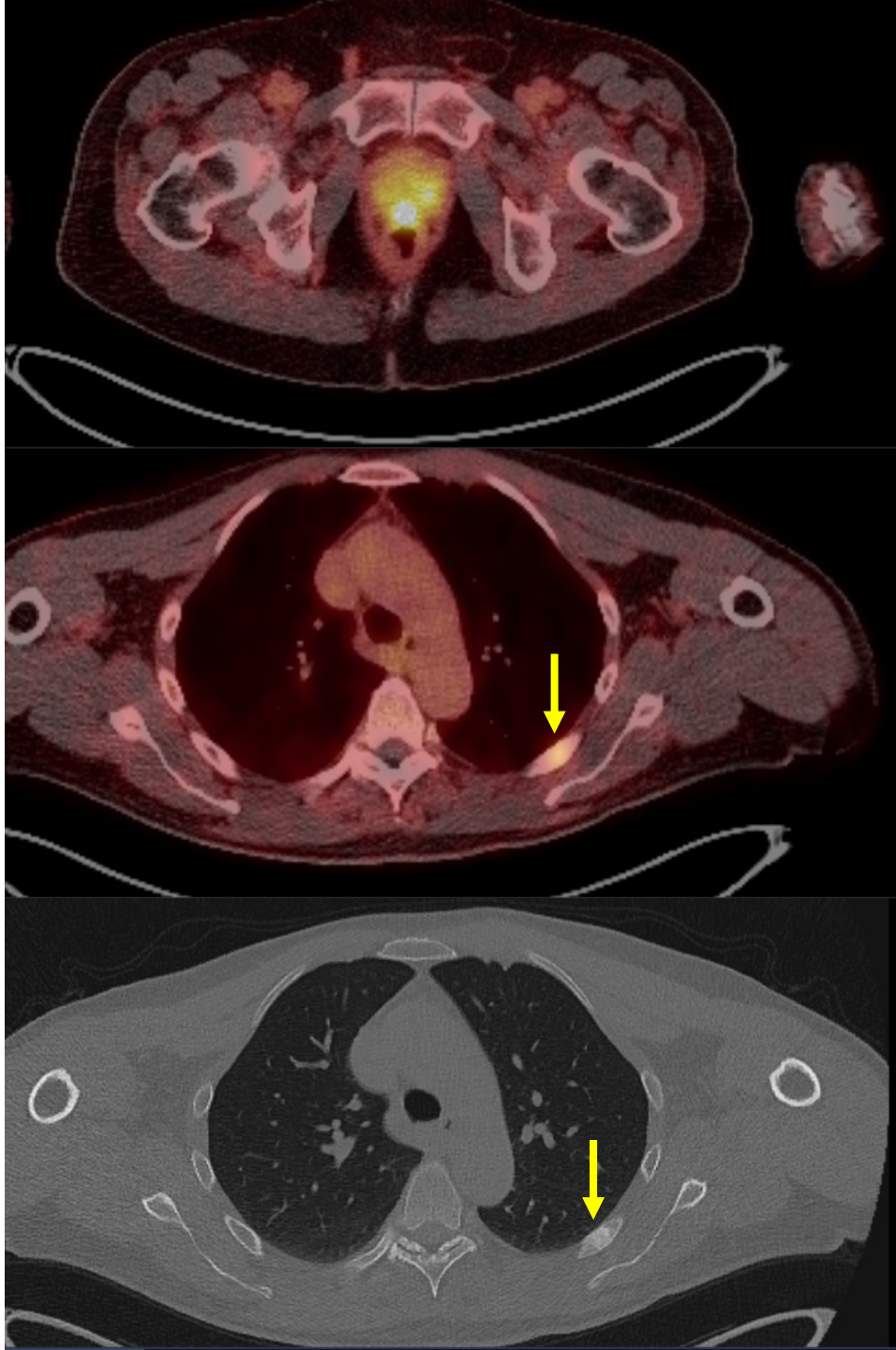
Radiology



66M PSA 9.76 ng/mL.
GS 4+5, TB3.

Rx Docetaxel; Pelvic RT; ADT x 2 years





NGI for unfavorable intermediate and high-risk - limitations

Multiple NGI tracers: varying sensitivity even within the PSMA family (polymetastatic invisible disease concept)

False +ve lesions: non-malignant conditions, higher for PSMA-1007 tracer

False -ve disease: 5-10% of patients

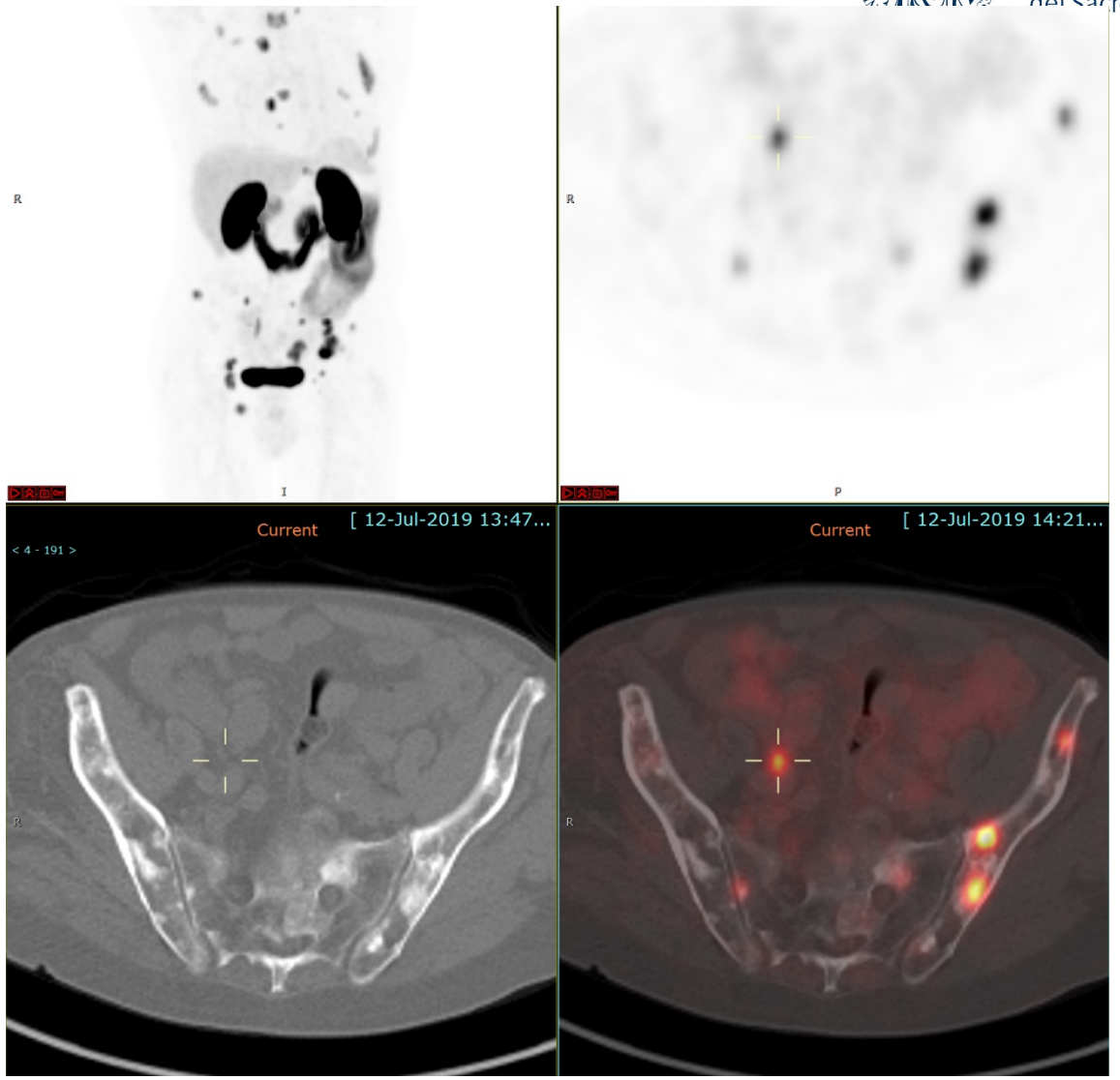
Biases: Will-Rogers effect, stage migration, lead-time and length time bias

Outcome impacts: Do management impacts ‘really’ change net patient outcomes?

