The added benefit of new imaging for (very) high-risk patients

Are bone scan and CT enough?

@ProfPadhani

Radiologist, Mount Vernon Cancer Centre, London

Professor of Cancer Imaging, Institute of Cancer Research, London

Co-Chair, International PI-RADS Committee

Conflicts of interest 2022

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	Siemens Healthineers
Receipt of honoraria or consultation fees:	Siemens Healthineers
Participation in a company sponsored speaker's bureau:	Siemens Healthineers
Stock shareholder:	Lucida Medical

Dimitris, 67 years old

- Medical history:
  - Controlled hypertension (on 2 hypertensives)
  - Acute urinary retention
  - ECOG PS: 0
- Assessment summary:
  - PSA: 33.3 ng/ml
  - DRE: cT3
  - mpMRI: cT3b cN0
  - Biopsy: ISUP grade group 4 [GS 5+3]
  - CT and bone scan: cM0

Should next-generation imaging be done after bone and CT scans in the clinical assessment?*

- Definitely Yes
- Maybe yes
- Uncertain
- Maybe not
- Definitely Not

* if you don't have to take into account regulatory approval and local restrictions

VOTE

Table 1. Stage-matched therapeutic strategies

Localised disease	Low risk	Active surveillance Brachytherapy RP Radical RT
	Intermediate risk	RP Radical RT ± neoadjuvant ADT Brachytherapy Active surveillance
	High risk	Long-term ADT + radical RT ± neoadjuvant docetaxel RP + pelvic lymphadenectomy
Locally advanced disease		Neoadjuvant ADT + radical RT + adjuvant ADT ± neoadjuvant docetaxel RP + pelvic lymphadenectomy
M0 CRPC	High risk	ADT + apalutamide ADT + darolutamide ADT + enzalutamide
Metastatic disease	Hormone-naive	ADT + abiraterone ADT + docetaxel ADT + enzalutamide ADT + apalutamide RT for low volume ADT alone for frail patients who cannot tolerate the above treatments Bone health agent
	Castration-resistant (first line)	Abiraterone Docetaxel Enzalutamide ^{223}Ra for patients unfit for above treatments (and bone-only metastases)
	Second line or post-docetaxel	Abiraterone Cabazitaxel Enzalutamide ^{223}Ra

^{223}Ra, radium-223; ADT, androgen deprivation therapy; M0 CRPC, non-metastatic castration-resistant prostate cancer; RP, radical prostatectomy; RT, radiotherapy.

ESMO 2020 guidelines

Patients with high-risk LAPC should be staged for metastases using CT (chest, abdomen and pelvis) and bone scan [III, B]

- Metastatic presence & distribution on conventional imaging is prognostic & predictive for the use of pelvis radiotherapy

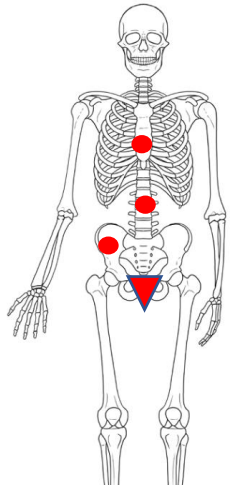
Patients with localised pelvic disease on routine imaging should not be denied radical local treatment solely because metastatic lesions are identified on novel imaging techniques

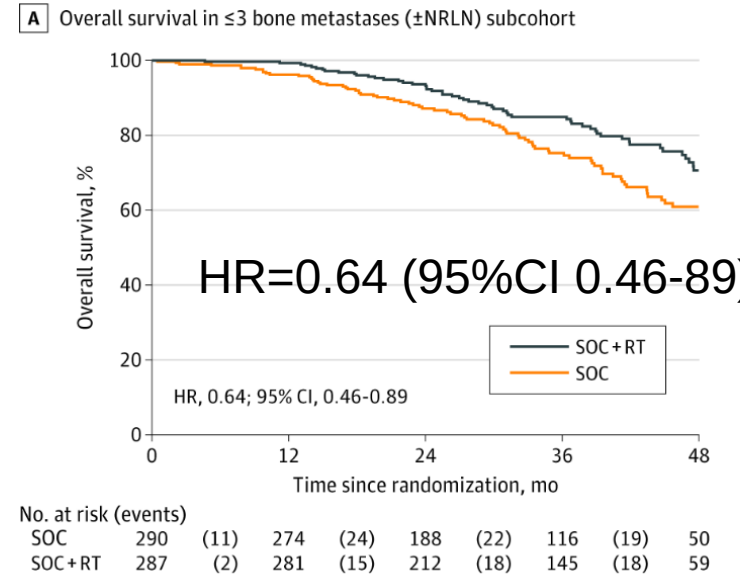
Parker C, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020 Sep;31(9):1119-1134

@ProfPadhani

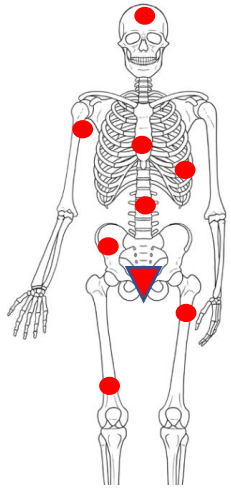
CT/BS risk assessments in men presenting with de-novo metastatic disease to decide the need for Rx intensification using prostate radiotherapy

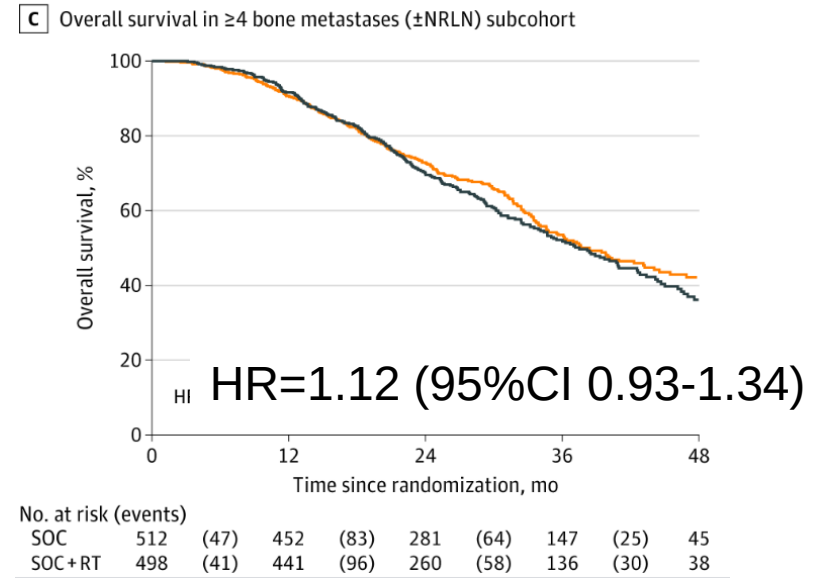
Low volume
≤3 bone metastases on bone scan





High volume
≥4 bone metastases on bone scan

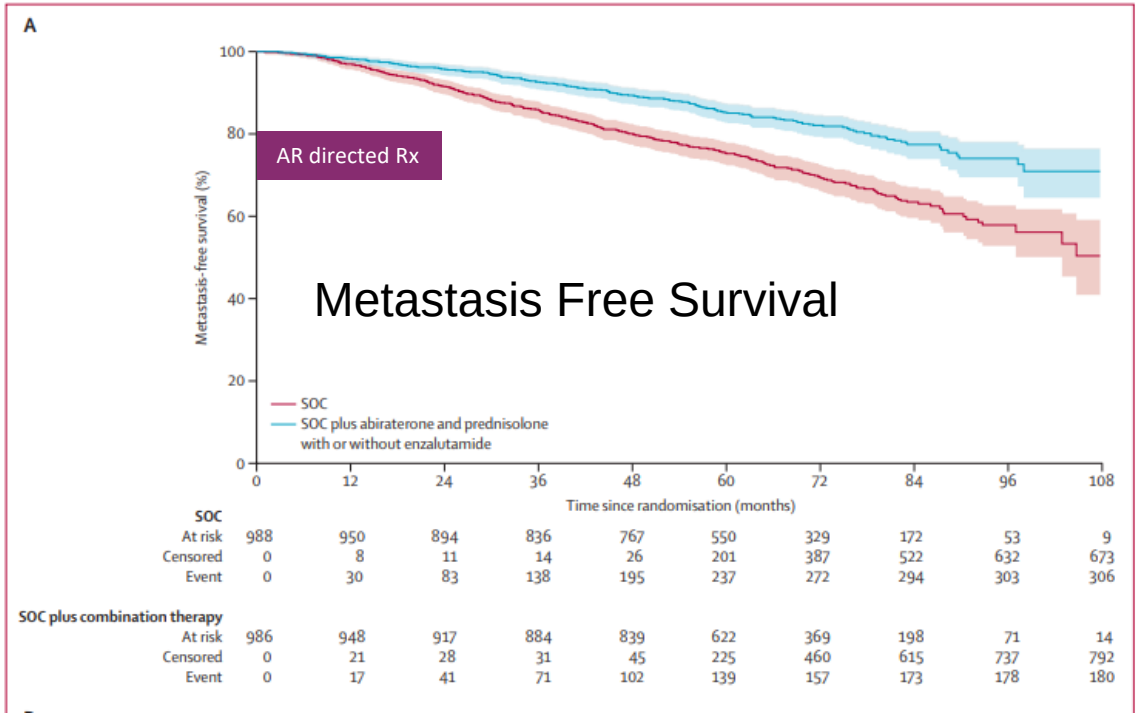


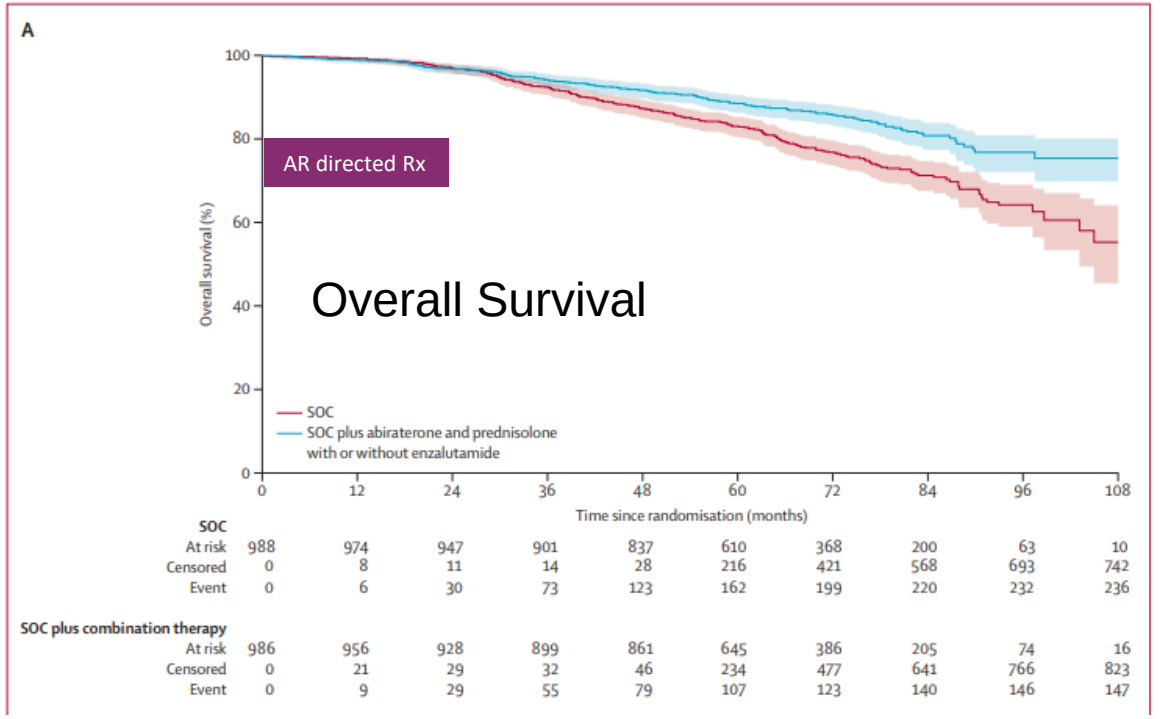


Ali A, et al. Association of Bone Metastatic Burden With Survival Benefit From Prostate Radiotherapy in Patients With Newly Diagnosed Metastatic Prostate Cancer: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Oncol.* 2021 Apr 1;7(4):555-563.

Drug approval: systemic therapy intensification for M0-LAPC defined on BS/CT/morphologic MRI

Among men with high-risk, CT/BS-defined non-metastatic prostate cancer, combination ADT+Abiraterone is associated with significantly higher rates of metastasis-free survival compared with ADT alone





Attard G, et al. Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled

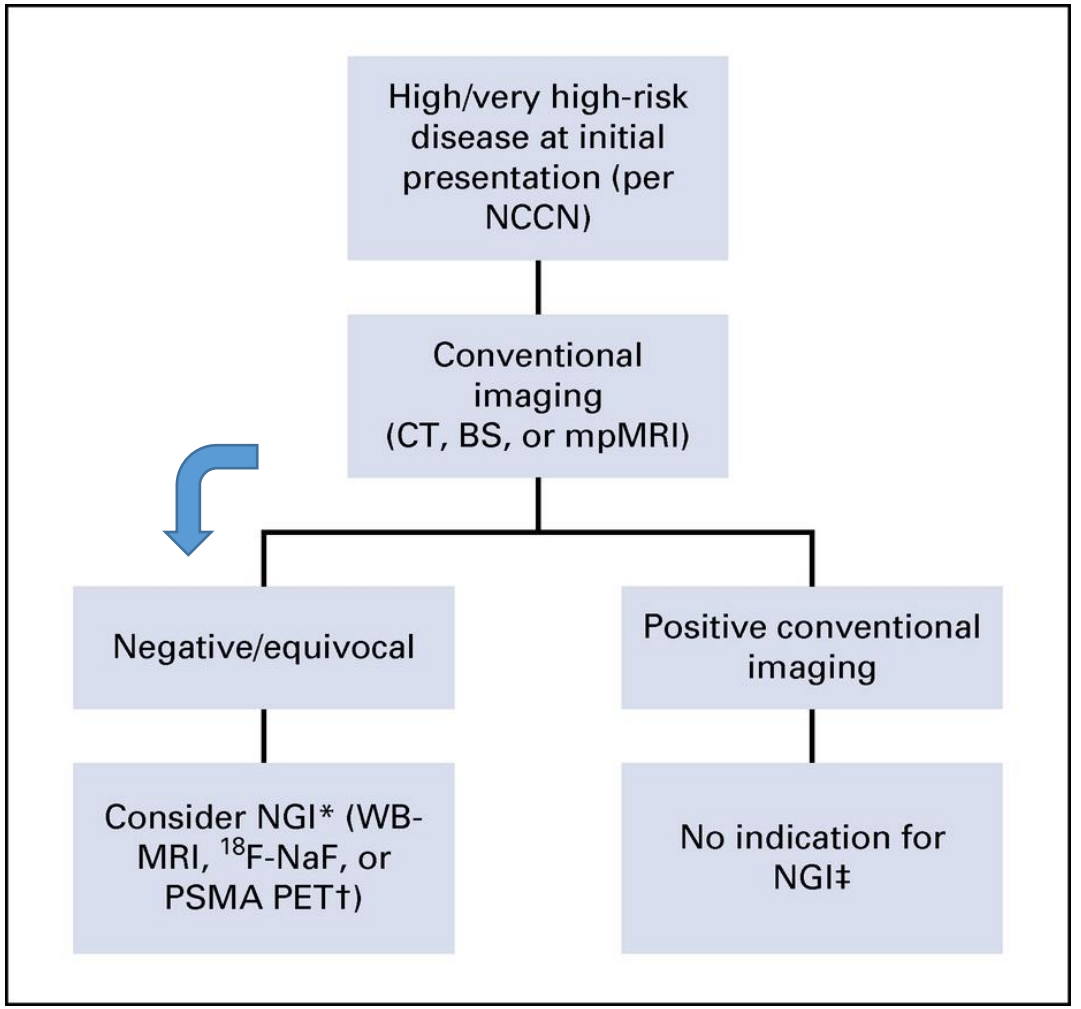
Newly Diagnosed Clinically High-Risk/Very High-Risk Localized, Locally Advanced Prostate Cancer

