

*Estadificación del cáncer de próstata localizado
de alto riesgo con PET-PSMA: visión crítica ·*
***Staging of localized high-risk prostate cancer
with PET-PSMA: a critical view***

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Nuclear Medicine
Bologna Italy

Conflict of Interest Disclosure

- I have the following potential conflict of interest to report

In the last 3 yrs I have received Speaker fees or travel grants from: *Novartis, Curium, Oncobeta, Recordati, GE, Astra Zeneca, Tema.*

Summary

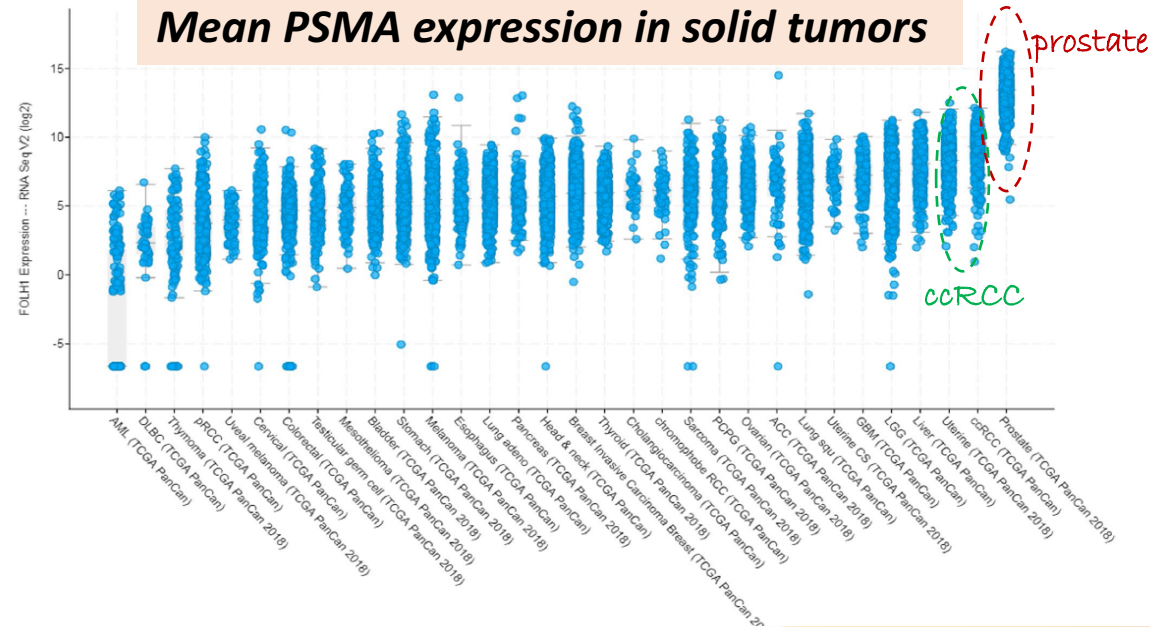
- *«...critical view....» main limitations of PSMA: expression and heterogeneity*
- *PSMA PET in staging localized HR (accuracy & prognosis)*
- *PSMA PET in staging localized HR (influence on treatment decision)*
- *Conclusions*

Despite it's name **PSMA** is not **Specific for Pca:**

4352

European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:4350–4368

Mean PSMA expression in solid tumors



Benign conditions PSMA +

	Bone-related conditions	Inflammatory and infectious processes	Benign neoplasms
Central and peripheral nervous system	–	Neurocysticercosis	Meningioma Schwannoma Peripheral nerve sheath tumor Neurofibromas
Cervical	–	–	Thyroid and parathyroid adenomas
Thoracic	–	Opacities and bronchiectasis Sarcoidosis Tuberculosis Anthraxosilicosis Berylliosis	Elastofibroma dorsi Pseudoangiomatous stromal hyperplasia of the breast Thymoma
Abdominal	–	Postsurgical inflammation Liver and splenic sarcoidosis Diverticulosis Amyloidosis of seminal vesicles Anal fistula	Angiolipoma Hepatic and splenic hemangiomas Adrenal adenoma Pancreatic serous cystadenoma
Skeletal, soft-tissues and vascular	Osteomyelitis Fracture Paget's Disease Hemangioma Osteogenerative Fibrous Osseous Defect Fibrous Dysplasia Sacral insufficiency after RT Osteochondroma Multiple Myeloma Polycythemia Rubra Vera Myelodysplasia	Nodular fasciitis	Dermatofibroma Acrochordon Fibromatosis Desmoid tumor Intramuscular myxoma Hemangiopericytoma Nasal Angiofibroma Angiolipoma Acrochordon Fibromatosis