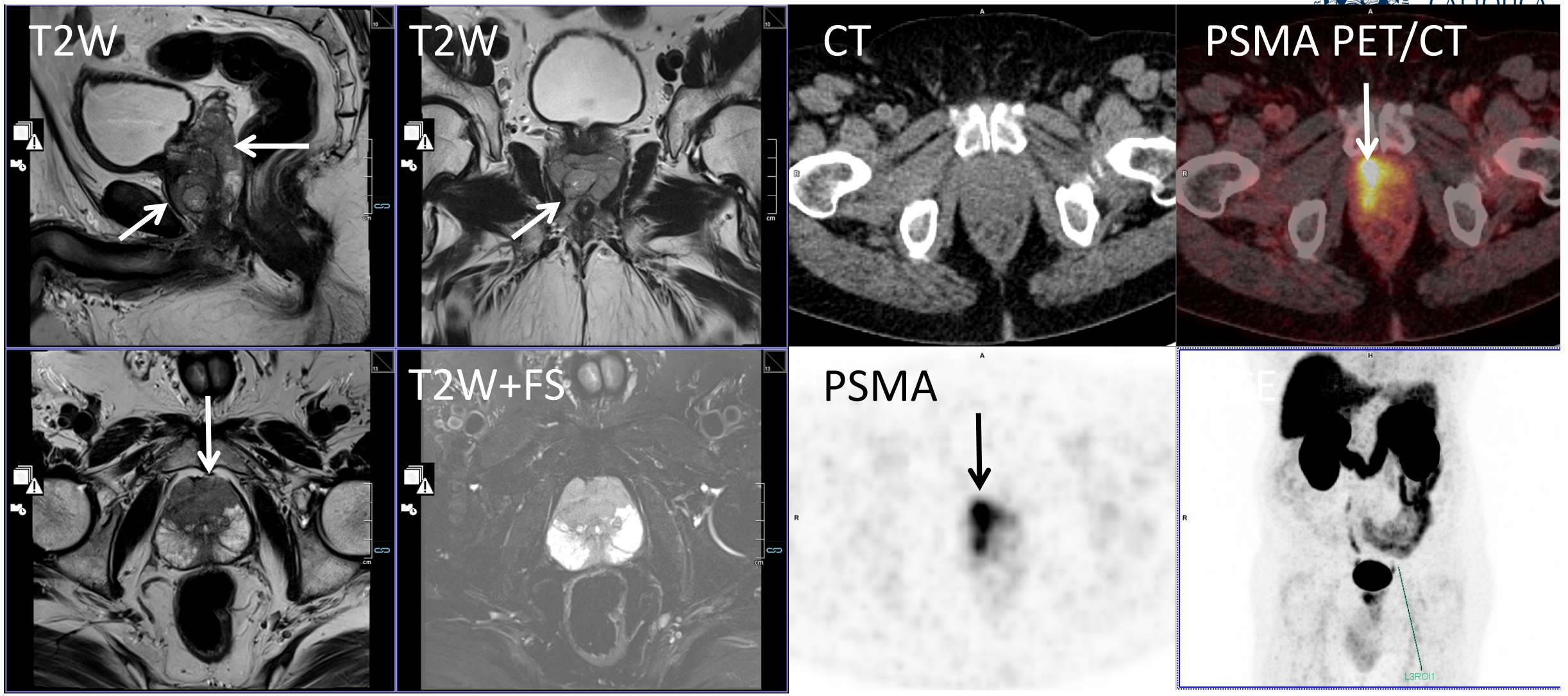
What about false -ve?

- 82M rising PSA on ADT.
- Even the CT scan shows more lesions than PSMA in this patient!
- The NM interpretation was that the PSMA ‘unseen’ lesions were ‘inactive’!!!!

Ga-PSMA-CT/PET

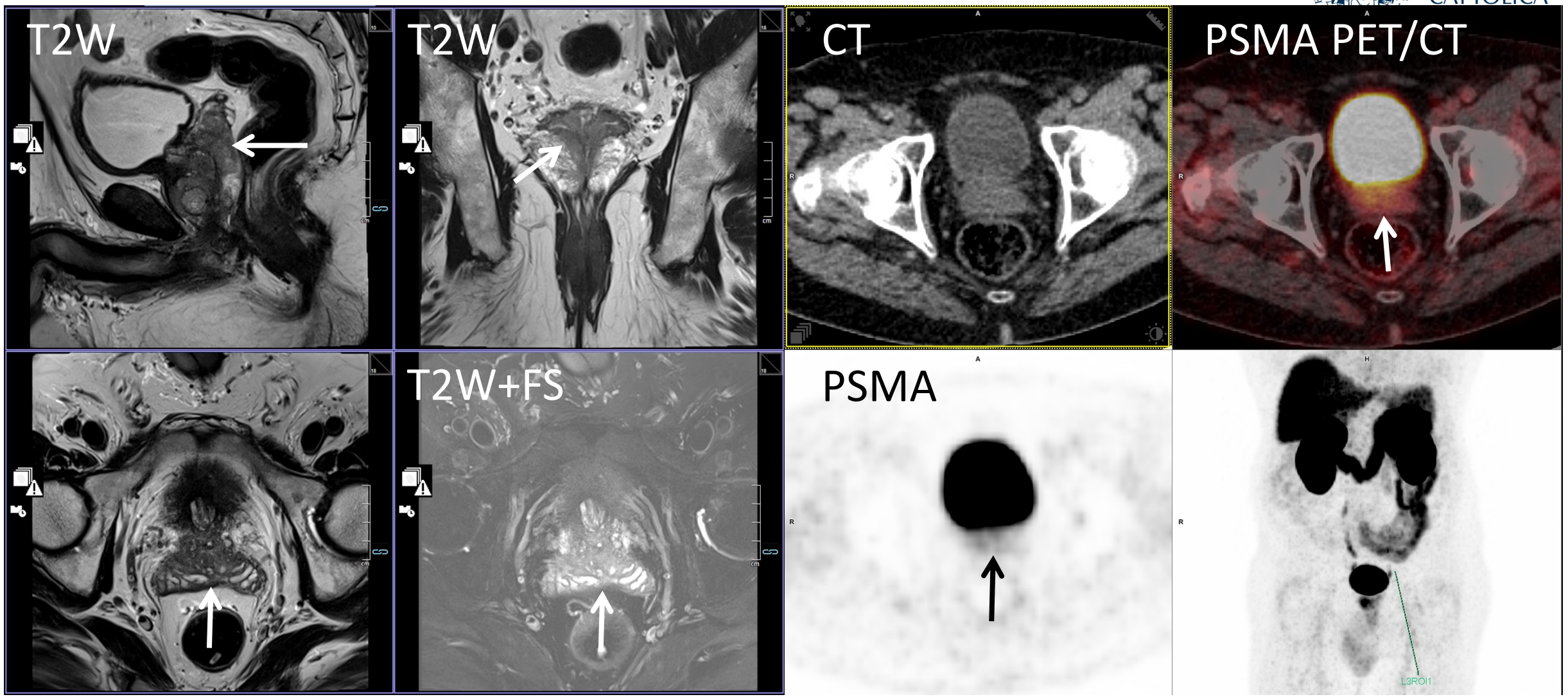


69M, PSA 10ng/mL, Asymptomatic, Routine check, DRE+ve



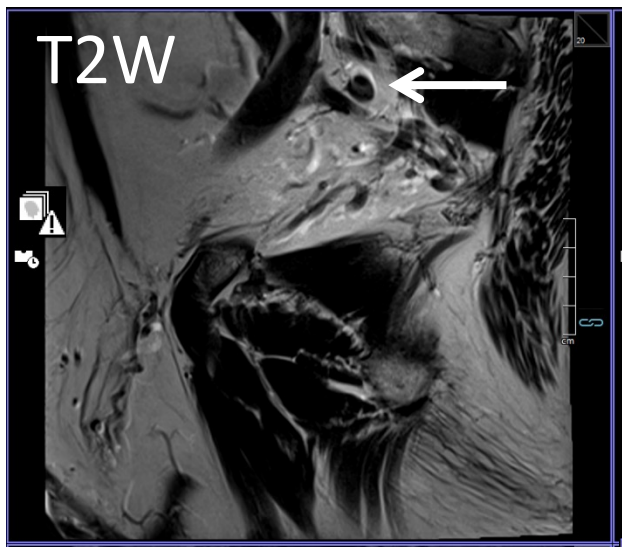
Anterior biopsy: GS4+5, 70% GS=4; Diffuse pattern adenocarcinoma; No small cell neuroendocrine differentiation