Recommendation 4.1. – negative conventional imaging

When conventional imaging is negative in patients with a high-risk of metastatic disease, NGI may add clinical benefit, although prospective data are limited

Recommendation 4.2. – suspicious conventional imaging

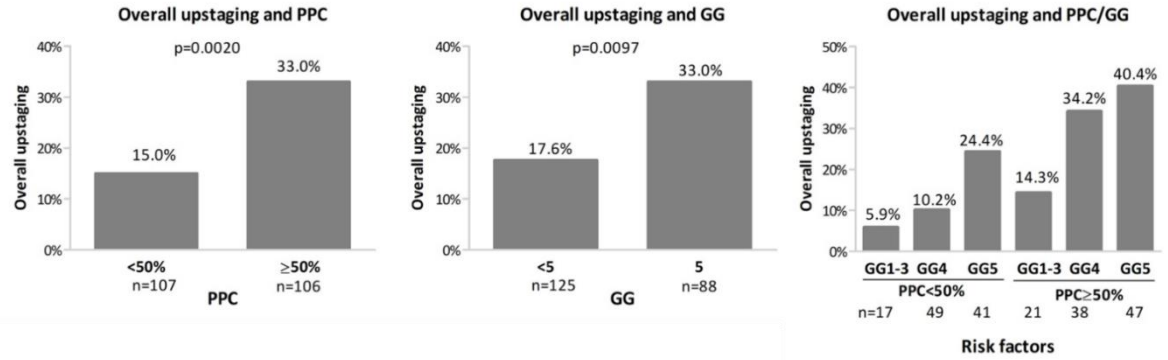
When conventional imaging is suspicious or equivocal, NGI may be offered for the clarification of equivocal findings or detection of additional sites of disease, which could potentially alter management, although prospective data are limited



Trabulsi EJ, et al. Optimum Imaging Strategies for Advanced Prostate Cancer: ASCO Guideline. J Clin Oncol. 2020 Jun 10;38(17):1963-1996.

Choosing the right man for PSMA-PET/CT for high-risk and conventional imaging N0/M0 disease → larger, more aggressive cancers

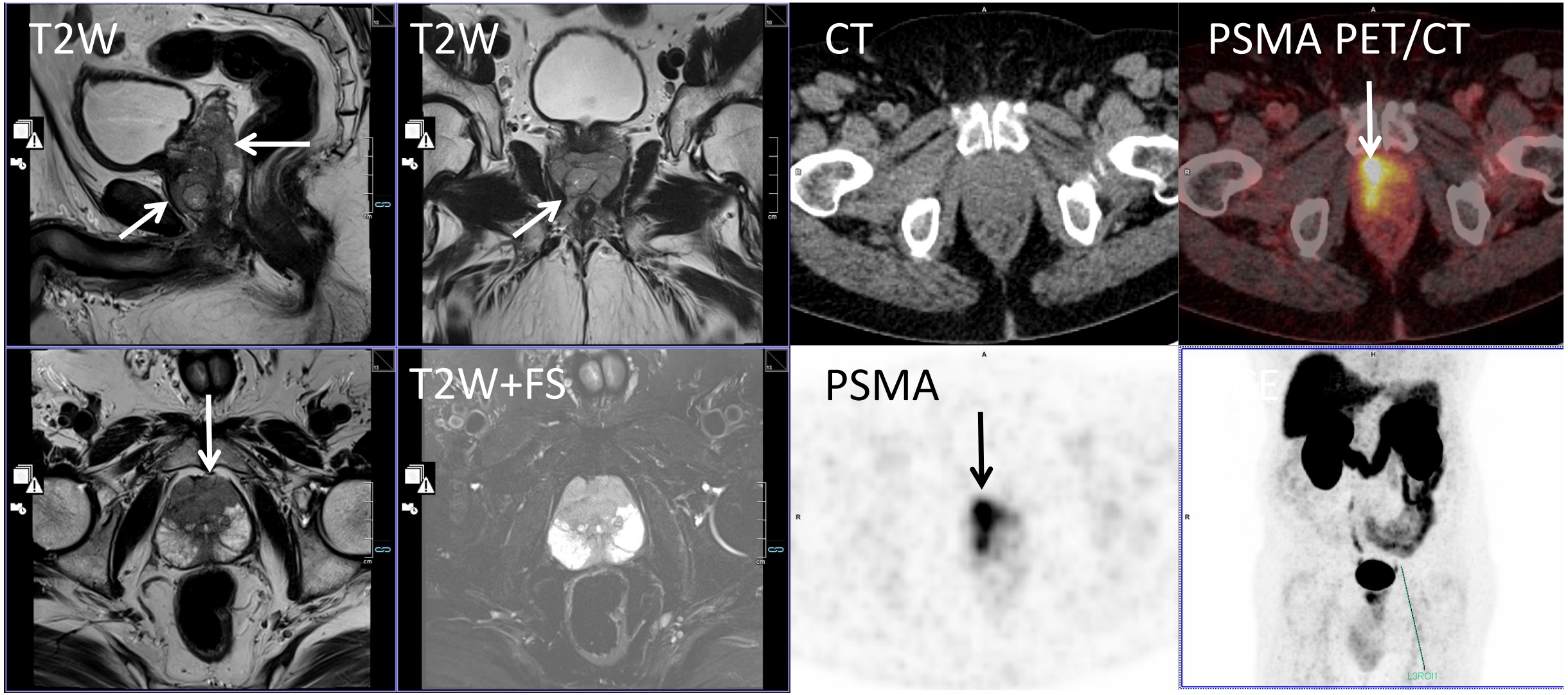
- >50% positive cores and GG4-5 disease are more likely to have occult nodal or metastatic disease on PSMA-PET/CT
  - 40% are PSMA-PET/CT positive
- The high specificity of PSMA means that patients may benefit from therapeutic intensification, including elective nodal radiotherapy & the use of advanced systemic therapy agents (ARSI+ADT)



	Multivariable analysis	
	Odds ratio (95% CI)	p value
Initial PSA	1.01 (0.99–1.02)	0.205
Percent positive cores	1.03 (1.01–1.04)	<0.001
Gleason grade group	2.15 (1.33–3.45)	0.002
cT stage	0.73 (0.40–1.34)	0.317

Ma TM, et al. Identifying the Best Candidates for PSMA PET/CT as the Primary Staging Approach Among Men with High-risk Prostate Cancer and Negative Conventional Imaging. Eur Urol Oncol. 2022 Feb;5(1):100-103.

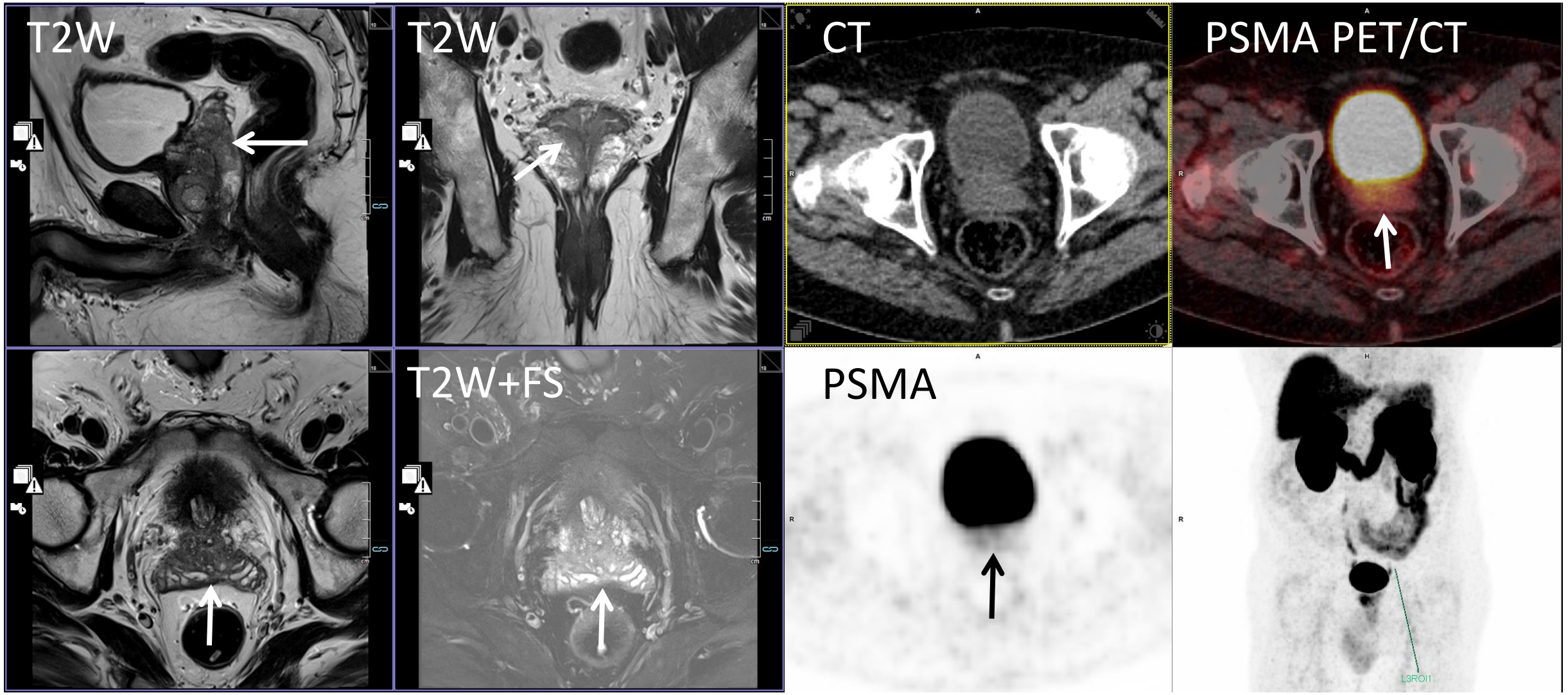
69M, PSA 10ng/mL, Asymptomatic, Routine check, DRE+ve



3TSkyra
@ProfPadhani

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

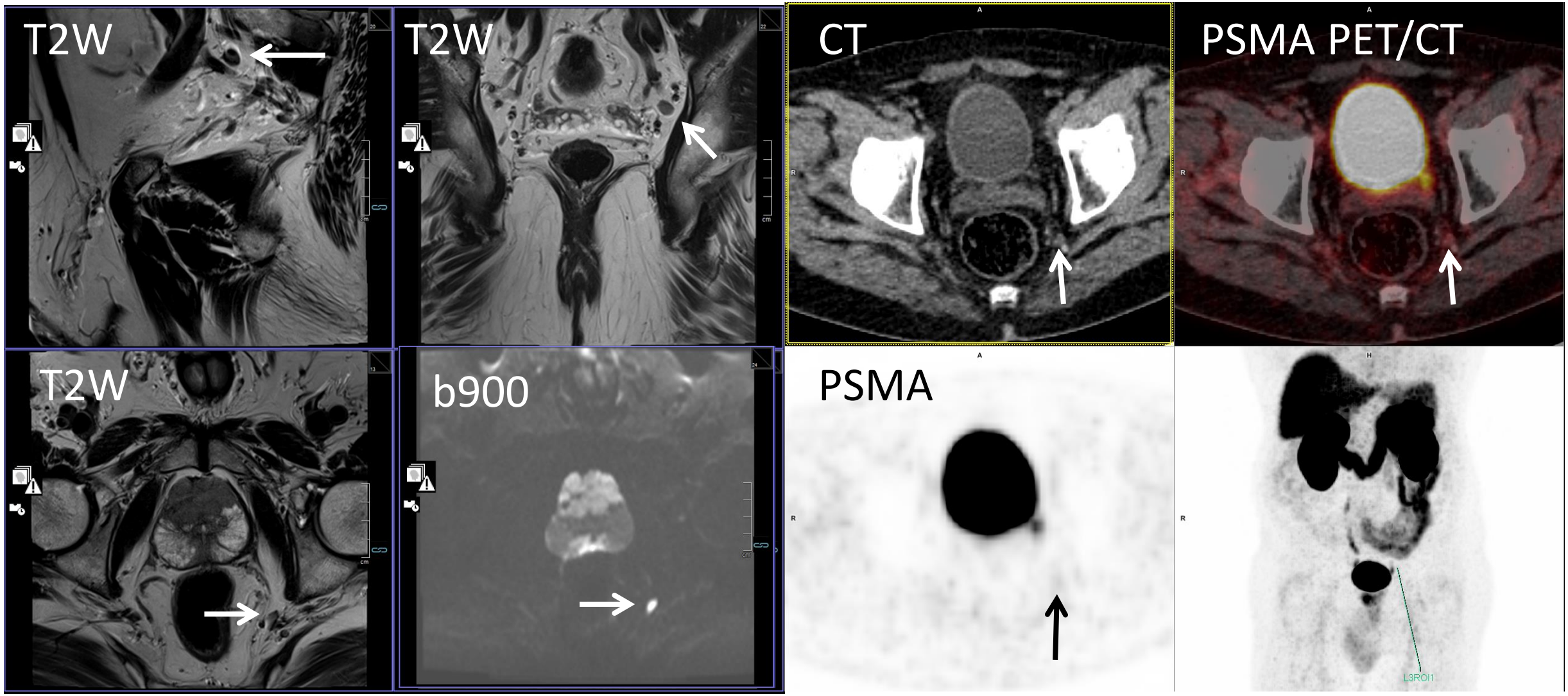
69M, PSA 10ng/mL, Asymptomatic, Routine check, DRE+ve



3TSkyra
@ProfPadhani

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

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



3TSkyra
@ProfPadhani

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

PSMA-PET/CT in LAPC - limitations

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

False -ve disease: 5-10% of patients

Multiple reporting standards: EANM E-PSMA guideline (2021), PROMISE guideline (2018), PSMA-RADS (2019)

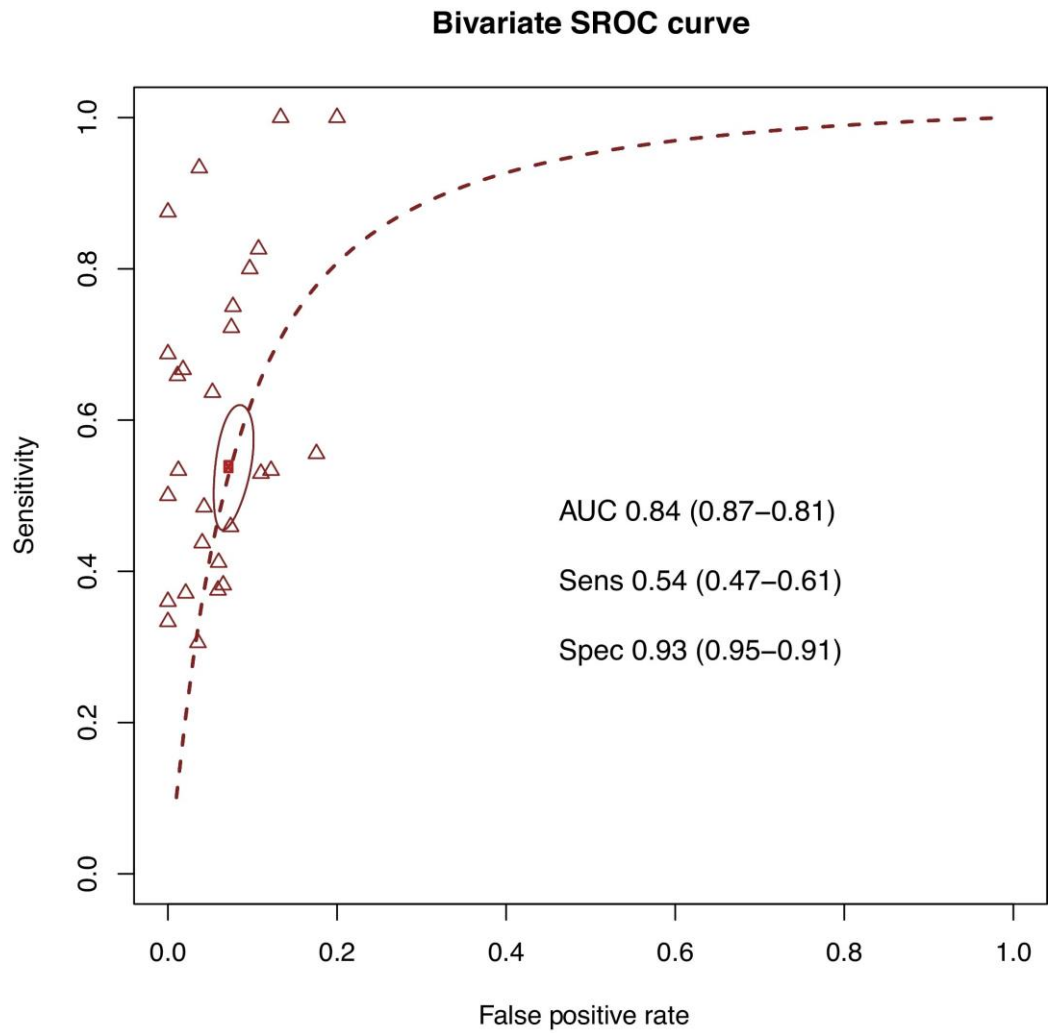
Biases: stage migration, lead-time and length time bias

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

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

*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.



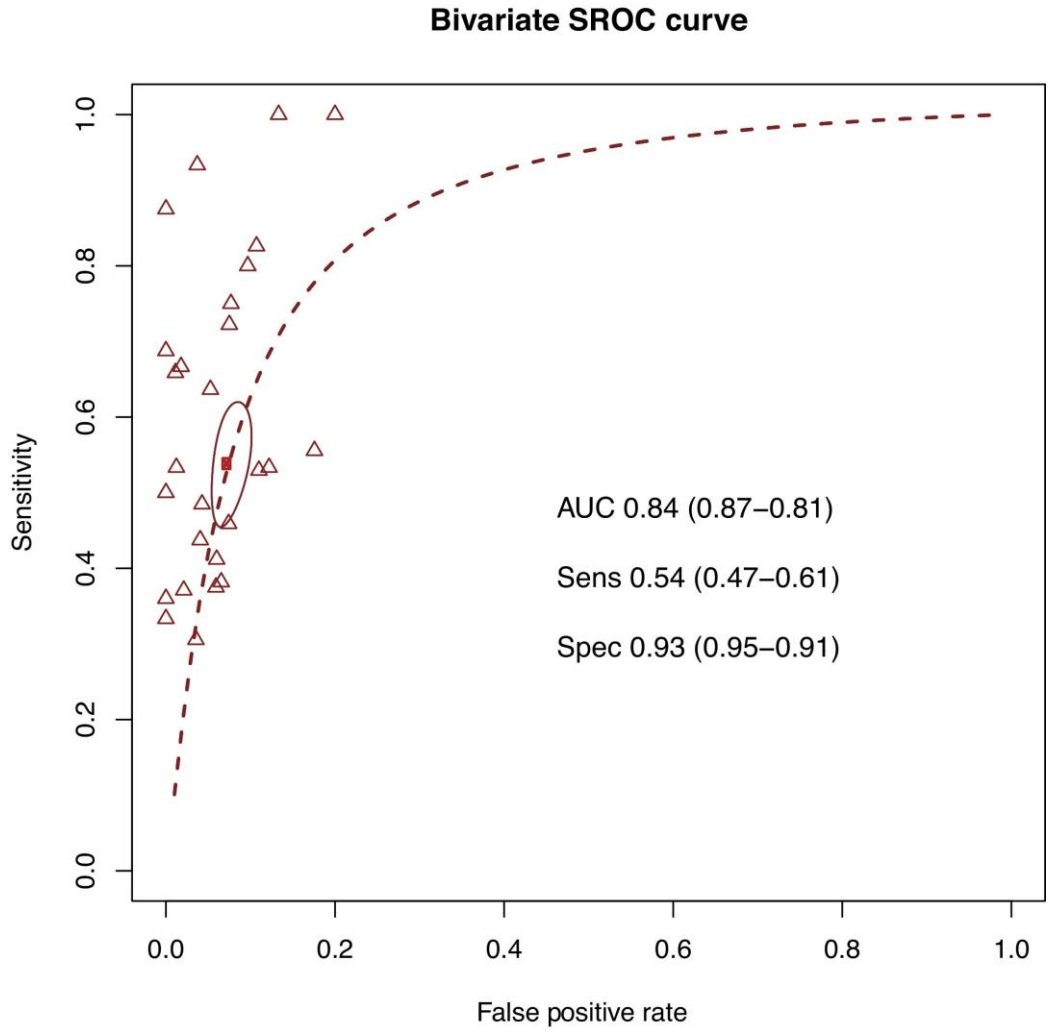
Stabile A, et al. Can Negative PSMA PET/CT Avoid the Need for Pelvic Lymph Node Dissection in Newly Diagnosed Prostate Cancer Patients? A Systematic Review and Meta-analysis with Backup Histology as Reference Standard. Eur Urol Oncol. 2022 Feb;5(1):1-17.

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-NO 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

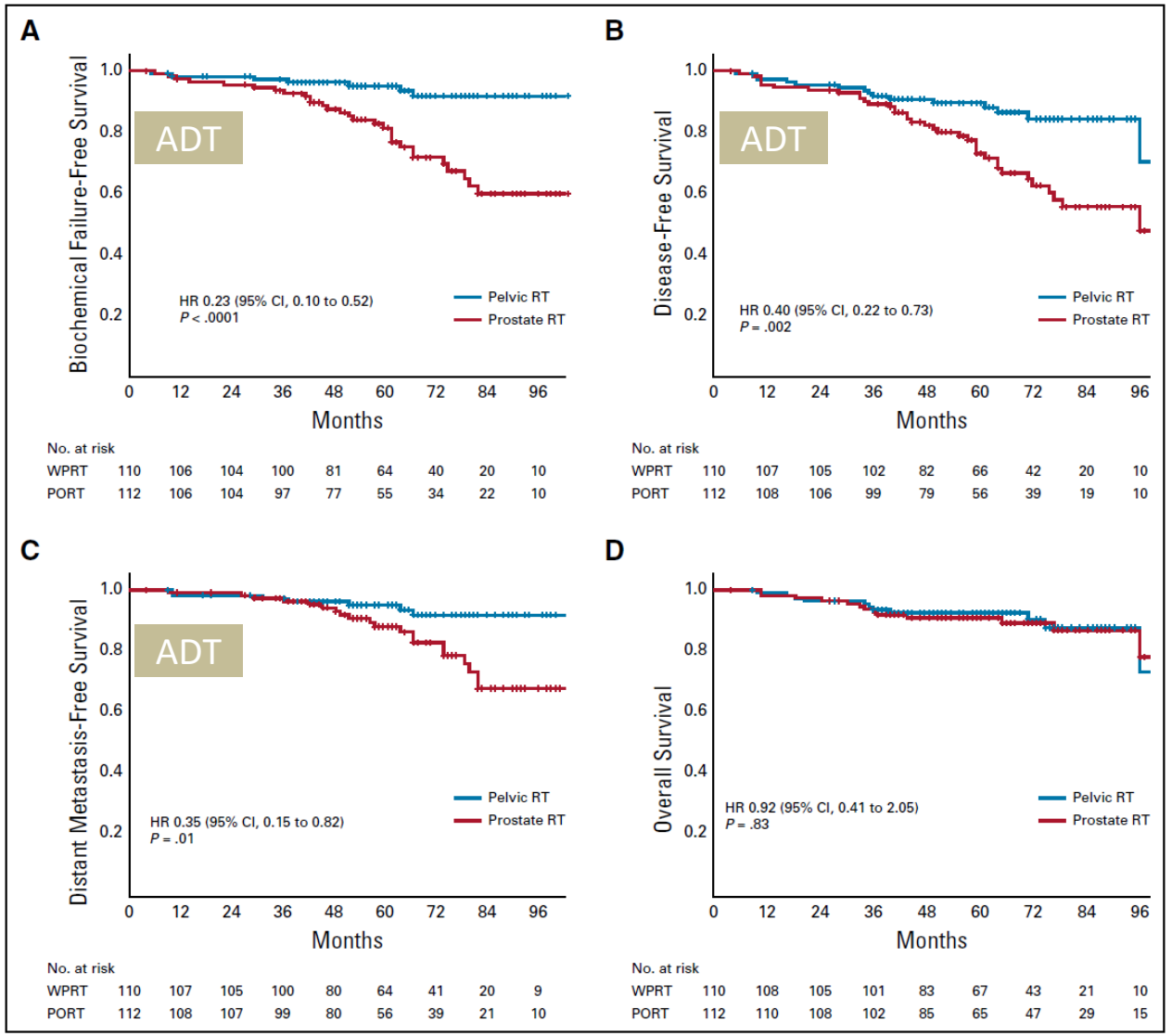


FIG 2. Kaplan-Meier estimates of biochemical failure-free survival (A), disease-free survival (B), distant metastasis-free survival (C), and overall survival (D). HR, hazard ratio; PORT, prostate-only radiotherapy; RT, radiotherapy; WPRT, whole-pelvic radiotherapy.

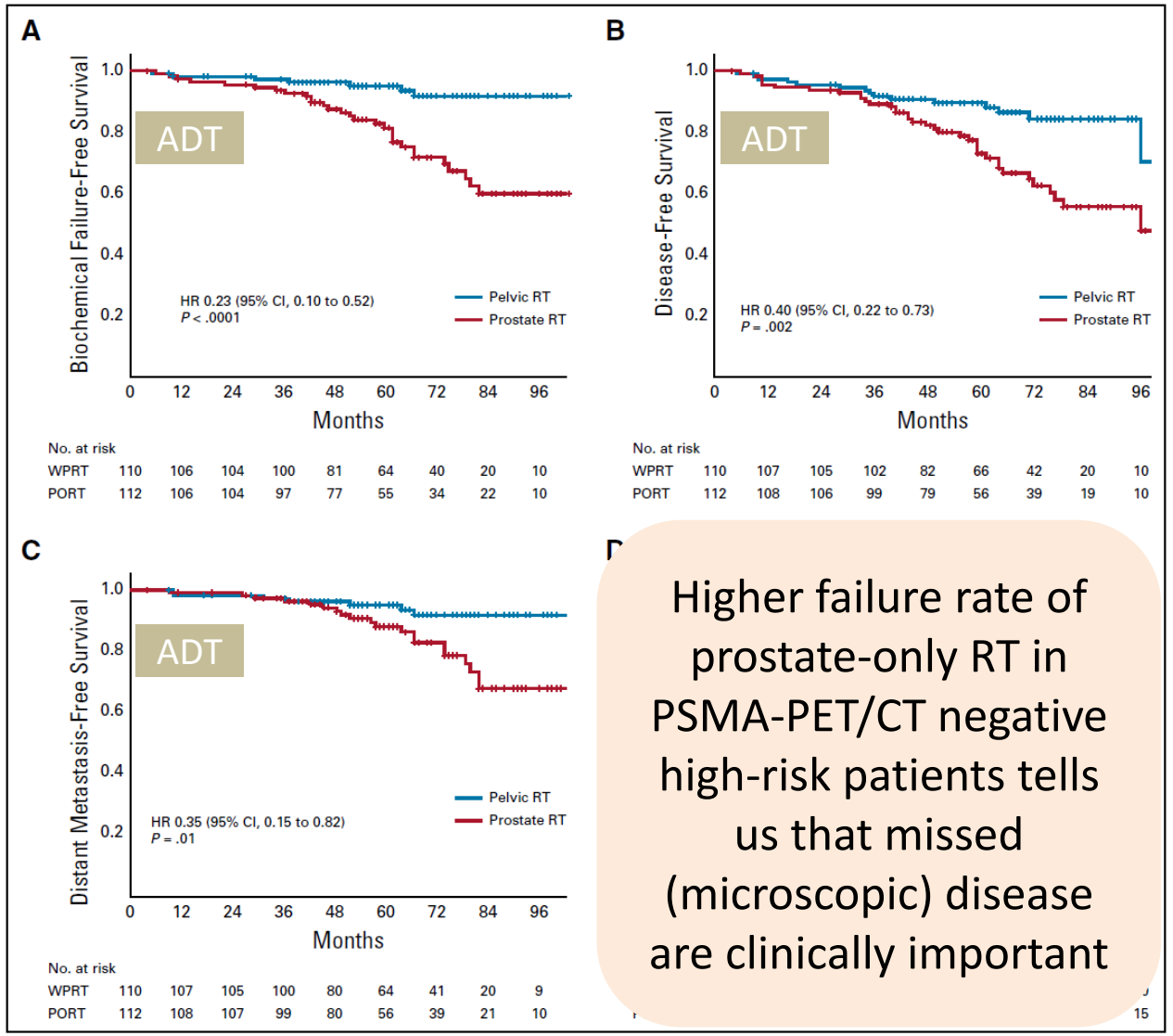
Murthy V, et al. Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial. J Clin Oncol. 2021 Apr 10;39(11):1234-1242.

Moderate rule-out ability of PSMA for nodal disease results in higher failure rates in PET-NO 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



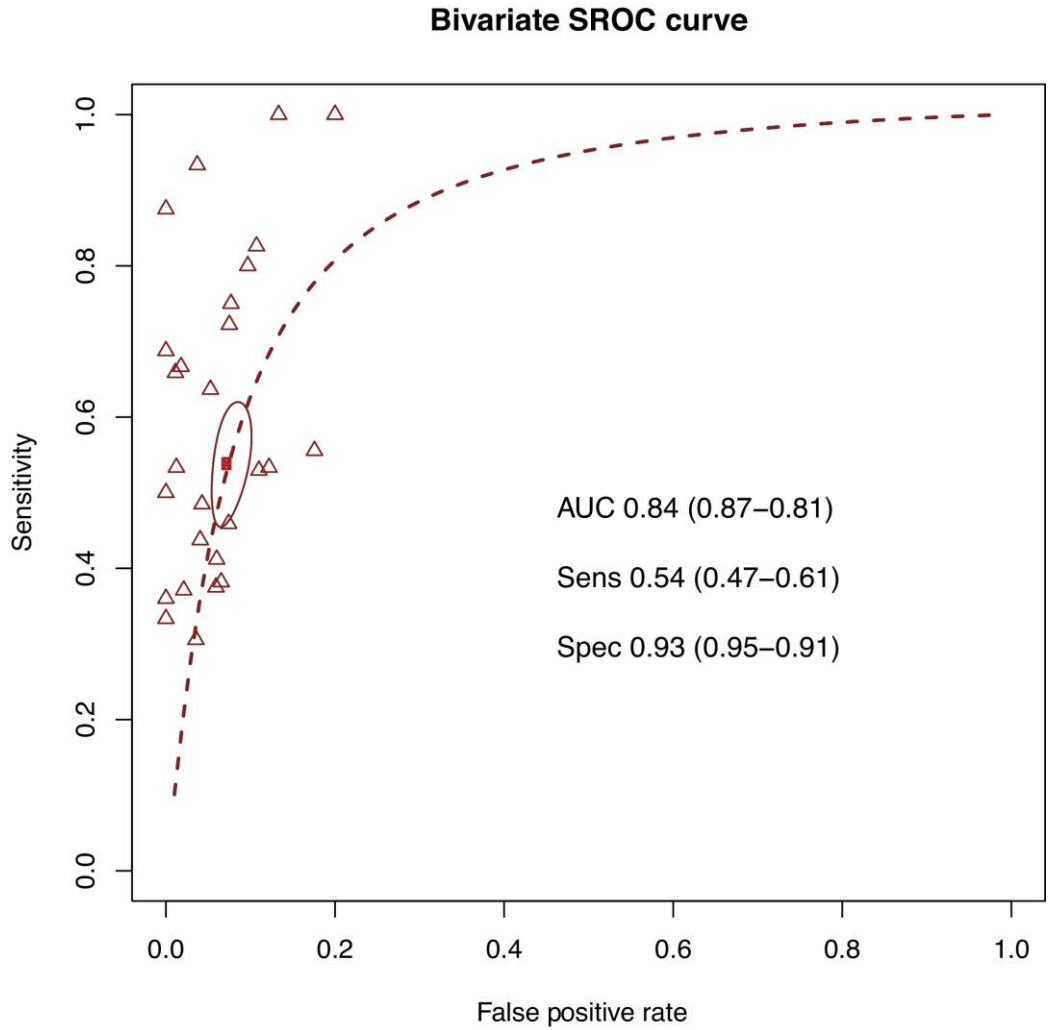
Higher failure rate of prostate-only RT in PSMA-PET/CT negative high-risk patients tells us that missed (microscopic) disease are clinically important

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.