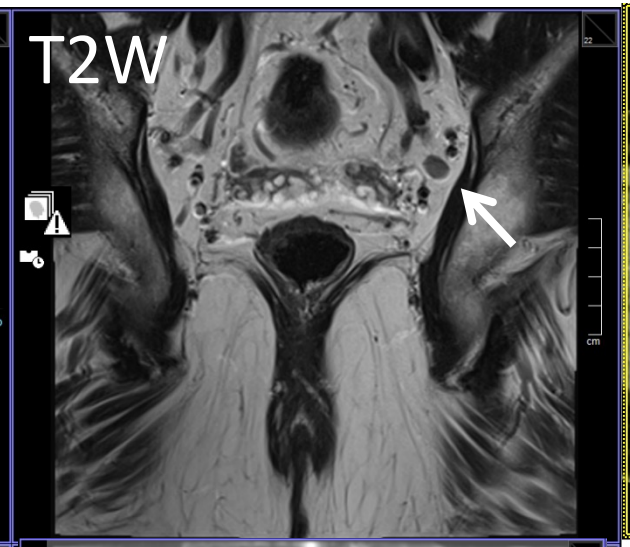
69M, PSA 10ng/mL, Asymptomatic, Routine check, DRE+ve

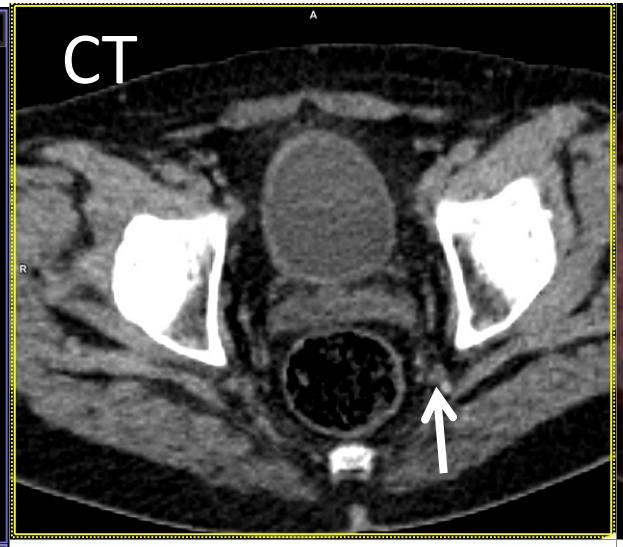


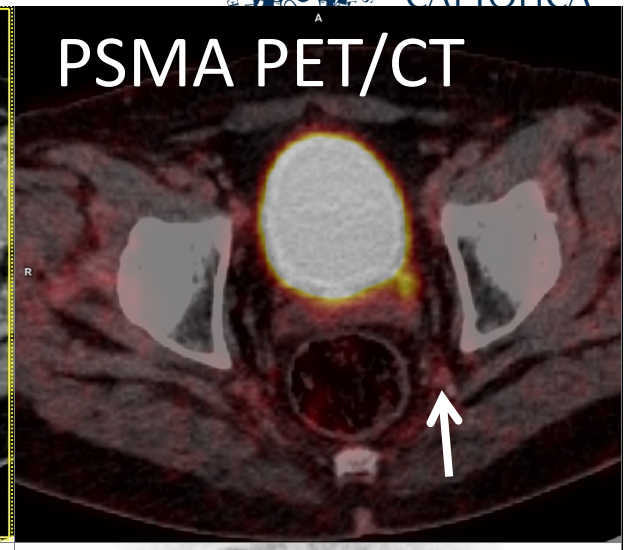
Base biopsy: GS4+5, 80% GS=4; Diffuse pattern adenocarcinoma; No small cell neuroendocrine differentiation

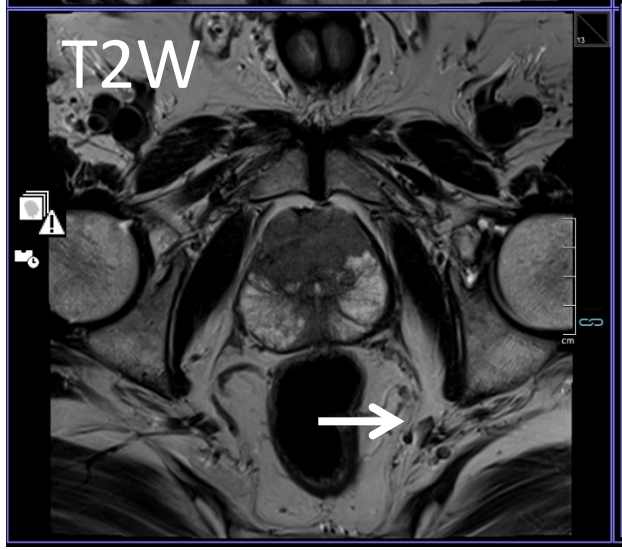
69M, PSA 10ng/mL, Asymptomatic, Routine check, DRE+ve