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

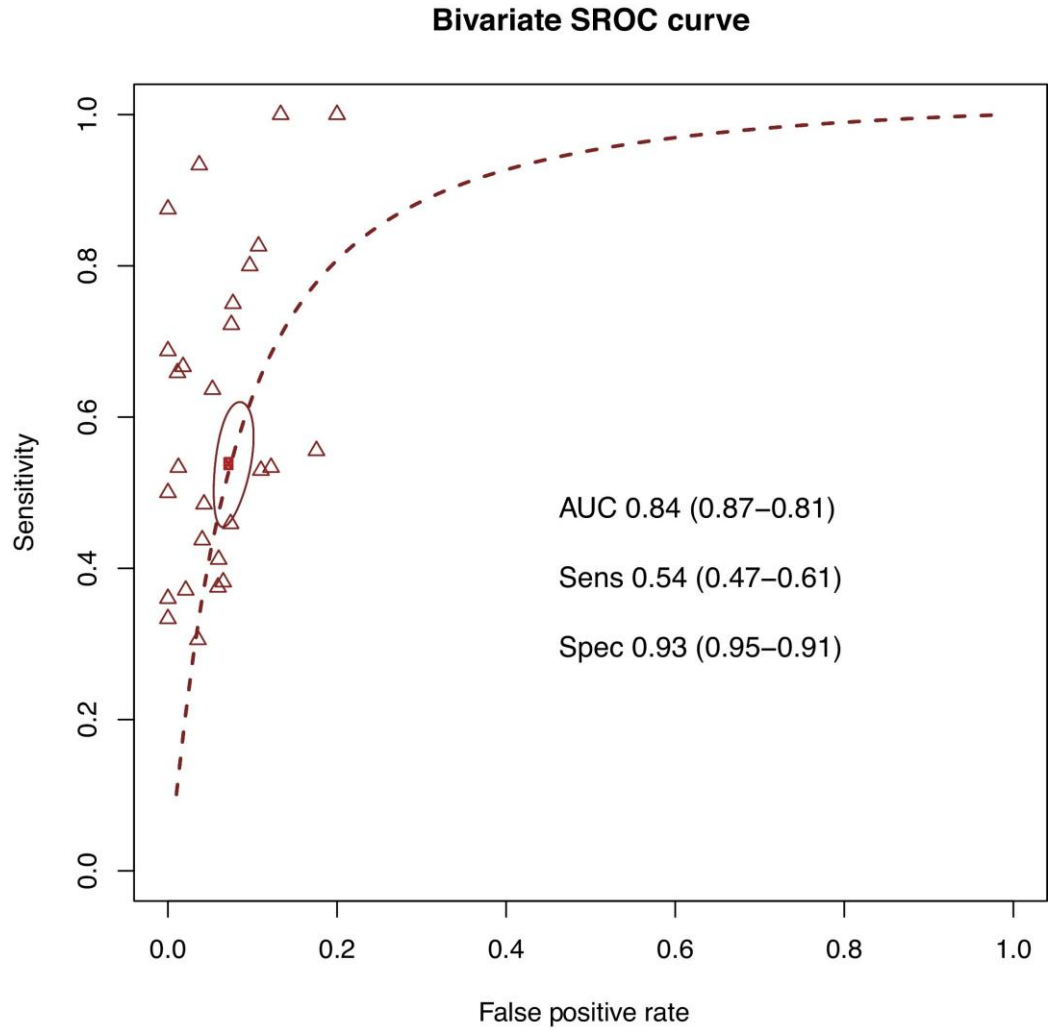


*Pouliot F, et al. A prospective phase II/III multi-center study of PSMA-targeted 18F-DCFPyL PET/CT imaging in patients with prostate cancer (OSPREY): a sub-analysis of regional and distant metastases detection rates at initial staging by 18F-DCFPyL PET/CT. J Clin Oncol 2020;38(6 Suppl):9.

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.

Can we do anything with seen PSMA+ nodes?

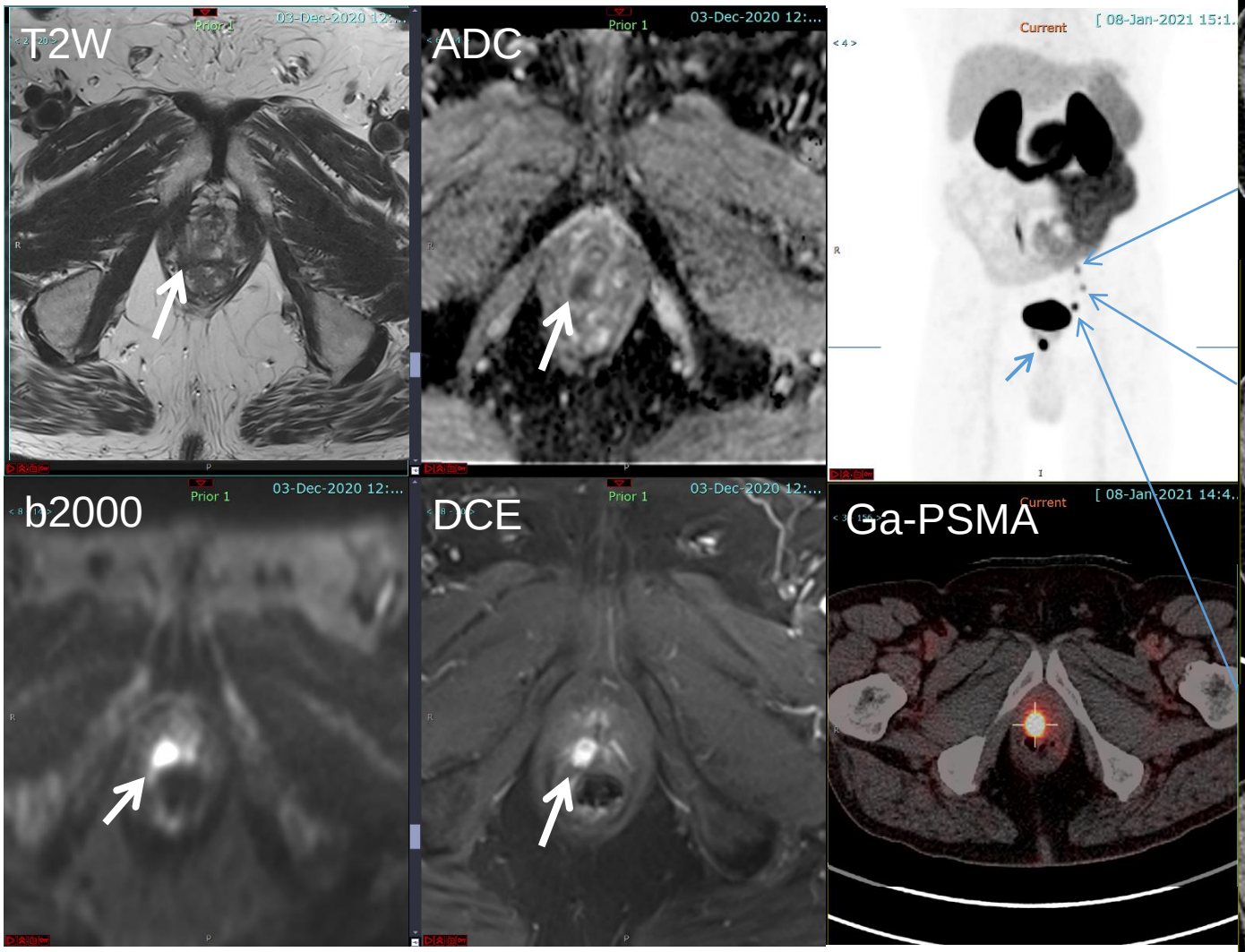
- Majority of small metastatic nodes are consistently missed
  - ≤2 mm → 0% detected
  - 2-4 mm → 25% detected
  - >5 mm → 49-63%*
- Patient/template level sensitivity > node/station level sensitivity
- Lymph-nodal therapies benefits are greatest for men with smaller nodes

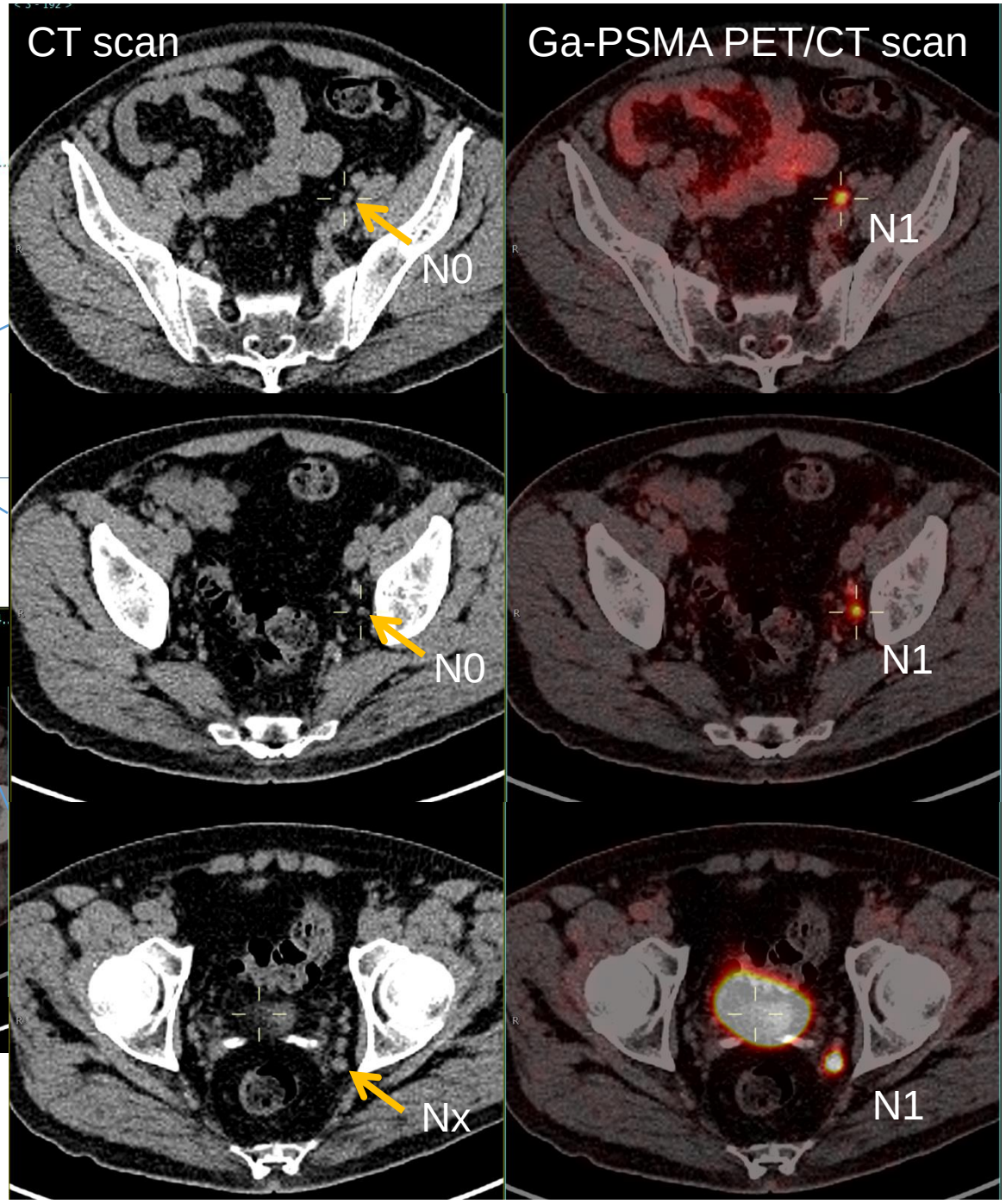


*Pouliot F, et al. A prospective phase II/III multi-center study of PSMA-targeted 18F-DCFPyL PET/CT imaging in patients with prostate cancer (OSPREY): a sub-analysis of regional and distant metastases detection rates at initial staging by 18F-DCFPyL PET/CT. J Clin Oncol 2020;38(6 Suppl):9.

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.

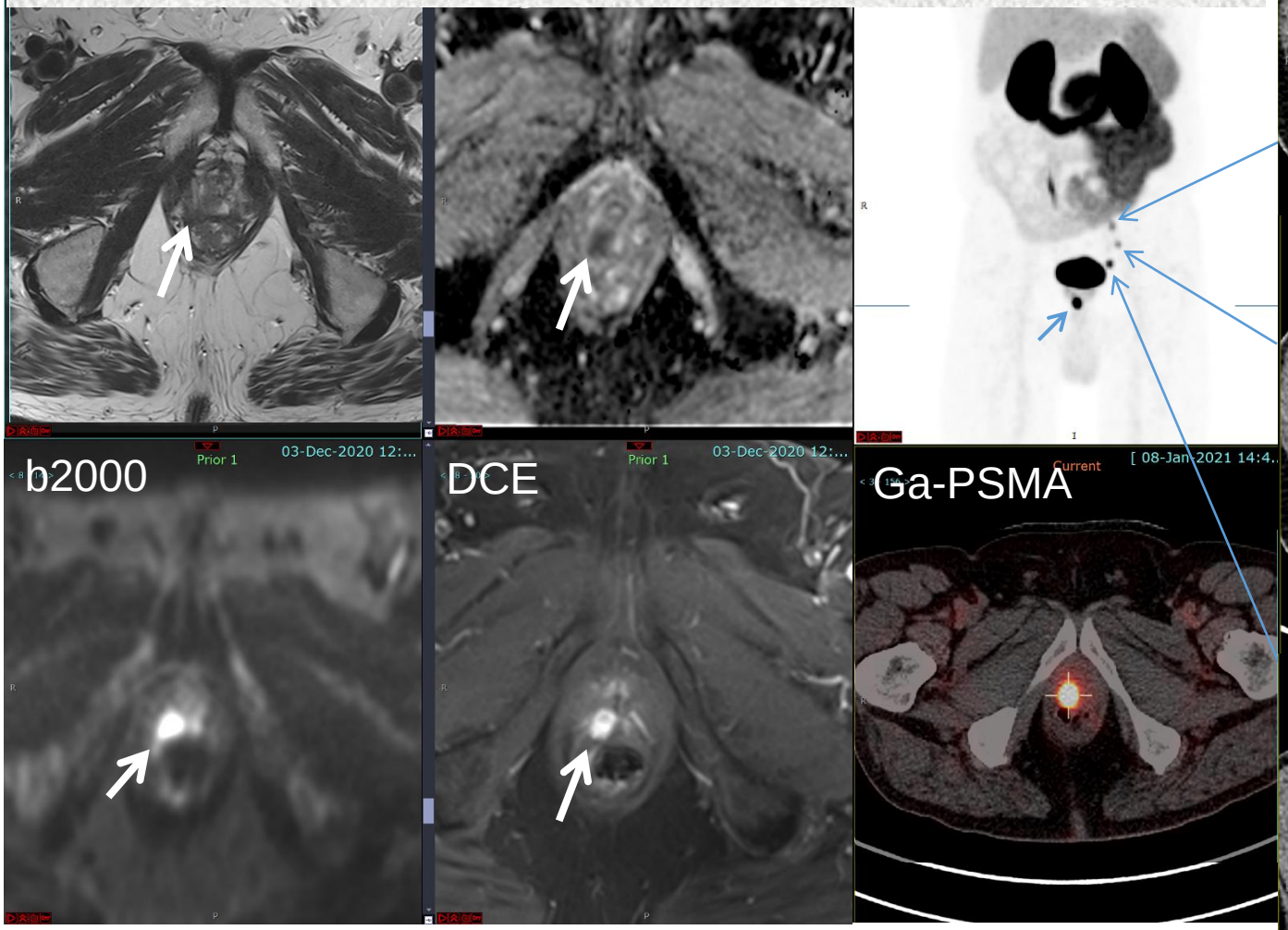
High-risk localised prostate cancer

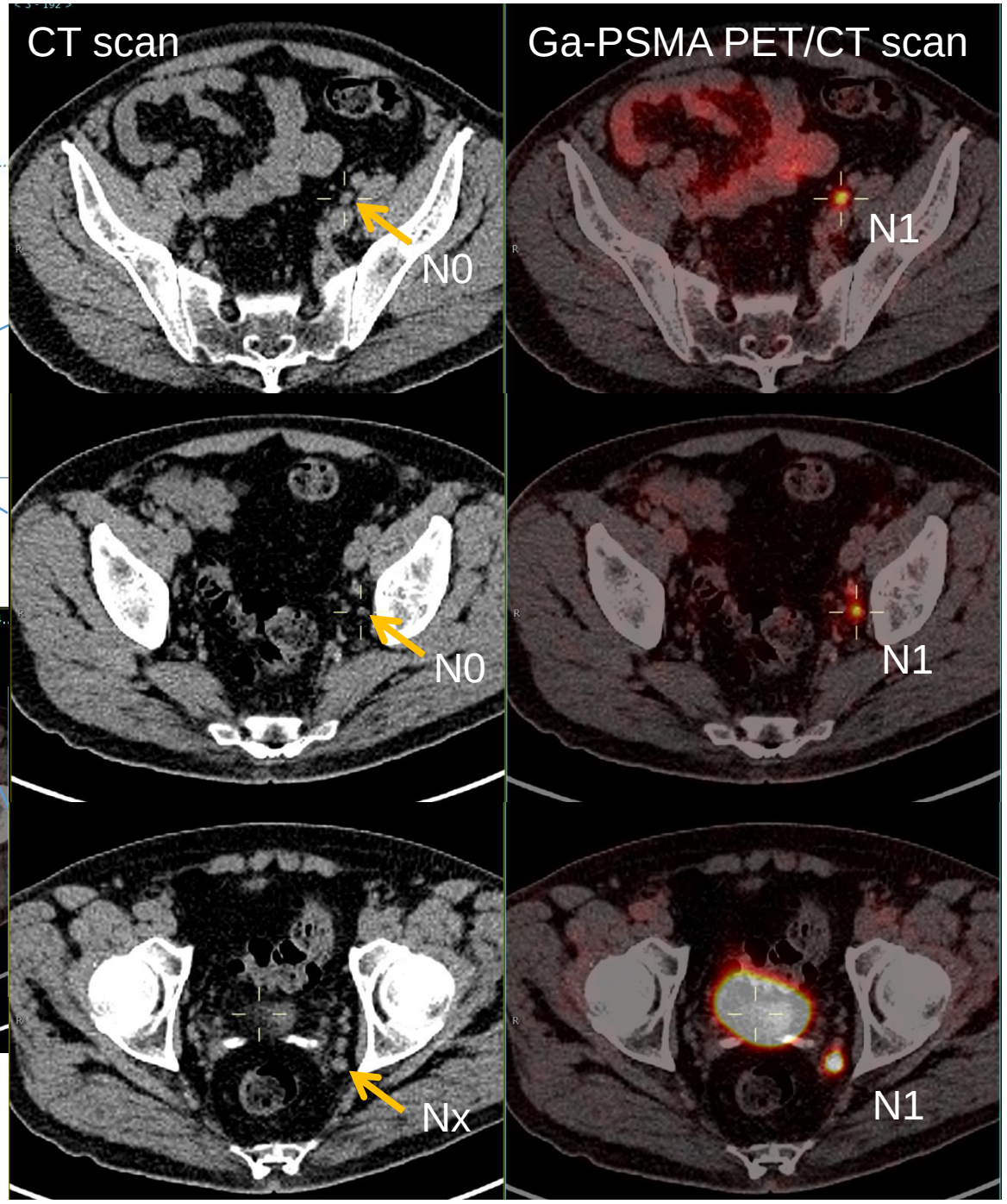




61M DRE+ve PSA 6.0 ng/mL. GS4+4 Equivocal LN on pelvic MRI
(Ga68-PSMA-PET/CT +ve 3 pelvic nodes)

So, do we treat only what we see at PSMA-PET/CT or go beyond?



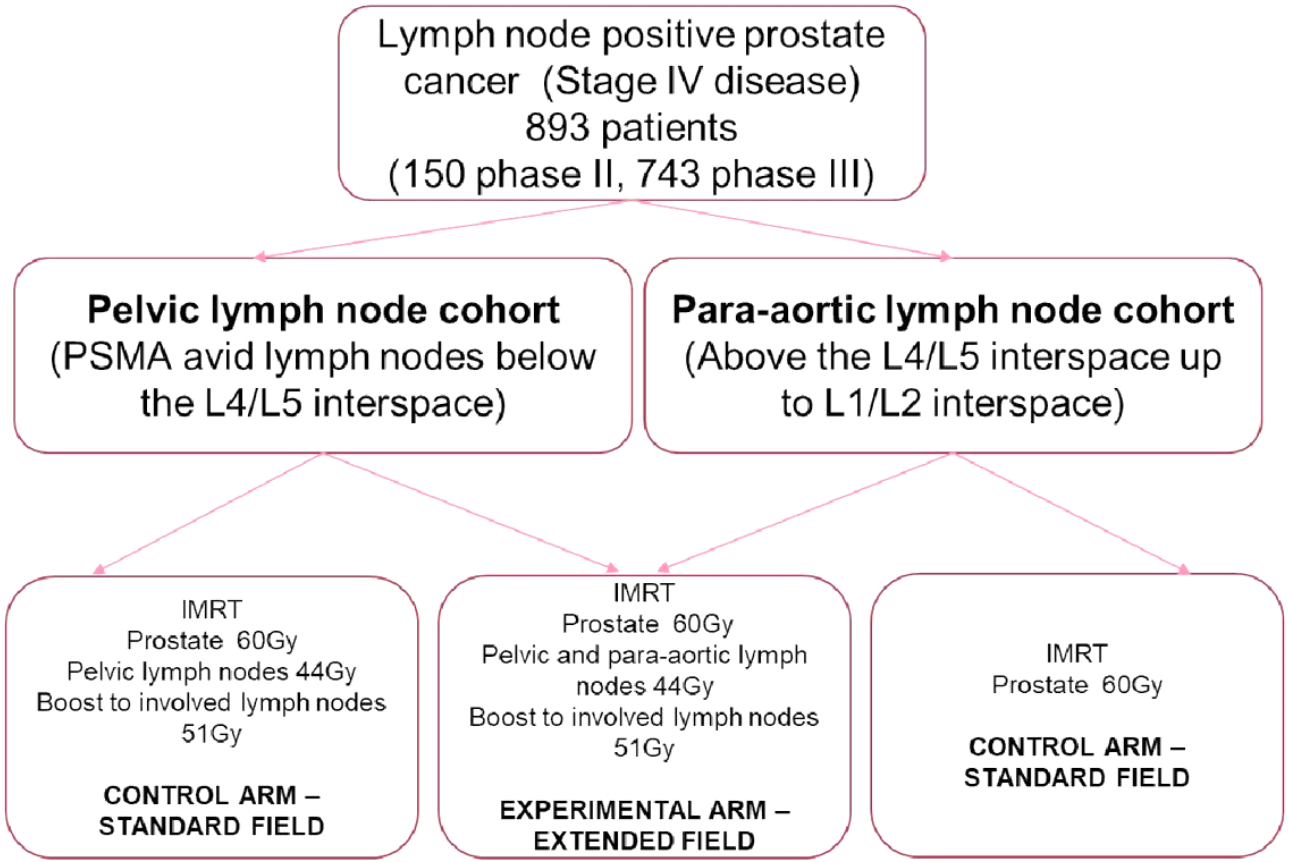


61M DRE+ve PSA 6.0 ng/mL. GS4+4 Equivocal LN on pelvic MRI
(Ga68-PSMA-PET/CT +ve 3 pelvic nodes)

ASCO GU 2022: 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

So, do we treat only what we see at PSMA-PET/CT or go beyond?

- Patients will be randomized (1:1) to standard field intensity-modulated radiotherapy (IMRT) (control) or extended field IMRT (experimental) with stratification by the extent of LN disease determined by PSMA-PET/CT (pelvic only vs. para-aortic).
- Endpoints:
  - Phase II: gastrointestinal toxicity
  - Phase III: metastasis-free survival



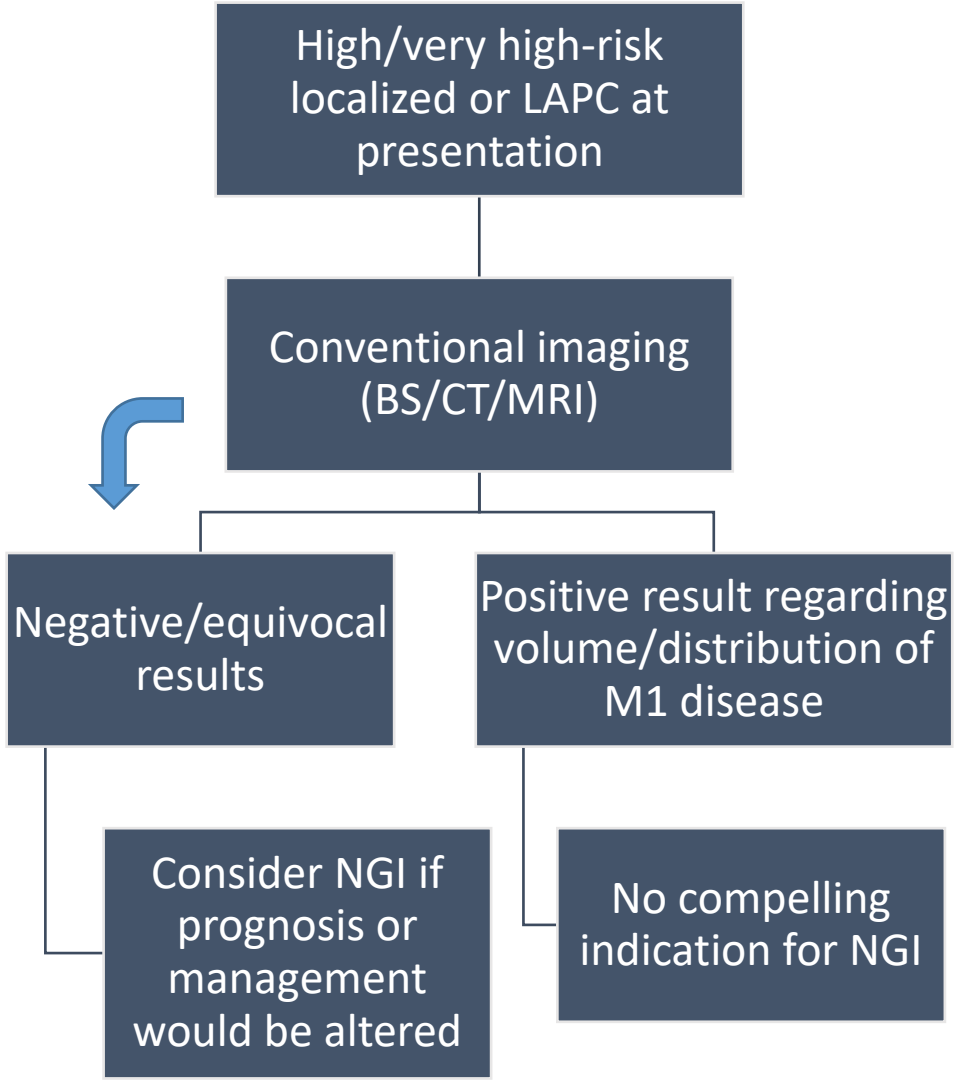
Newly Diagnosed Clinically High-Risk/Very High-Risk Localized, Locally Advanced Prostate Cancer

Recommendation 4.1. – negative conventional imaging

When conventional imaging is negative in patients with a high risk of metastatic disease, NGI may add clinical benefit, although prospective data are limited

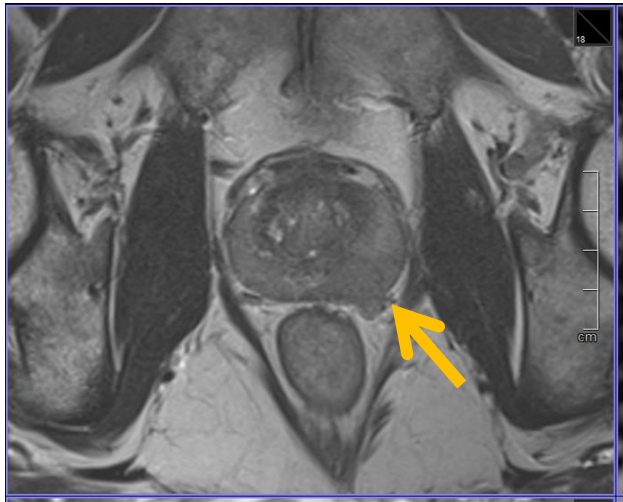
Recommendation 4.2. – suspicious conventional imaging

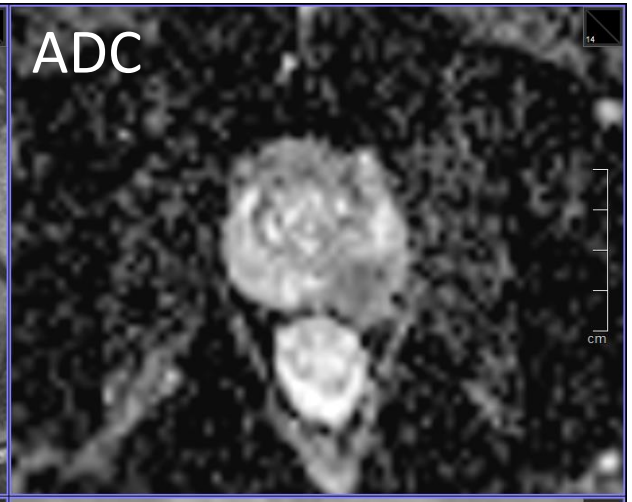
When conventional imaging is suspicious or equivocal, NGI may be offered for the clarification of equivocal findings or detection of additional sites of disease, which could potentially alter management, although prospective data are limited