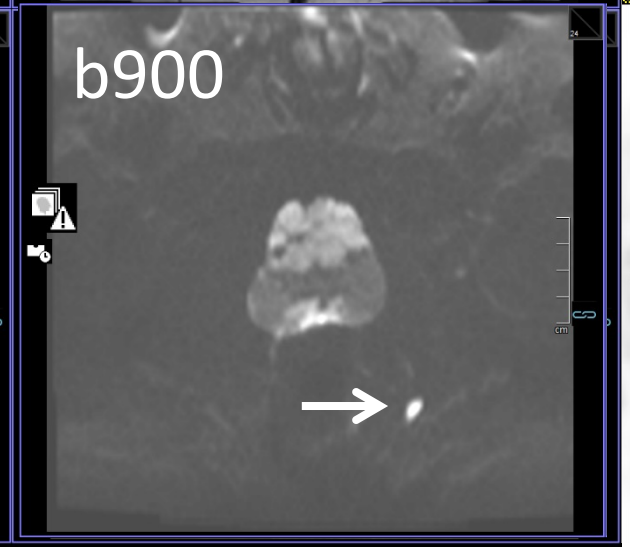


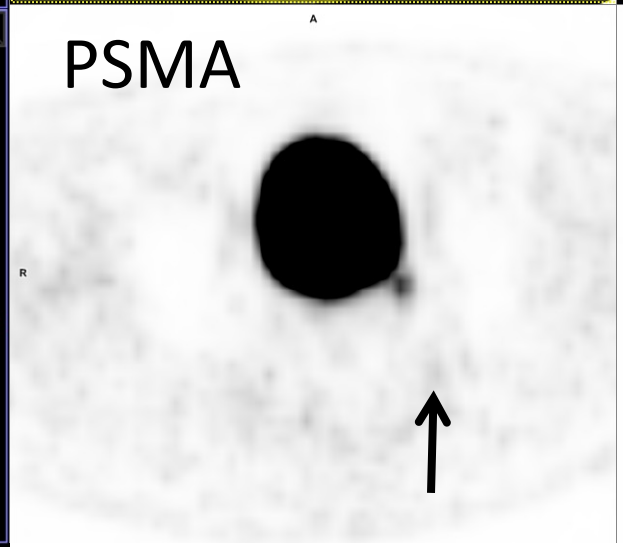


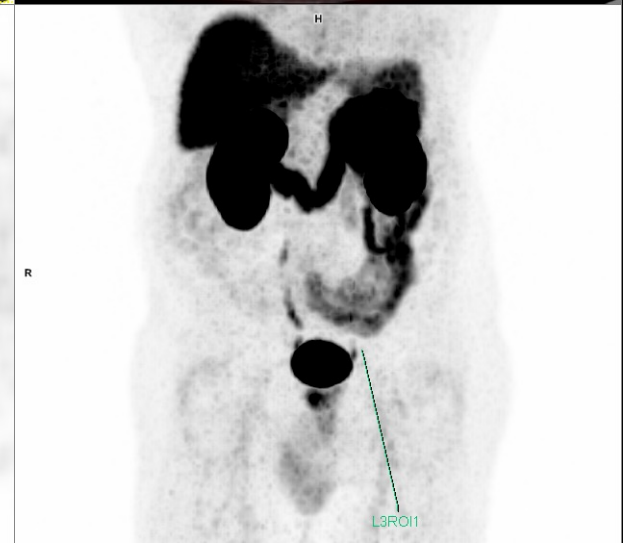






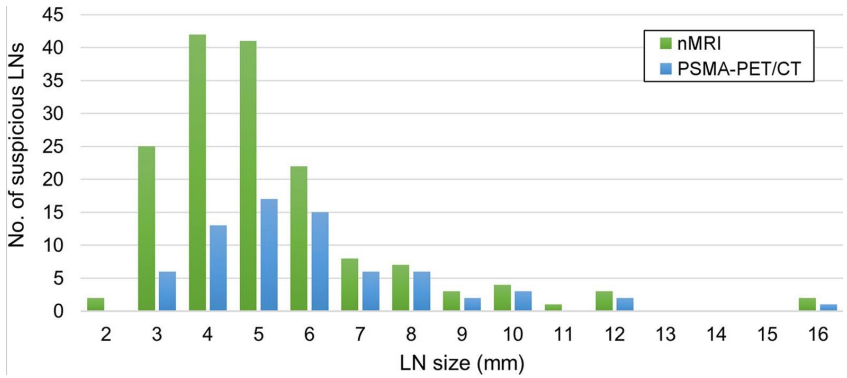


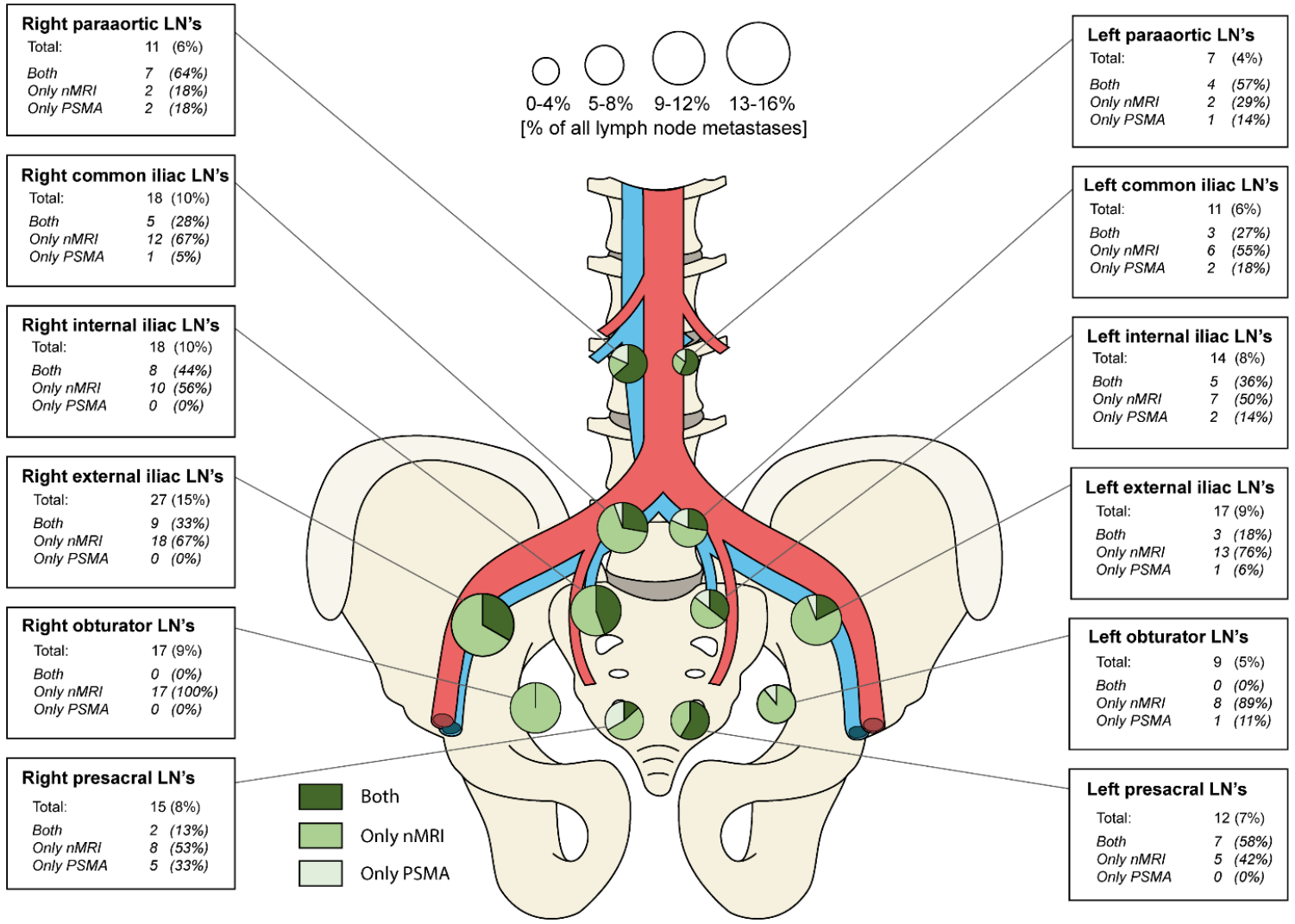




Base biopsy: GS4+5, 80% GS=4; Diffuse pattern adenocarcinoma; No small cell neuroendocrine differentiation

Does PSMA see all nodal disease?





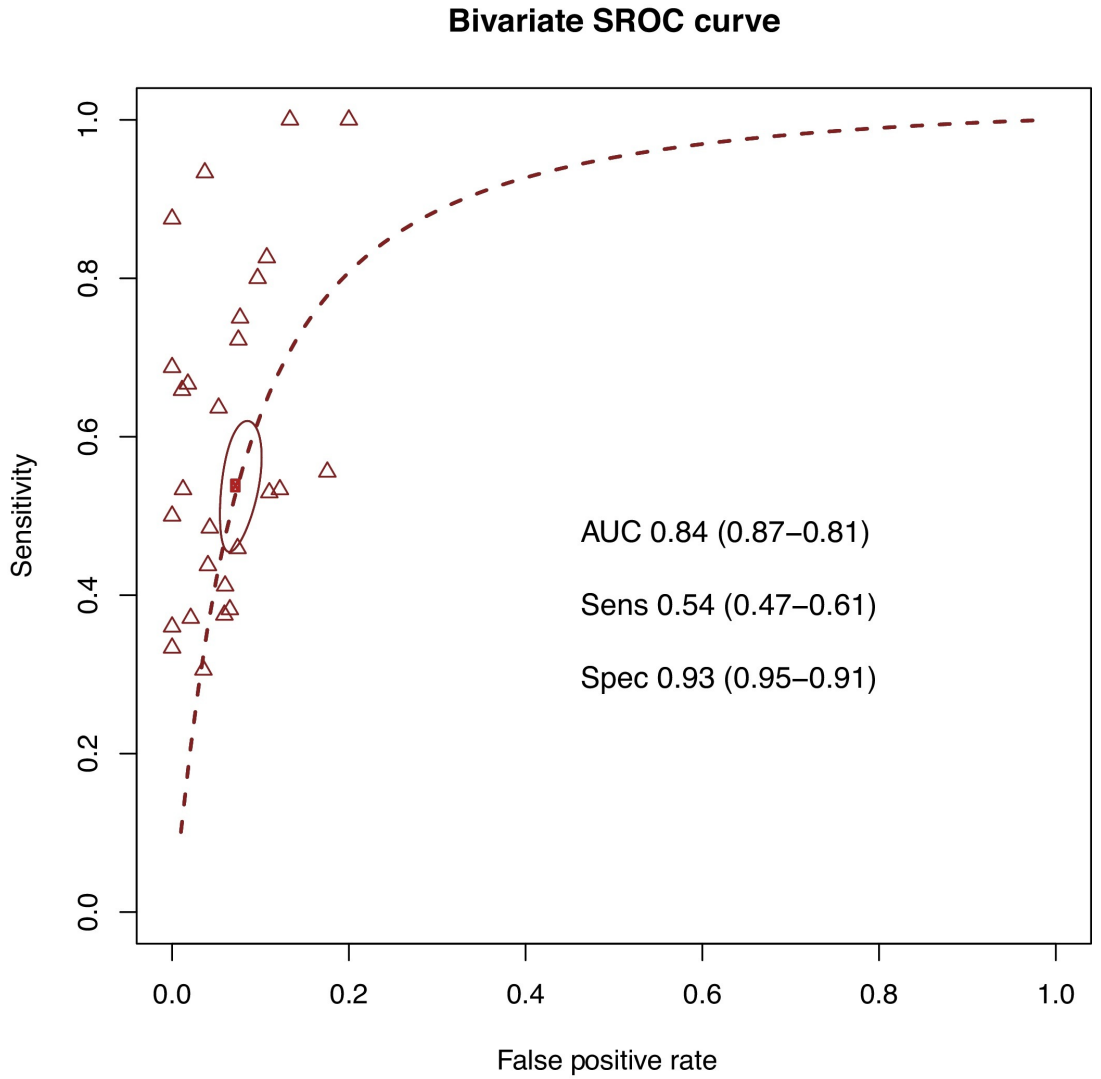
Schilham MGM, et al. Head-to-Head Comparison of ^{68}Ga-Prostate-Specific Membrane Antigen PET/CT and Ferumoxtran-10-Enhanced MRI for the Diagnosis of Lymph Node Metastases in Prostate Cancer Patients. J Nucl Med. 2021 Sep 1;62(9):1258-1263.