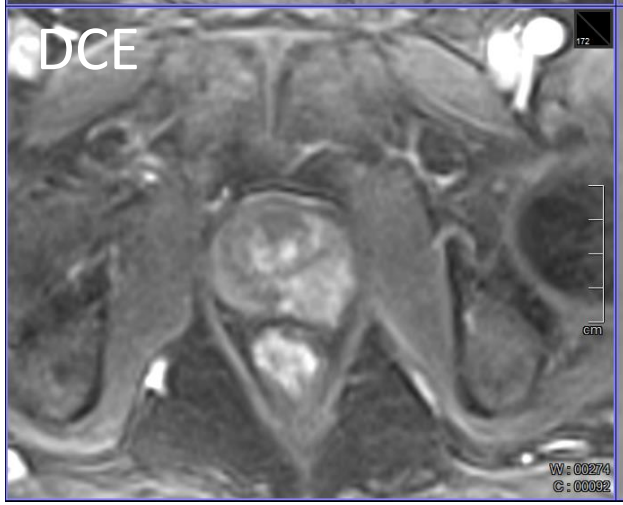


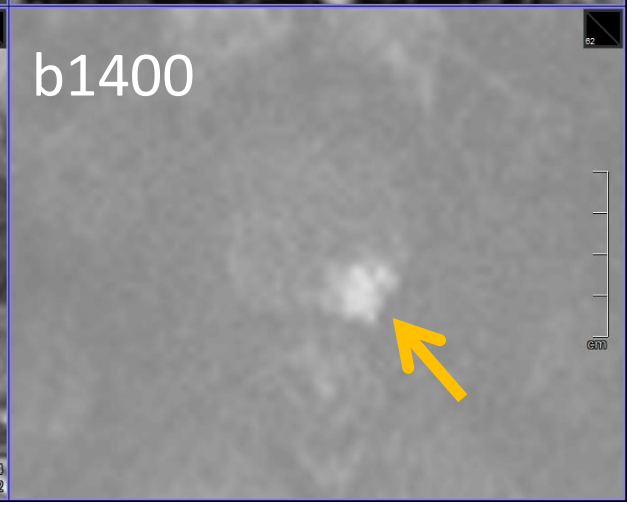
Trabulsi EJ, et al. Optimum Imaging Strategies for Advanced Prostate Cancer: ASCO Guideline. J Clin Oncol. 2020 Jun 10;38(17):1963-1996.

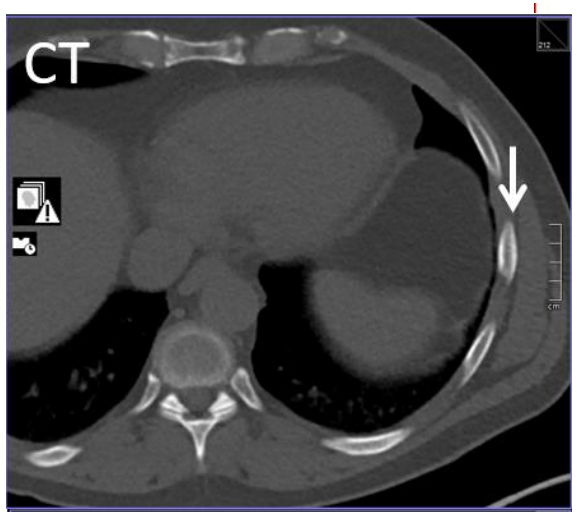
55 yo. Biopsy naïve. Caucasian. Hemospermia. PSA 3.32 ng/mL; PSAD 0.11. DRE-abnormal.
MRI gland volume 30mL. ECE+ SVI+. PI-RADS 5 lesion.

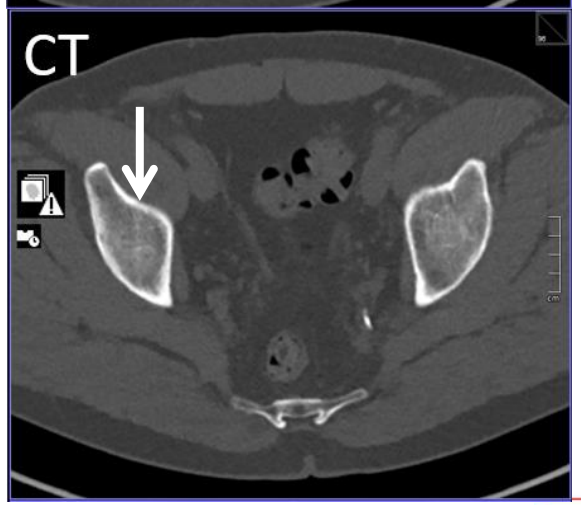


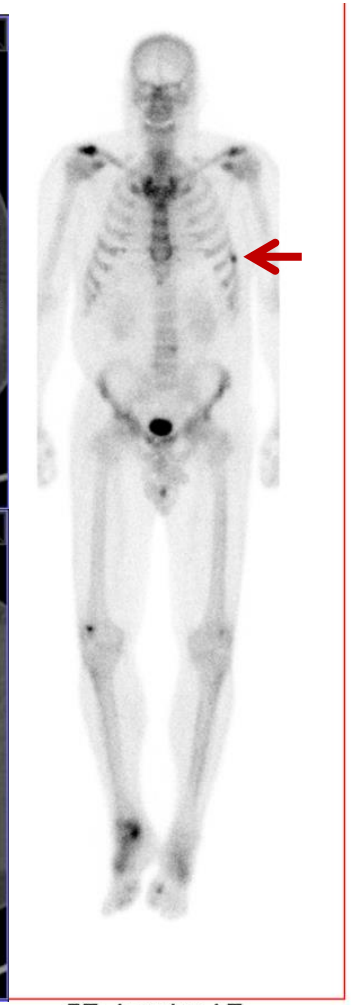




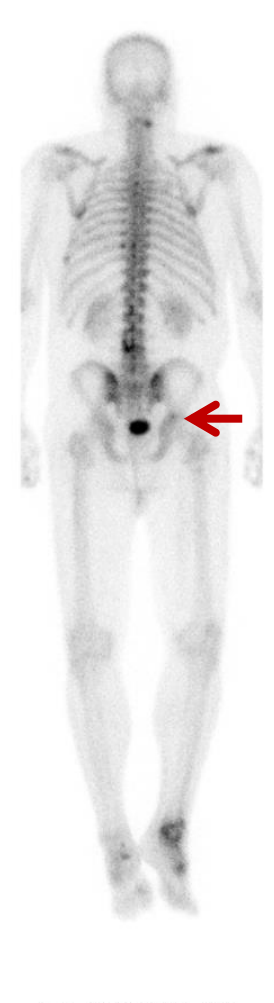






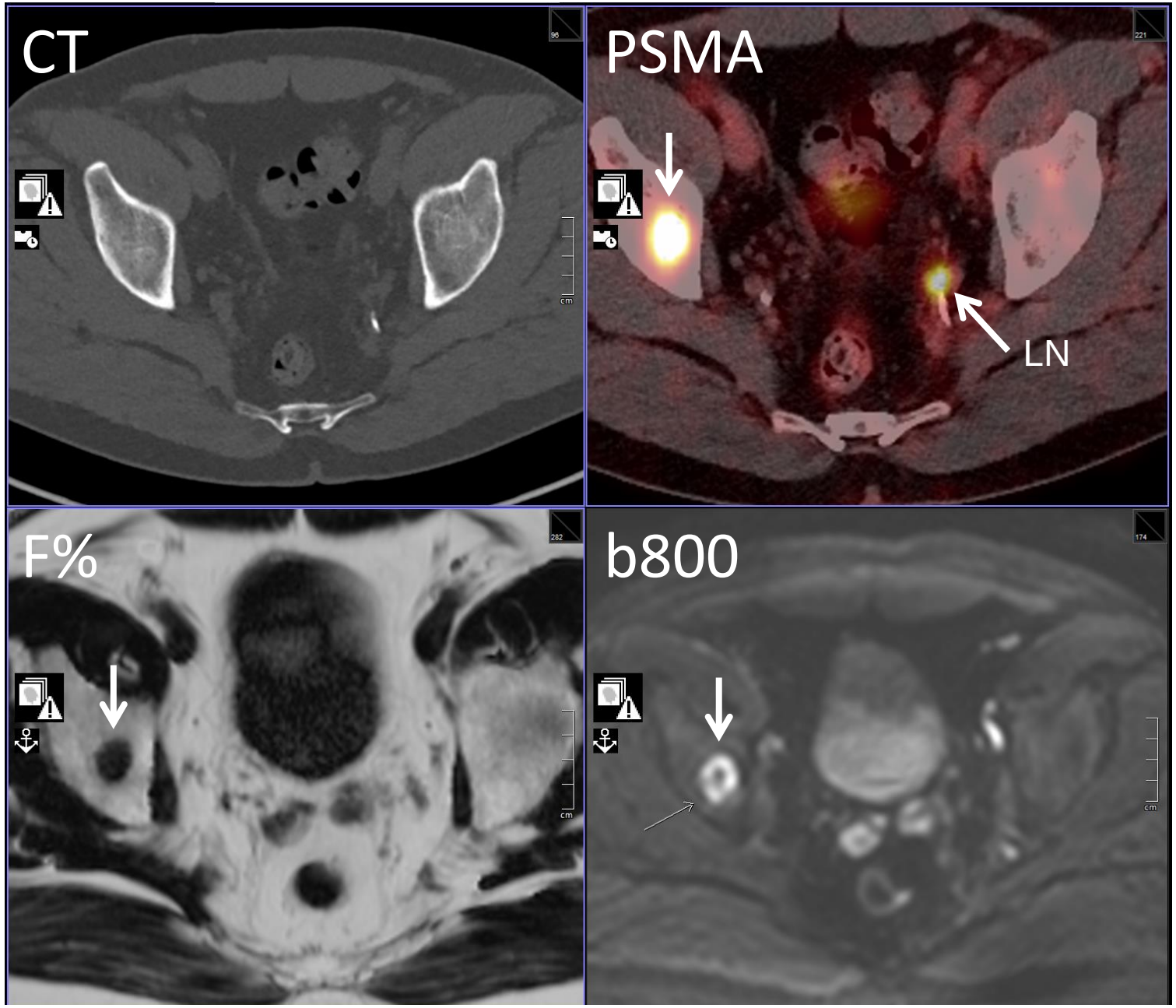


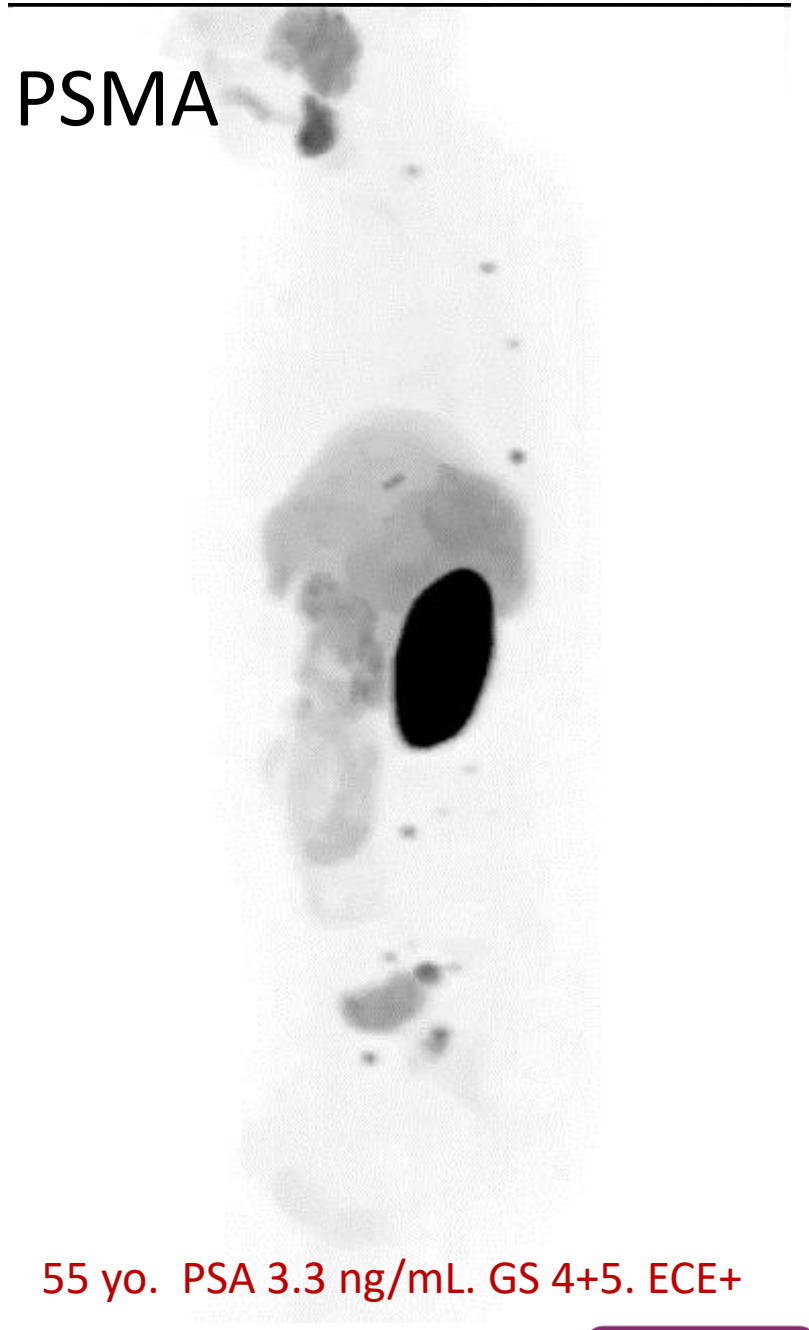
RT Anterior LT



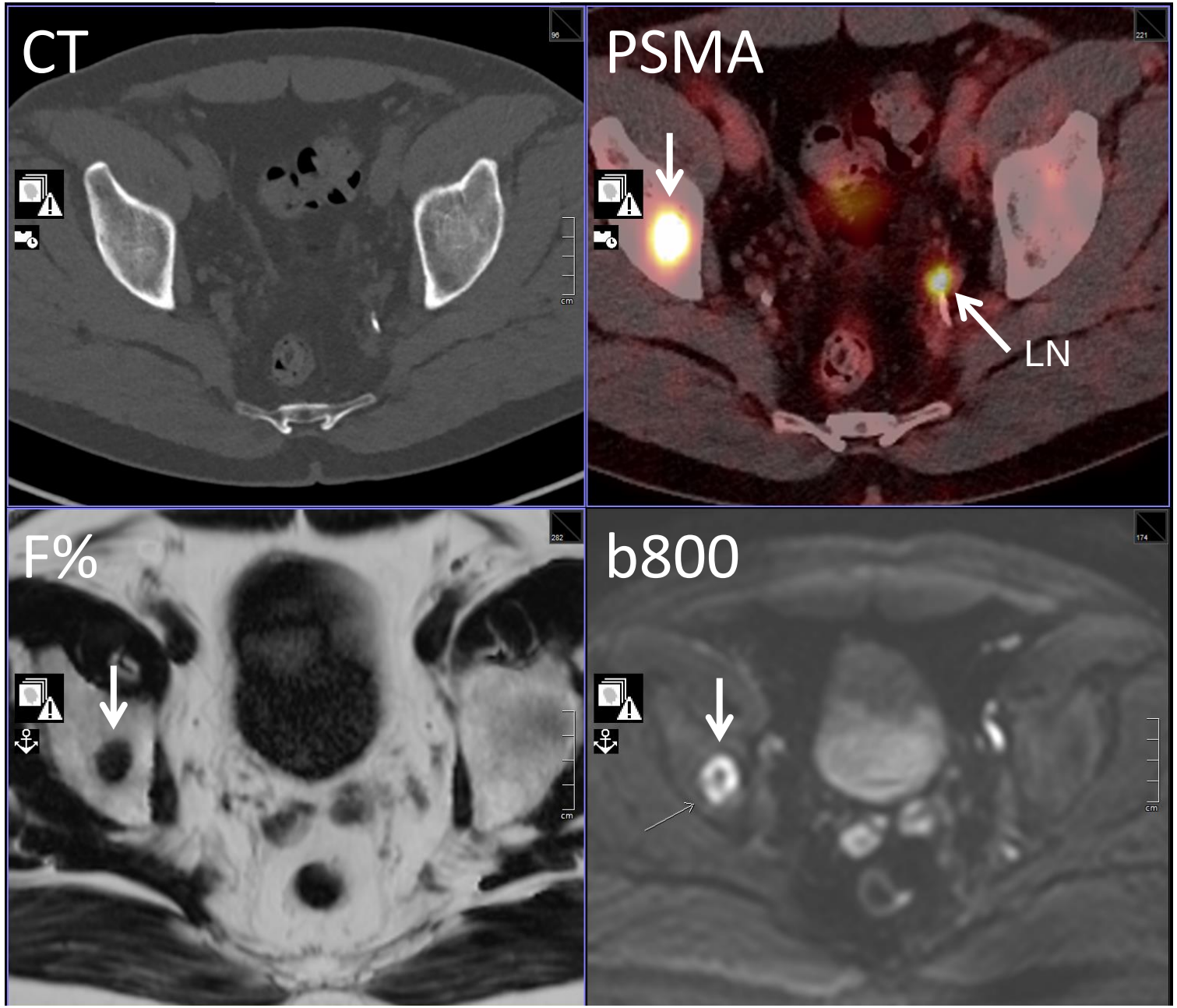
LT Posterior RT

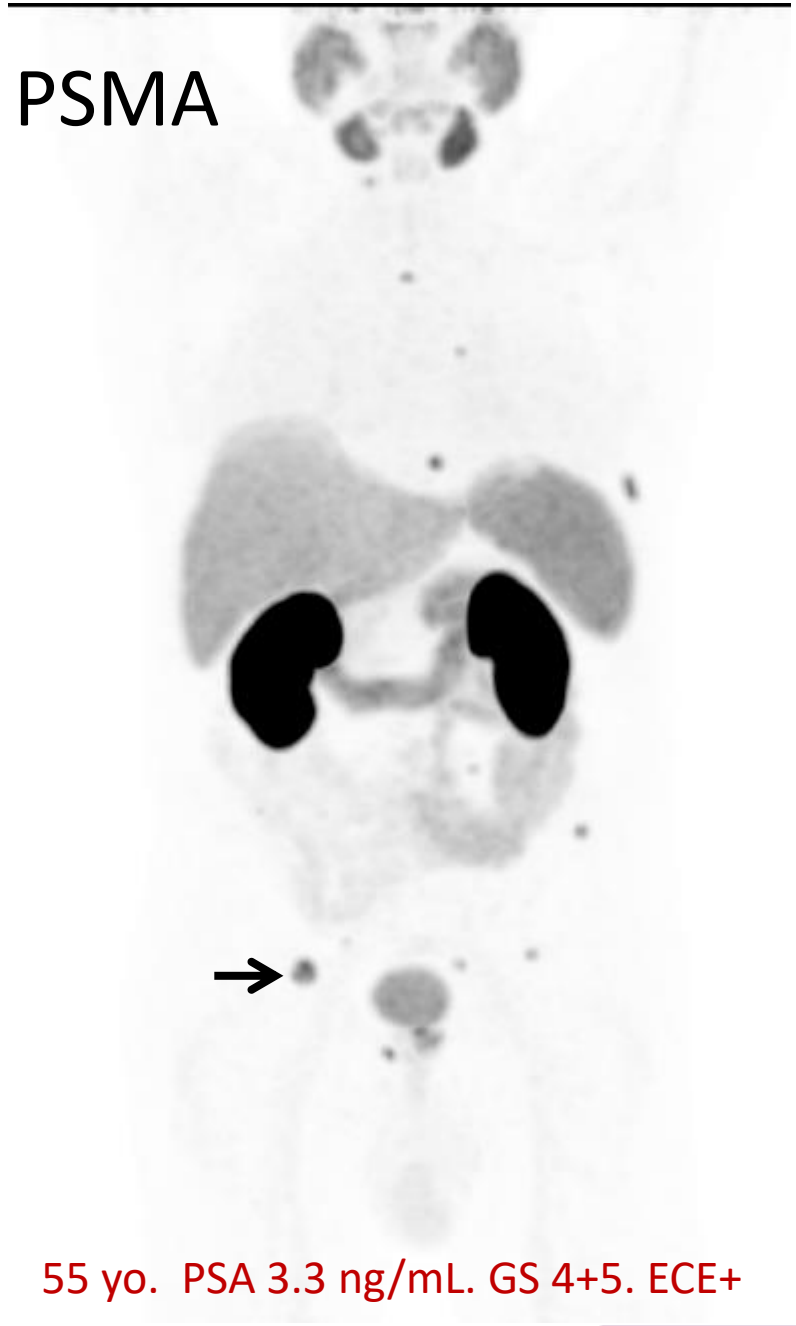
Left posterior base GS4+5=9 (15% GS5)



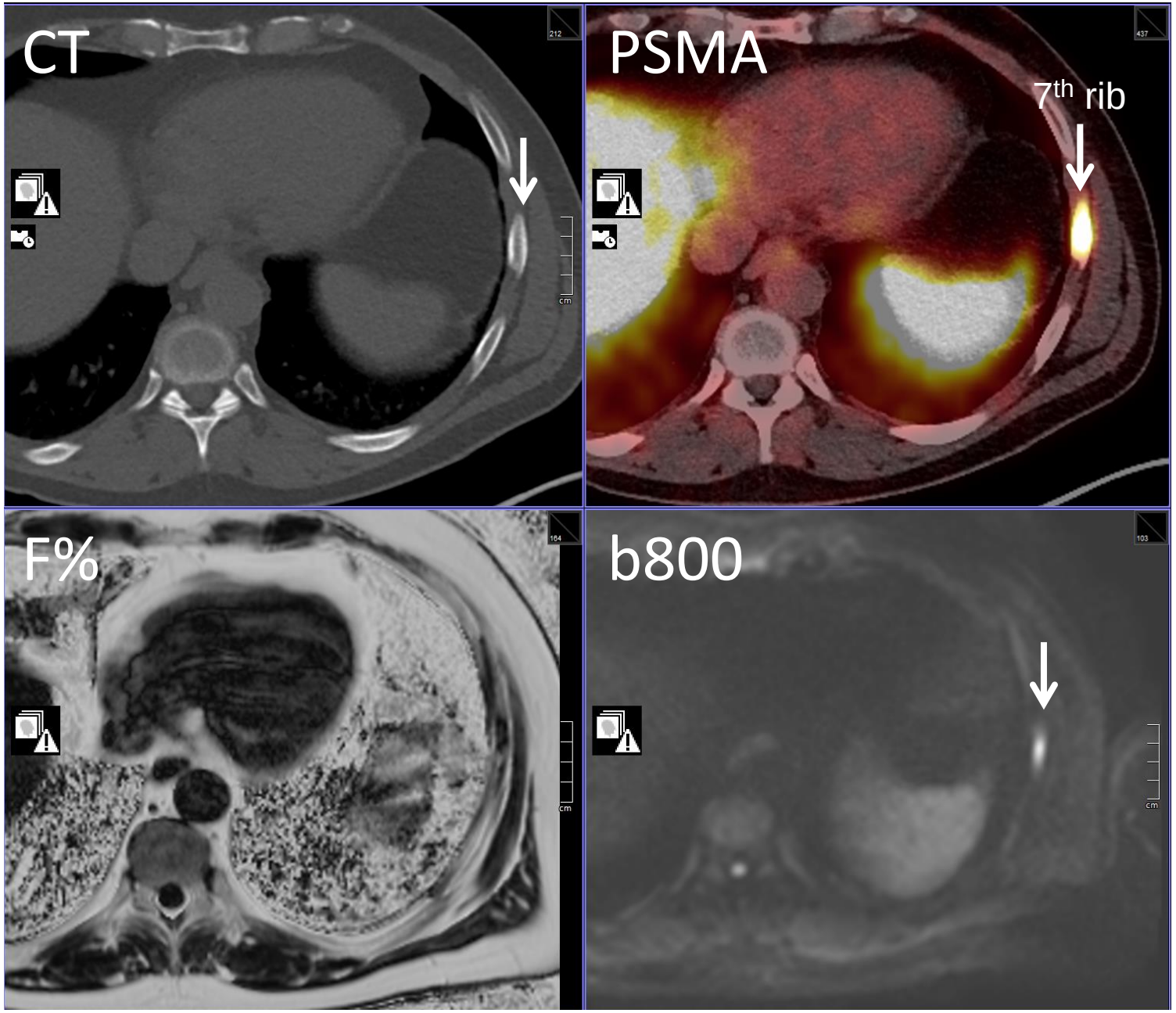


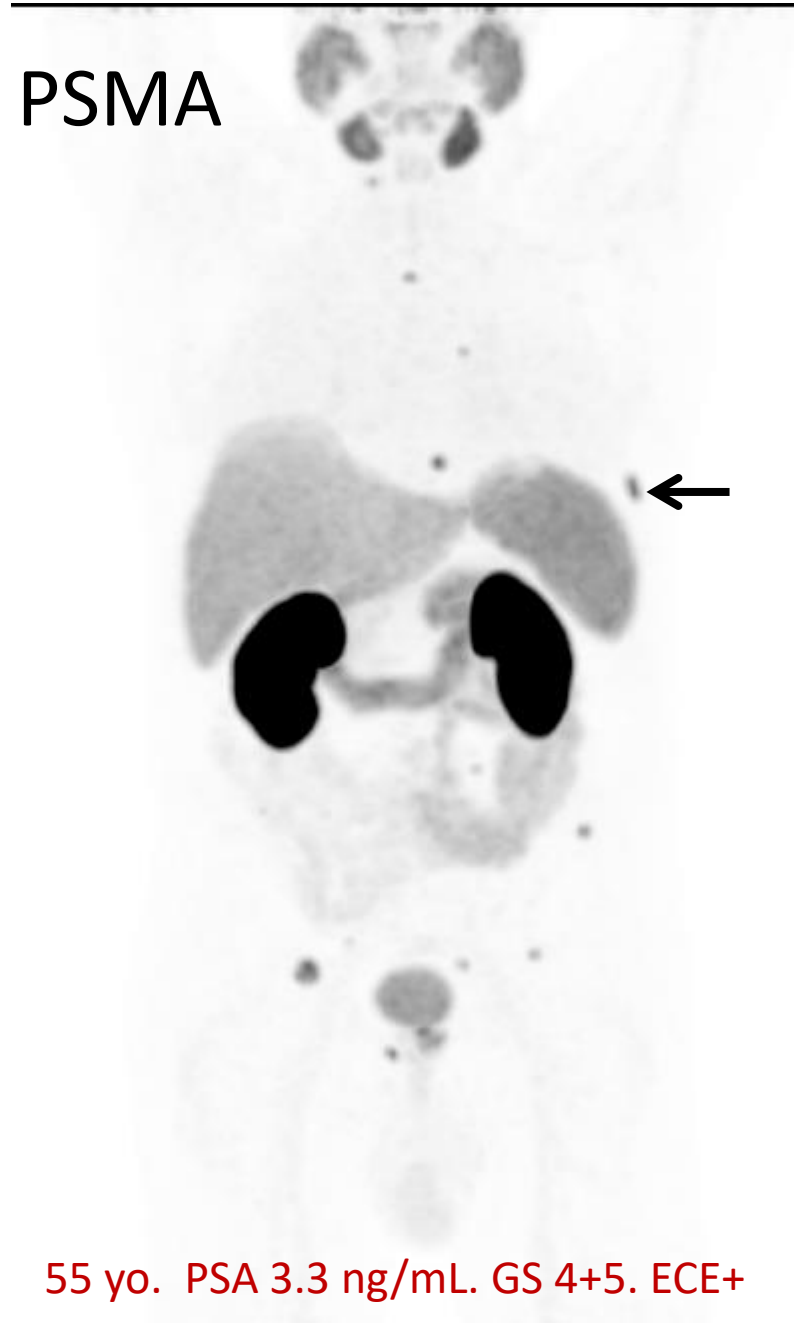
55 yo. PSA 3.3 ng/mL. GS 4+5. ECE+





55 yo. PSA 3.3 ng/mL. GS 4+5. ECE+





55 yo. PSA 3.3 ng/mL. GS 4+5. ECE+

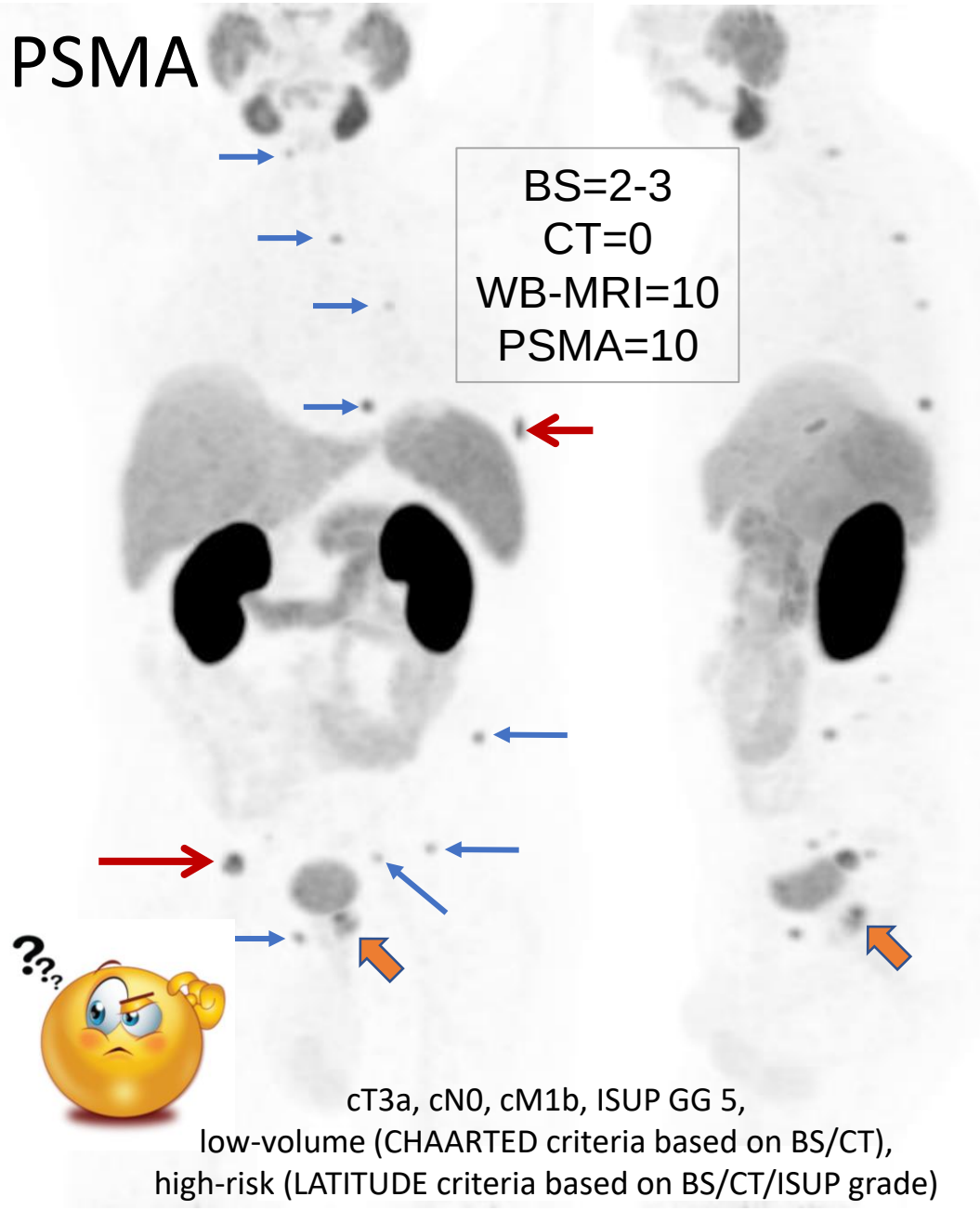
Clarity on disease load BUT not on management plan regarding pelvic RT

Polymetastatic disease on NGI | OMD on conventional imaging

Management plan regarding pelvic therapy??