Detection rates of PSMA-PET/CT for nodal disease in surgical series

- Majority of small metastatic nodes are consistently missed
  - ≤2 mm → 0% detected
  - 2-4 mm → 25% detected
  - >5 mm → 49-63%*
- Patient/template level sensitivity > node/station level sensitivity
- Lymph-nodal therapies benefits are greatest for men with smaller nodes

Are these µMa important?

*Pouliot F, et al. A prospective phase II/III multi-center study of PSMA-targeted 18F-DCFPyL PET/CT imaging in patients with prostate cancer (OSPREY): a sub-analysis of regional and distant metastases detection rates at initial staging by 18F-DCFPyL PET/CT. J Clin Oncol 2020;38(6 Suppl):9.



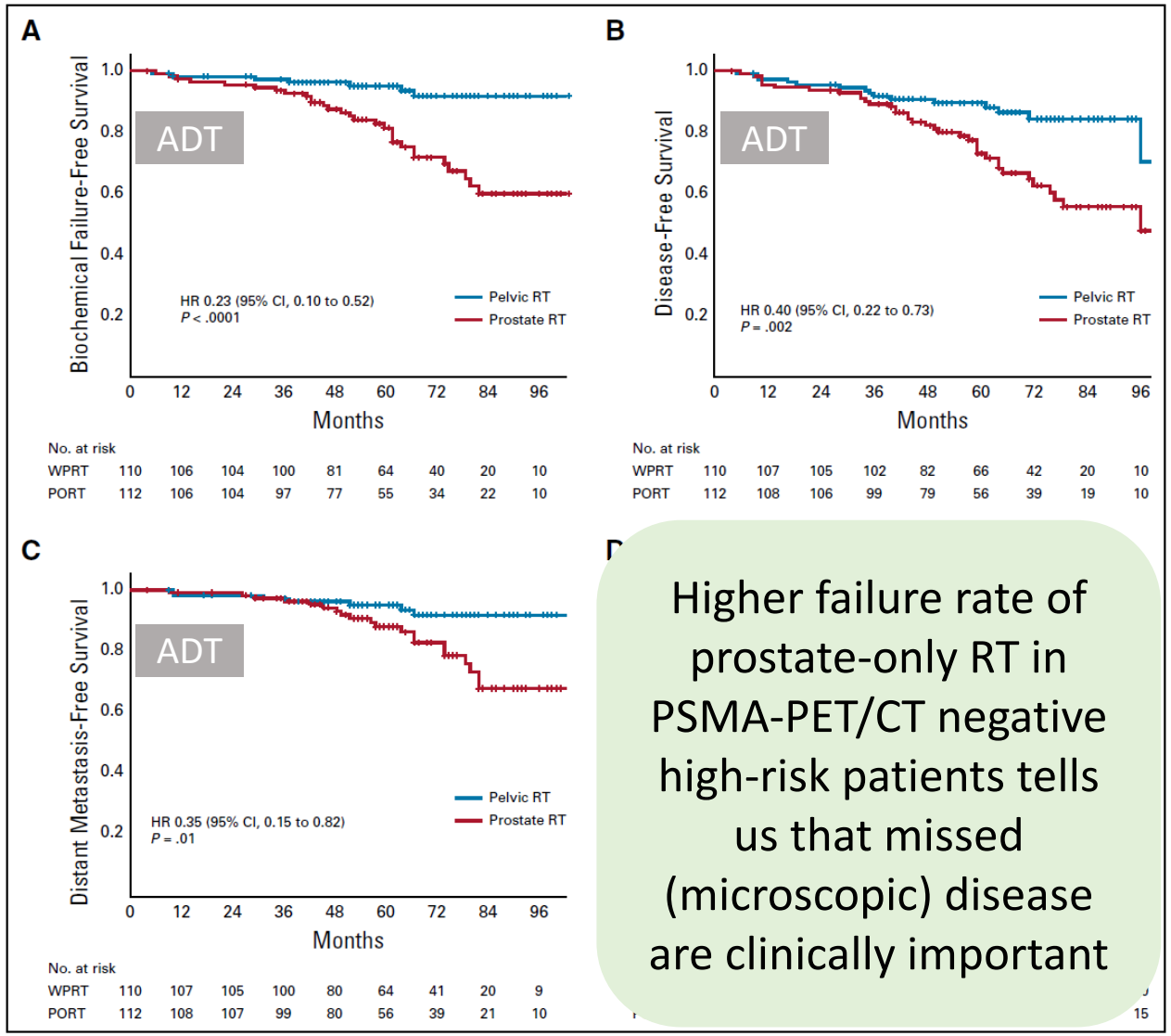
Stabile A, et al. Can Negative PSMA PET/CT Avoid the Need for Pelvic Lymph Node Dissection in Newly Diagnosed Prostate Cancer Patients? A Systematic Review and Meta-analysis with Backup Histology as Reference Standard. Eur Urol Oncol. 2022 Feb;5(1):1-17.

Moderate rule-out ability of PSMA for nodal disease results in higher failure rates in PET-N0 disease with prostate-only radiotherapy

High-risk and very high-risk, locally advanced, node negative PCa

- 224 men
- Very high-risk (NCCN) = 50%
- T3B/T4 = 48%
- 82% were node negative on PSMA-PET/CT

Randomized to prostate only or whole-pelvic radiotherapy (prostate + pelvic nodes, including common iliac) + 2 yrs adjuvant ADT



Higher failure rate of prostate-only RT in PSMA-PET/CT negative high-risk patients tells us that missed (microscopic) disease are clinically important

FIG 2. Kaplan-Meier estimates of biochemical failure-free survival (A), disease-free survival (B), distant metastasis-free survival (C), and overall survival (D). HR, hazard ratio; PORT, prostate-only radiotherapy; RT, radiotherapy; WPRT, whole-pelvic radiotherapy.

Murthy V, et al. Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial. J Clin Oncol. 2021 Apr 10;39(11):1234-1242.

NGI for unfavorable intermediate and high-risk - limitations

Multiple NGI tracers: varying sensitivity even within the PSMA family (polymetastatic invisible disease concept)

False +ve lesions: non-malignant conditions, higher for PSMA-1007 tracer

False -ve disease: 5-10% of patients

Biases: Will-Rogers effect, stage migration, lead-time and length time bias

Outcome impacts: Do management impacts ‘really’ change net patient outcomes?