1. Do you treat the pelvis with RT with radical intent? – Yes!
2. What should be the duration of adjuvant ADT/Abiraterone? – 2 years or lifetime?
3. Is chemotherapy a valid option for high-volume µM1A?

PSMA



cT3a, cN0, cM1b, ISUP GG 5,
low-volume (CHAARTED criteria based on BS/CT),
high-risk (LATITUDE criteria based on BS/CT/ISUP grade)
metastatic prostate cancer

PSMA-PET/CT in LAPC - limitations

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

False -ve disease: 5-10% of patients

Multiple reporting standards: EANM E-PSMA guideline (2021), PROMISE guideline (2018), PSMA-RADS (2019)

Biases: stage migration, lead-time and length time bias

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

PSMA-PET/CT in LAPC - limitations

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

False -ve disease: 5-10% of patients

Multiple reporting standards: EANM E-PSMA guideline (2021), PROMISE guideline (2018), PSMA-RADS (2019)

Biases: stage migration, lead-time and length time bias

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

Next generation imaging advantages

Improves lesion characterizations (specificity)

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

Improves bone response categorizations

Survival biases of Next Generation Imaging

@ProfPadhani

Improves lesion characterizations (specificity)

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

Improves bone response categorizations

Survival biases of Next Generation Imaging

@ProfPadhani

Stage-migrations &
Will-Rogers effect

Improves lesion characterizations (specificity)

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

Improves bone response categorizations

Survival biases of Next Generation Imaging

@ProfPadhani

Lead-time bias

Stage-migrations & Will-Rogers effect

Length-time bias

"Survival biases occur by the detection of 'important' & 'unimportant' diseases – only if management strategies are not adjusted to take account the new information"

- **Stage-migration/Will-Rogers bias**: improved subgroup survivals due to reclassifications related to improved sensitivity & specificity
- **Lead-time bias**: overestimations of survival durations due to earlier detection of important disease, if early standard therapy has no beneficial impacts
- **Length-time bias**: overestimations of survival durations due to the over-diagnosis and over-treatments of indolent disease

The “one size fits all” Rx paradigm is a workaround due to current diagnostic limitations

Improved outcomes can only rise from accurate information

Stage migration is a statistical aberration related to higher accuracy

Only perceptions are changed (sub-group analysis), not the disease state

Over-diagnosis harm of indolent disease detection & lead time bias of µM+ is a clinical management limitation NOT a diagnostic harm

Stage migration due to high sensitivity is countered by high specificity which reduces false alarms and over-treatments

Net benefit needs to be considered

“Survival biases harm occur by the detection of ‘important’ & ‘unimportant’ diseases – only if management strategies are not adjusted to take account the new information”


JNM
The Journal of Nuclear Medicine

search

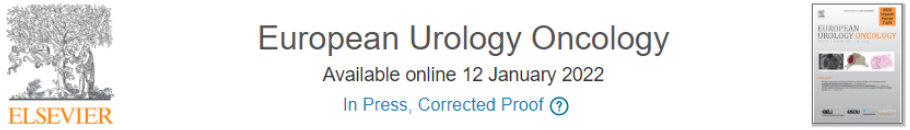
Home | Content | Subscriptions | Authors | Info | About | More

Other | Editorial

Role of Prostate-Specific Membrane Antigen-Positron Emission Tomography in Metastatic Prostate Cancer: We have the answers

Kelsey L. Pomykala, Ken Herrmann, Anwar R. Padhani, Michael S. Hofman, Elisabetta Lalumera and Stefano Fanti

Journal of Nuclear Medicine June 2022, jnumed.122.264394; DOI: https://doi.org/10.2967/jnumed.122.264394


ELSEVIER

European Urology Oncology

Available online 12 January 2022

In Press, Corrected Proof

Facts and Myths About Stage Migration: Should the Will Rogers Phenomenon Ride off into the Distance?

Stefano Fanti [a, b], Elisabetta Lalumera [c], Rodney Hicks [d]

The “one size fits all” Rx paradigm is a workaround due to current diagnostic limitations.

Improved outcomes can only rise from accurate information

Stage migration is a statistical aberration related to higher accuracy

Only perceptions are changed (sub-group analysis), not the disease state

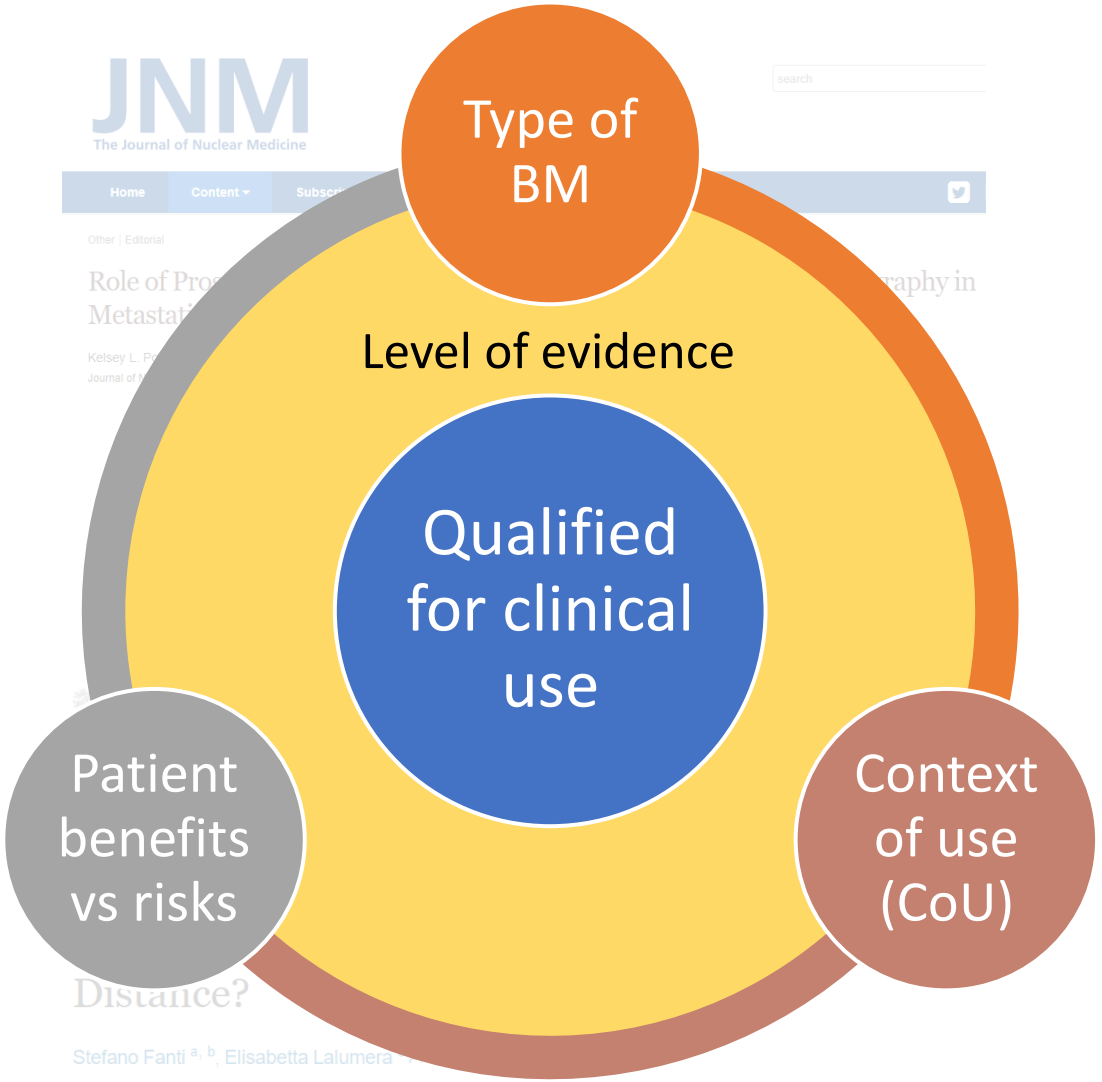
Over-diagnosis harm of indolent disease detection & lead time bias of µM+ is a clinical management limitation NOT a diagnostic harm

Stage migration due to high sensitivity is countered by high specificity which reduces false alarms and over-treatments

Net benefit needs to be considered

Regulator: Context of use and patient risk determines the evidence needed to support BM qualification.

- Diagnostic BM: there is no need to show improved outcomes of the management changes
- If improved outcomes claims are made (prognostic risk-stratification or predicts outcomes to specific Rx), then separate management impacts on quantity and quality of life endpoints are needed



PSMA-PET/CT in LAPC - limitations

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

False -ve disease: 5-10% of patients

Multiple reporting standards: EANM E-PSMA guideline (2021), PROMISE guideline (2018), PSMA-RADS (2019)

Biases: stage migration, lead-time and length time bias

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

PSMA-PET/CT in LAPC - limitations

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

False -ve disease: 5-10% of patients

Multiple reporting standards: EANM E-PSMA guideline (2021), PROMISE guideline (2018), PSMA-RADS (2019)

Biases: stage migration, lead-time and length time bias

Outcome impacts: Do management impacts ‘really’ change 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] 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]

ELSEVIER

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 outcomes impacts:

"The value of imaging BM 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

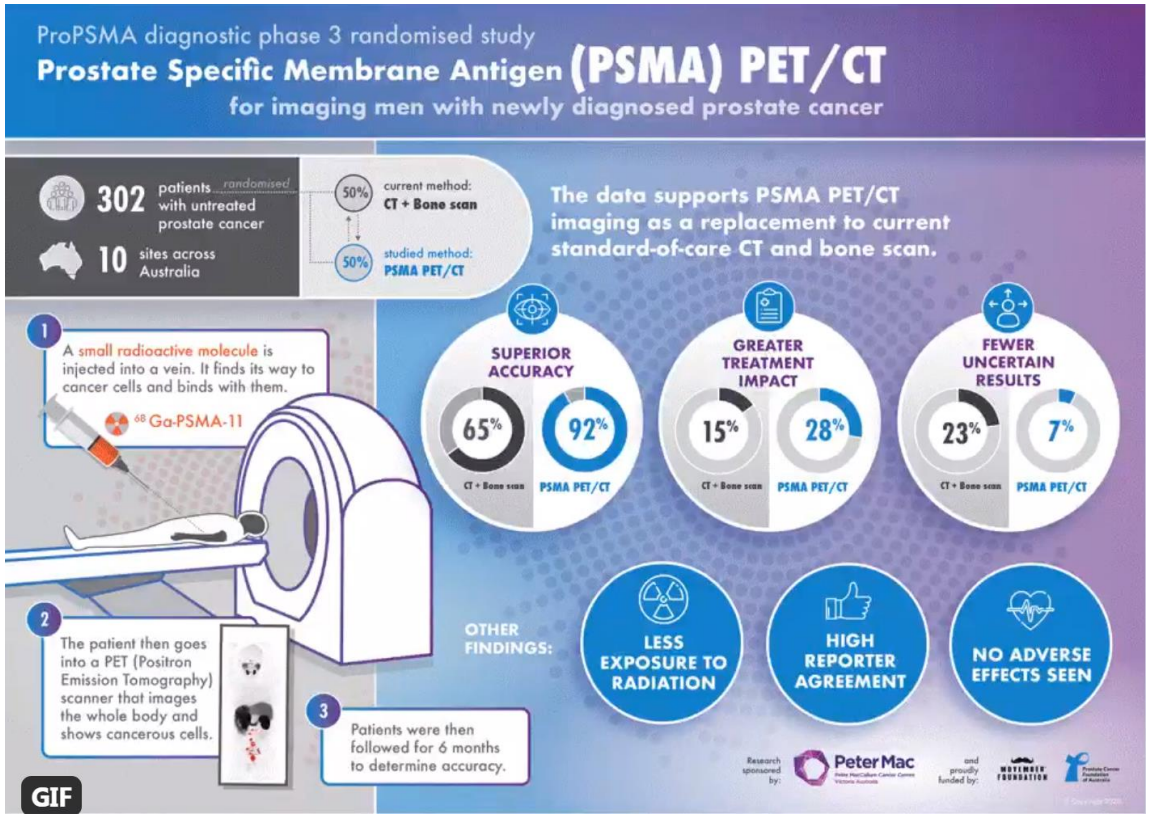
- Unfavourable intermediate and high-risk localised disease, PSMA-PET/CT compared to CT/BS
  - 87/150 (30%) patients had confirmed pelvic nodal or distant metastatic disease

Michael Hofman
@DrMHofman

#ProPSMA randomised study online in @thelancet:

PSMA PET/CT can replace CT/bone scans in men with aggressive prostate ca:
✓Accuracy 92% v 65%
✓Management impact 28% v15%
✓Uncertain findings 7% v 23%
✓Radiation dose 8 v 19mSv

bit.ly/propsma @gu_onc @pcfa @movember



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

Considerable uncertainty regarding NGI impacts on outcome in high-risk prostate cancer

Guideline	statement
EAU 2022	*"when using PSMA PET/CT or whole-body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes"*
AUA/ASTRO 2022	*"… the panel …. underscores the current uncertainty regarding an incremental oncologic benefit of altering treatment based on the identification of metastases with molecular imaging among patients with negative conventional imaging."*
ASCO Consensus Panel 2020	*"the consequence of using PSMA PET/CT imaging is that "this may alter treatment decisions with unknown consequences on the overall disease course"*

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 during Rx
  - Adjuvant phase of Rx

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

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.

Take home points – PSMA-PET/CT in LAPC

- High sensitivity and specificity imaging has the potential to change the disease course/improve outcomes for men with high-risk localized and locally advanced prostate cancer
- Major biases can arise from higher sensitivity and specificity imaging including stage/grade migration, lead, and length time bias
- Escalation & de-escalation therapy changes are brought about; net benefits remain unknown
- The availability and application of treatment for µM (seen on PSMA-PET/CT), may NOT result in meaningful clinical improvements
  - Prospective clinical trials of NGI with meaningful endpoints (QoL and quantity of life) are essential to do

Dimitris, 67 years old

- Medical history:
  - Controlled hypertension (on 2 hypertensives)
  - Acute urinary retention
  - ECOG PS: 0
- Assessment summary:
  - PSA: 33.3 ng/ml
  - DRE: cT3
  - mpMRI: cT3b cN0
  - Biopsy: ISUP grade group 4 [GS 5+3]
  - CT and bone scan: cM0

Should next-generation imaging be done after bone and CT scans in the clinical assessment?*

- Definitely Yes
- Maybe yes
- Uncertain
- Maybe not
- Definitely Not

* if you don't have to take into account regulatory approval and local restrictions

VOTE

Twitter: @Profpadhani
Youtube: anwar padhani

Be impartial → take an unbiased view of the facts and avoid the pitfalls of group thinking, railroading, filtering, compromising

Innovate → work together to introduce new creative thinking to address challenges and make changes for the betterment of patients

Insightful → develop more accurate and deeper understanding, based on analyses of the facts, experience and intuition, that sees things beyond the present