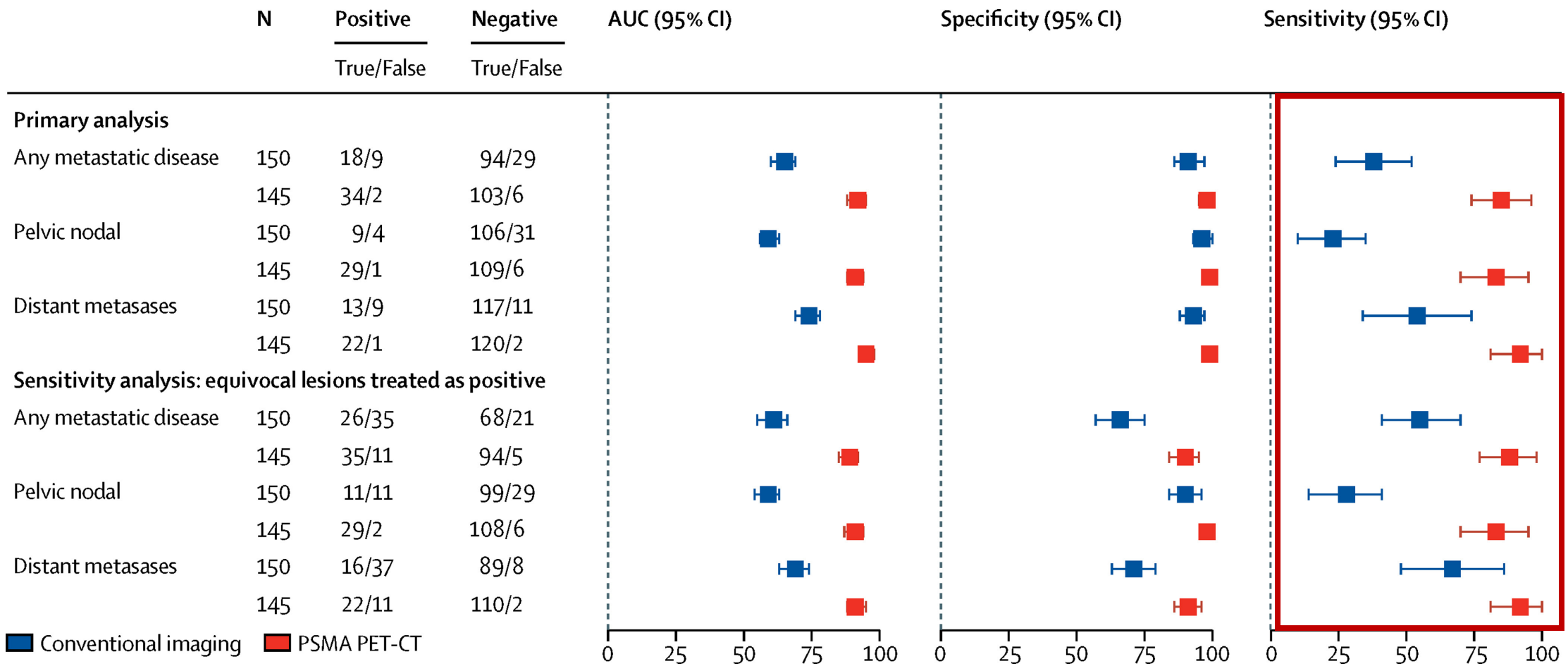
Improves detection (sensitivity): indolent (diagnosis), µM (staging) & µPD (therapy monitoring)

Improves lesion characterizations (specificity)

Survival biases of Next Generation Imaging

@ProfPadhani

Sensitivity improvements outweigh specificity for Ga-PSMA-PET/CT > CT/BS (SPECT)

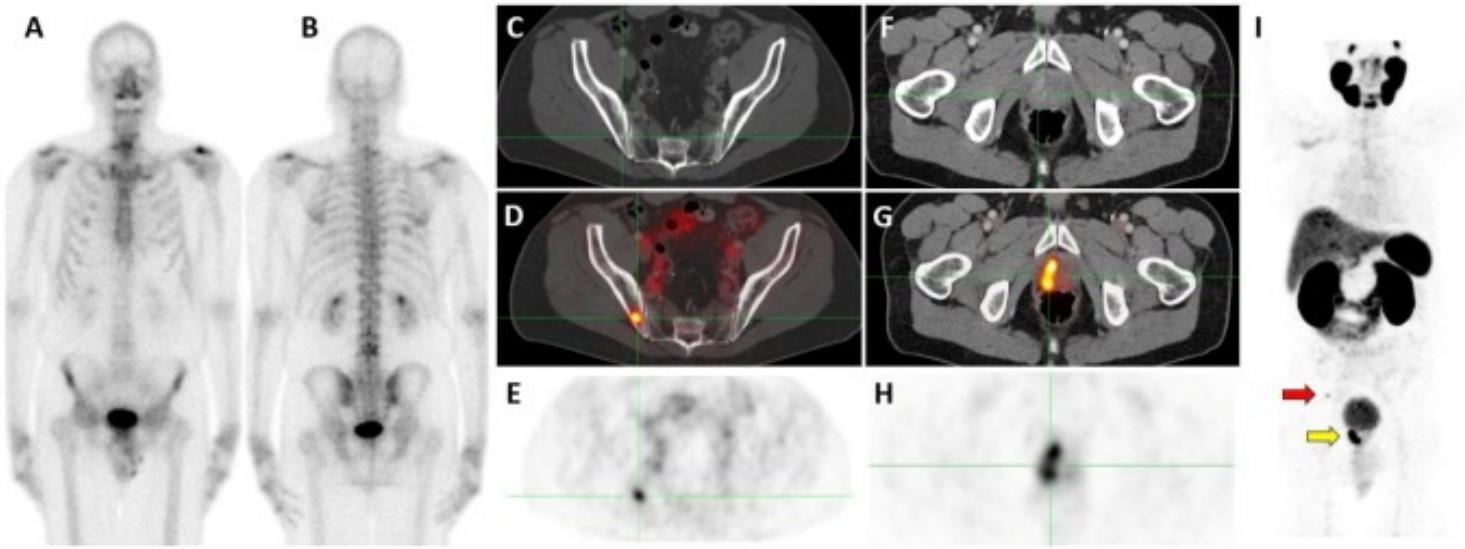


Hofman MS, et al. PSMA PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet. 2020 Apr 11;395(10231):1208-1216.

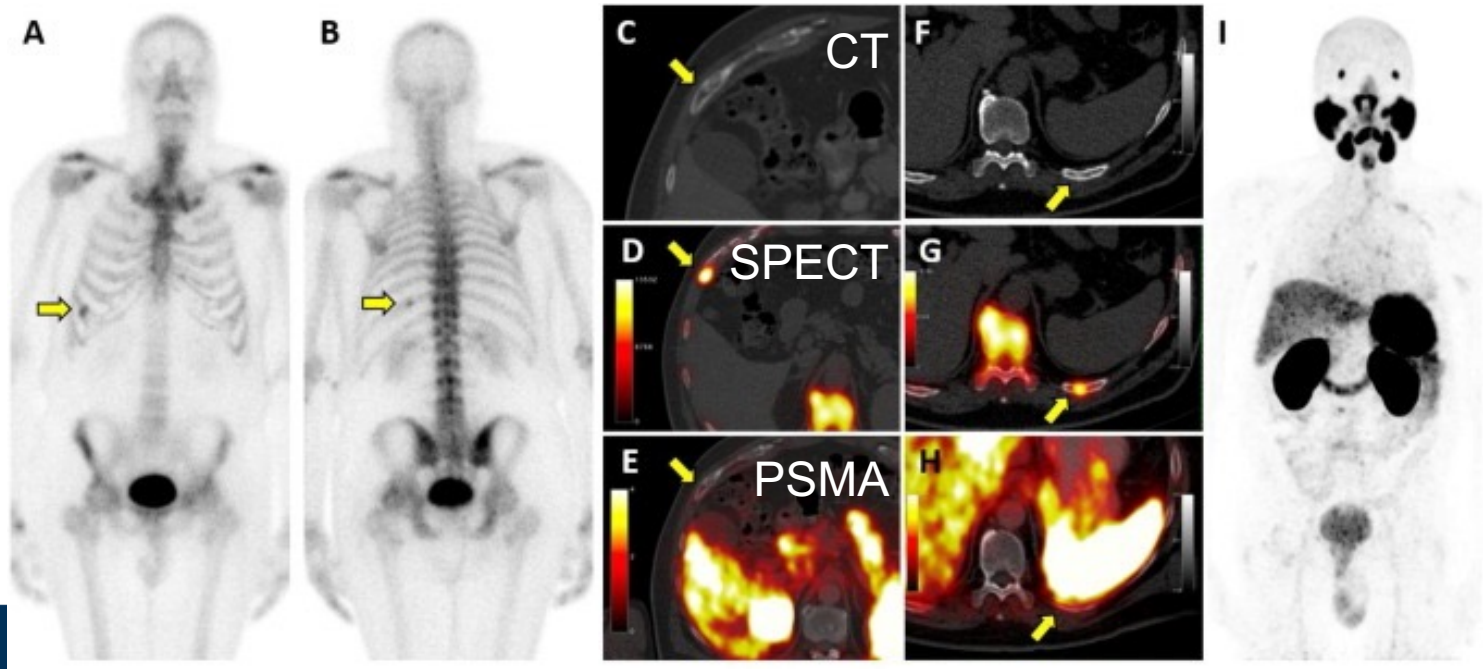
PSMA-PET/CT vs CI (Sensitivity>Specificity)

- Intermediate & high-risk staging (n=168; HR =74%)
- PSMA upstaging due to sensitivity (22%); downstaging due to specificity (7%)
- PSMA vs CI non-concordance ≈30% of patients; LN> M1b> M1c
- PSMA did not confirm 5/12 (42%) pts with suspicious M1b on CT/BS!

Higher sensitivity for M1b



Higher specificity for M1b



Lenis AT, et al. PSMA-PET/CT Compared with Conventional Imaging for Initial Staging of Treatment-naïve Intermediate- and High-risk Prostate Cancer: A Retrospective Single-center Study. Eur Urol Oncol. 2022 Oct;5(5):544-552.

NGI for unfavorable intermediate and high-risk - limitations

Multiple NGI tracers: varying sensitivity even within the PSMA family (polymetastatic invisible disease concept)

False +ve lesions: non-malignant conditions, higher for PSMA-1007 tracer

False -ve disease: 5-10% of patients

Biases: Will-Rogers effect, stage migration, lead-time and length time bias

Outcome impacts: Do management impacts ‘really’ change net patient outcomes?

European Urology
Available online 31 January 2022
In Press, Corrected Proof

Platinum Opinion

Modern Imaging in Prostate Cancer: Do We Treat Patients, or Their Scans?

Malcolm D. Mason [a], Theodorus H. van der Kwast [b], Nicolas Mottet [c], Daniela E. Oprea-Lager [d], Olivier Rouvière [e, f], EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guidelines Panel [†]

Platinum Opinion

When What You See Is Not Always What You Get: Raising the of Evidence for New Diagnostic Imaging Modalities

Nora Sundahl [a,b,], Silke Gillessen [c,d,e,f], Christopher Sweeney [g,h], Piet Ost [a]*

[a] *Department of Radiation Oncology, Ghent University Hospital, Ghent, Belgium;* [b] *Division of Radiotherapy and Imaging, Institute of Cancer R London, UK;* [c] *Oncology Institute of Southern Switzerland, Bellinzona, Switzerland;* [d] *Universita della Svizzera Italiana, Lugano, Switzerland;* [e] *Univ Bern, Bern, Switzerland;* [f] *Division of Cancer Science, University of Manchester, Manchester, UK;* [g] *Dana-Farber Cancer Institute, Boston, MA, USA;* [h] *E and Women's Hospital, Harvard Medical School, Boston, MA, USA*

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

COMMENTS AND CONTROVERSIES

Newly Diagnosed High-Risk Prostate Cancer in an Era of Rapidly Evolving New Imaging: How Do We Treat?

Maha Hussain, MD[1]; Daniel Lin, MD[2]; Fred Saad, MD[3]; Neha Vapiwala, MD[4]; Brian Francis Chapin, MD[5]; Howard Sandler, MD, MS[6]; ...

COMMENTS AND CONTROVERSIES

Strategies for Evaluation of Novel Imaging in Prostate Cancer: Putting the Horse Back Before the Cart

Check for updates

Neha Vapiwala, MD[1]; Michael S. Hofman, MBBS[2,3]; Declan G. Murphy, MB[2,3]; Scott Williams, MD[2,3]; and Christopher Sweeney, MBBS[4]

Show More

comments and contro

Evolving Role of Prostate-Specific Membrane Antigen-Positron Emission Tomography in Metastatic Hormone-Sensitive Prostate Cancer: More Questions than Answers?

Maha Hussain, MD[1]; Michael A. Carducci, MD[2]; Noel Clarke, MBBS[3]; Sarah E. Fenton, MD, PhD[1]; Karim Fizazi, MD, PhD[4]; Silke Gillessen, MD, PhD[5,6,7]; Heather Jacene, MD[8]; Michael J. Morris, MD[9]; Fred Saad, MD[10]; Oliver Sartor, MD[11]; Mary-Ellen Taplin, MD[12]; Neha Vapiwala, MD[13]; Scott Williams, MD[14]; and Christopher Sweeney, MD[12]

European Urology
Available online 31 January 2022
In Press, Corrected Proof

Platinum Opinion

Modern Imaging in Prostate Cancer: Do We Treat Patients, or Their Scans?

Malcolm D. Mason [a], Theodorus H. van der Kwast [b], Nicolas Mottet [c], Daniela E. Oprea-Lager [d], Olivier Rouvière [e, f], EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guidelines Panel †

Platinum Opinion

When What You See Is Not Always What You Get: Raising the of Evidence for New Diagnostic Imaging Modalities

Nora Sundahl [a,b,], Silke Gillessen [c,d,e,f], Christopher Sweeney [g,h], Piet Ost [a]*

[a] Department of Radiation Oncology, Ghent University Hospital, Ghent, Belgium; [b] Division of Radiotherapy and Imaging, Institute of Cancer R London, UK; [c] Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; [d] Universita della Svizzera Italiana, Lugano, Switzerland; [e] Univ Bern, Bern, Switzerland; [f] Division of Cancer Science, University of Manchester, Manchester, UK; [g] Dana-Farber Cancer Institute, Boston, MA, USA; [h] and Women's Hospital, Harvard Medical School, Boston, MA, USA

Clinical view → show net outcomes impacts:

"The value of novel imaging comes when it is shown that NGI helps maximize Rx benefits, minimize undertreatments, reduce or prevents overtreatments while tempering toxicity & costs"

Hussain M, et al.

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

COMMENTS AND CONTROVERSIES

Newly Diagnosed High-Risk Prostate Cancer in an Era of Rapidly Evolving New Imaging: How Do We Treat?

Maha Hussain, MD[1]; Daniel Lin, MD[2]; Fred Saad, MD[3]; Neha Vapiwala, MD[4]; Brian Francis Chapin, MD[5]; Howard Sandler, MD, MS[6]; ...

COMMENTS AND CONTROVERSIES

Strategies for Evaluation of Novel Imaging in Prostate Cancer: Putting the Horse Back Before the Cart

Check for updates

Neha Vapiwala, MD[1]; Michael S. Hofman, MBBS[2,3]; Declan G. Murphy, MB[2,3]; Scott Williams, MD[2,3]; and Christopher Sweeney, MBBS[4]

Show More

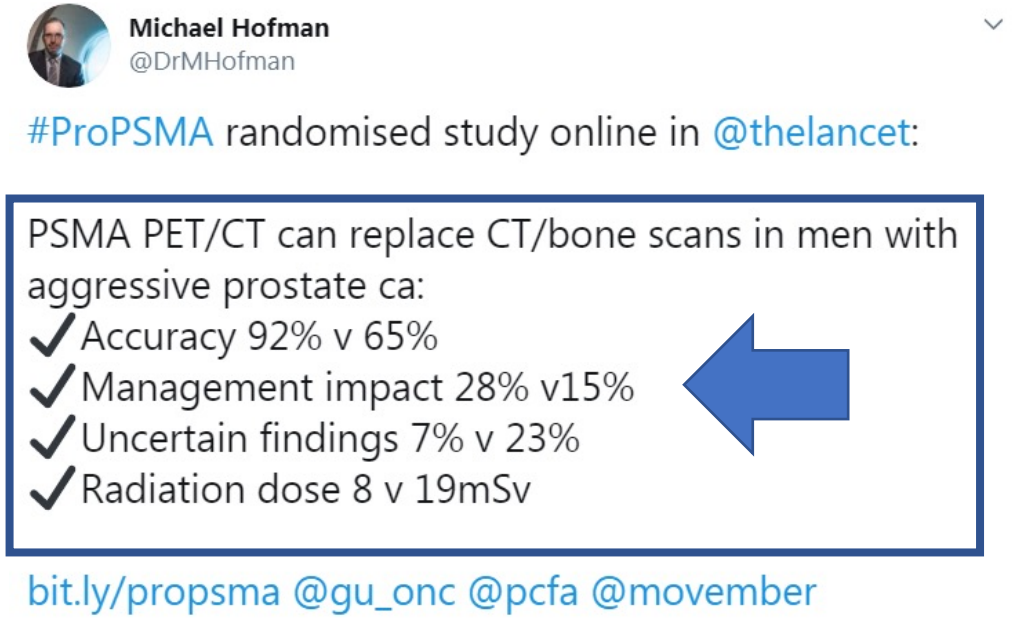
comments and contro

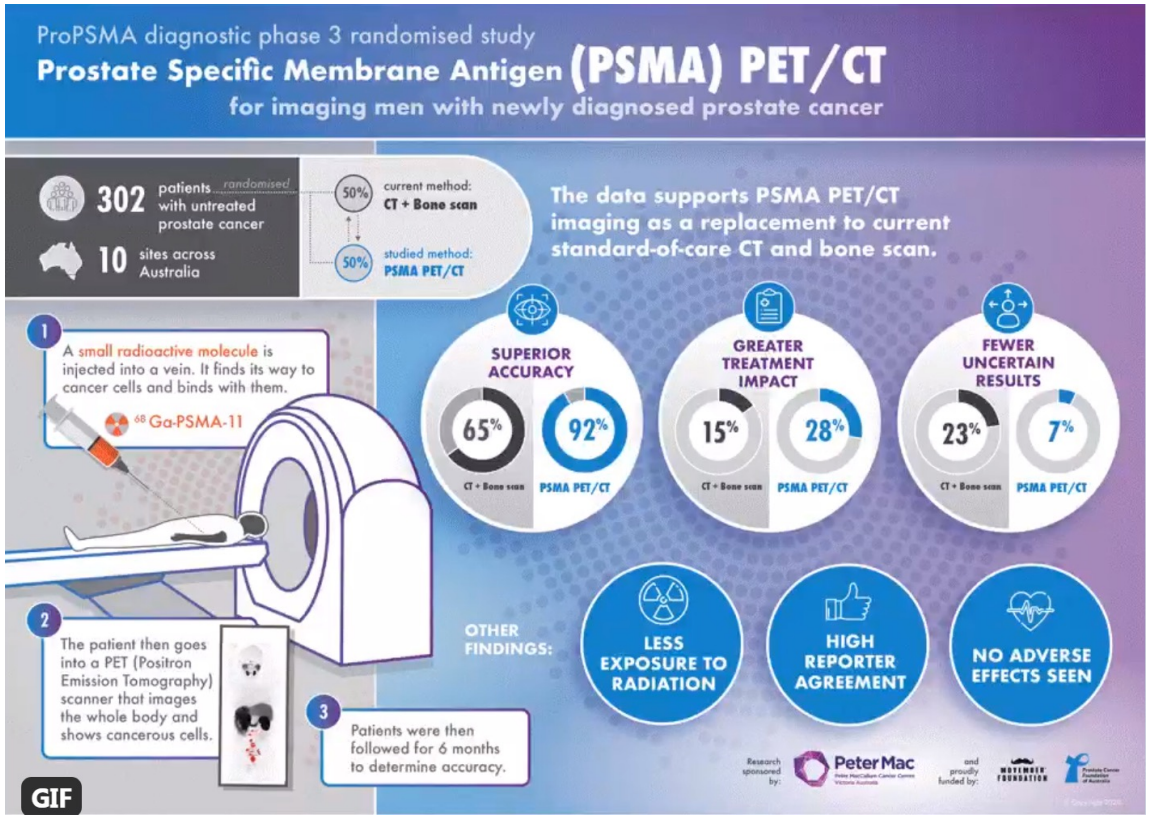
Evolving Role of Prostate-Specific Membrane Antigen-Positron Emission Tomography in Metastatic Hormone-Sensitive Prostate Cancer: More Questions than Answers?

Maha Hussain, MD[1]; Michael A. Carducci, MD[2]; Noel Clarke, MBBS[3]; Sarah E. Fenton, MD, PhD[1]; Karim Fizazi, MD, PhD[4]; Silke Gillessen, MD, PhD[5,6,7]; Heather Jacene, MD[8]; Michael J. Morris, MD[9]; Fred Saad, MD[10]; Oliver Sartor, MD[11]; Mary-Ellen Taplin, MD[12]; Neha Vapiwala, MD[13]; Scott Williams, MD[14]; and Christopher Sweeney, MD[12]

PSMA-PET/CT compared with BS/CT scans

- Unfavourable intermediate and high-risk localised disease, PSMA-PET/CT compared to CT/BS
  - 87/150 (30%) patients had confirmed pelvic nodal or distant metastatic disease





Hofman MS, et al. PSMA-PET/CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet. 2020 Apr 11;395(10231):1208-1216

How often does low-volume disease on BS become high-volume on PSMA-PET/CT?

- 79 men with EAU high-risk (prevalence of bone disease 21%)
- Head-to-head study of BS (± SPECT) vs F-PSMA-PET/CT
  - DCFPyL (51%); PSMA-1007 (39%) and PSMA-7 (10%)
- Change in risk group in 15/79
- Treatment changes occurred in almost 20% of cases

		F-PSMA			
		M0	LVD	HVD*	
CT chaarted risk criteria for mHSPC	M0	60	7	5	70
	LVD	2	3	4	9
	HVD	-	-	-	-

Bodar YJL, et al. A prospective, multicenter head-to-head comparative study in patients with primary high-risk prostate cancer investigating the bone lesion detection of conventional imaging and ^{18}F-PSMA-PET/CT. Urol Oncol. 2022 PMID: 36588019.

Do management changes after PSMA-PET/CT alter the patient outcomes (risk-benefit ratio) in high-risk localized/locally advanced prostate cancer?

Literature suggests the escalation use of PSMA-PET/CT in LAPC

Practice often shows the de-escalation use of PSMA-PET/CT in BCR

Limited list of ongoing randomized studies:

- PRISMA-PET - Primary Staging of Prostate Cancer: a Randomized Controlled Trial Comparing 18F-PSMA-1007 PET/CT to Conventional Imaging. NCT05123300
- PSMA PET/CT guided intensification of therapy in patients at risk of advanced prostate cancer (PATRON): a pragmatic phase III randomized controlled trial (CT/BS vs CT/BS/PSMA). NCT04557501
- PEARLS: A Multicenter Phase II/III Trial of Extended Field Radiotherapy for Androgen Sensitive Prostate Cancer Patients with PSMA-avid Pelvic and Para-Aortic Lymph Nodes at Presentation. ISRCTN36344989.

High-risk prostate cancer imaging & Rx recommendations

- Perform both conventional imaging (BS/CT) and PSMA-PET/CT
  - CT component of PET/CT is often sufficient
  - BS contribution is often minimal
- Primary tumor Rx clinical decision is based on conventional imaging findings
- High specificity of PSMA means that N1/M1 disease should be trusted
  - Treatment intensifications
  - Adjuvant phase of Rx

Hussain M, et al. Evolving Role of PSMA-PET/CT in Metastatic Hormone-Sensitive Prostate Cancer: More Questions than Answers? J Clin Oncol. 2022 2022 Sep 10;40(26):3011-3014.

Imaging findings		Treatment recommendations for newly diagnosed high-risk disease	
CIM	PSMA		
-	-	Standard of care (SOC) of localised PCa	
-	+	Pelvic PMA LN+: SOC of prostate cancer and regional LN+	
		Beyond pelvic nodes 1. Prioritise clinical trials 2. Manage as high-risk with local and adjuvant metastatic therapy	
+	±	Pelvis LN+ on CIM	SOC of prostate cancer and regional LN+
		Pelvis LN on CIM & PSMA	SOC of prostate cancer and regional LN+
		CIM+ for M1	SOC for mHSPC by M1 disease state

NGI in CT/BS-M0 unfavourable & high-risk localized

NGI (P
nodes

- Do n

NGI in
abirate

- If NG
alon
- If NG
cons

Manag
need t

Or do we?

n
n

CO 2021)

ADT

e

GI
l trials

ARC
Advanced Radiology Center

UNIVERSITY OF CAMBRIDGE

CANCER RESEARCH UK | CAMBRIDGE CENTRE

Delivering a New Paradigm for Personalised Medicine

UNIVERSITÀ CATTOLICA del Sacro Cuore

Special thanks to:

- ✓ **Anwar Padhani**
- ✓ Salvatore Annunziata
- ✓ Daniele Pizzuto

Gemelli

The Mark Foundation™ for Cancer Research

wellcome