European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:4350–4368

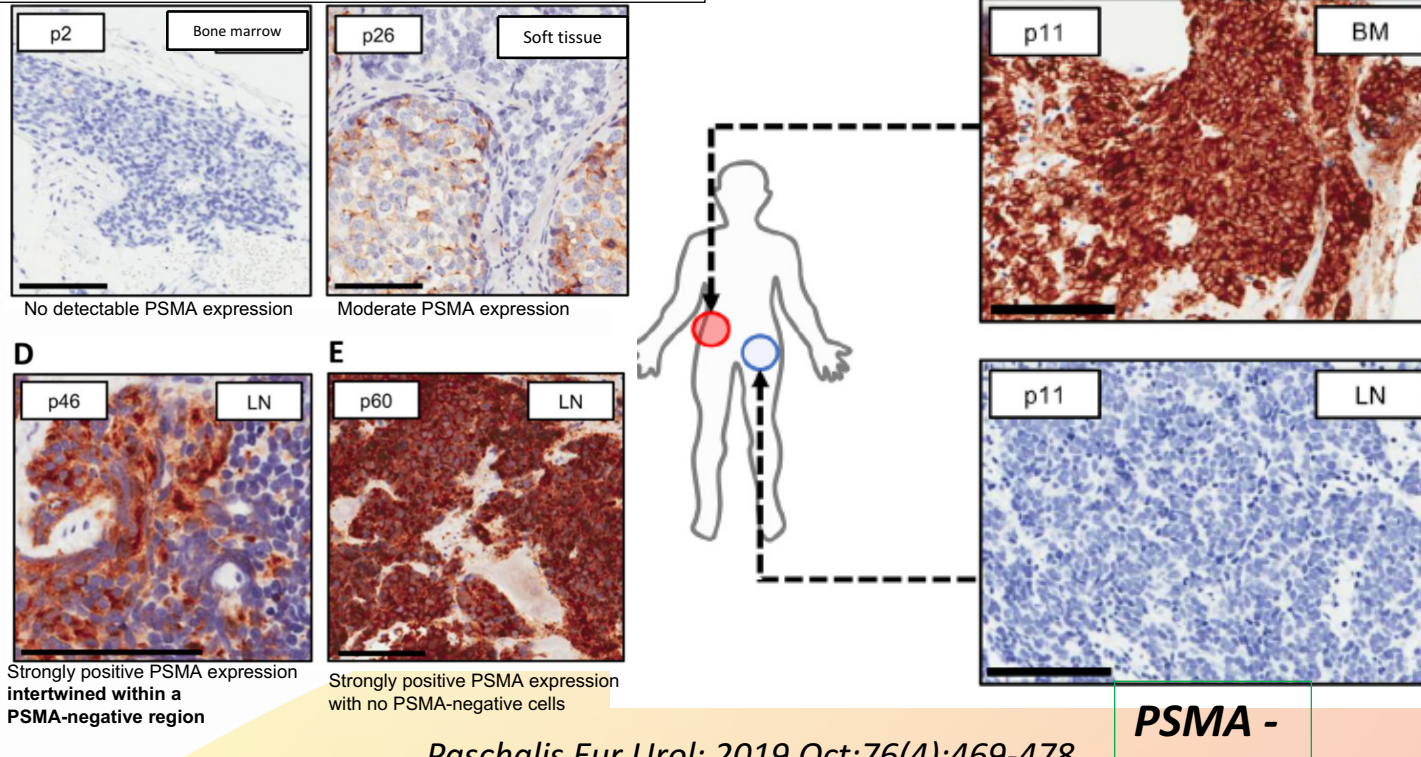
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...moreover PSMA is not overexpressed in all Prostate cancer cells

PSMA expression Heterogeneity in PCa

PSMA different IHC expression in 60 patients



Expression of mPSMA exhibits marked intra- and inter-patient heterogeneity

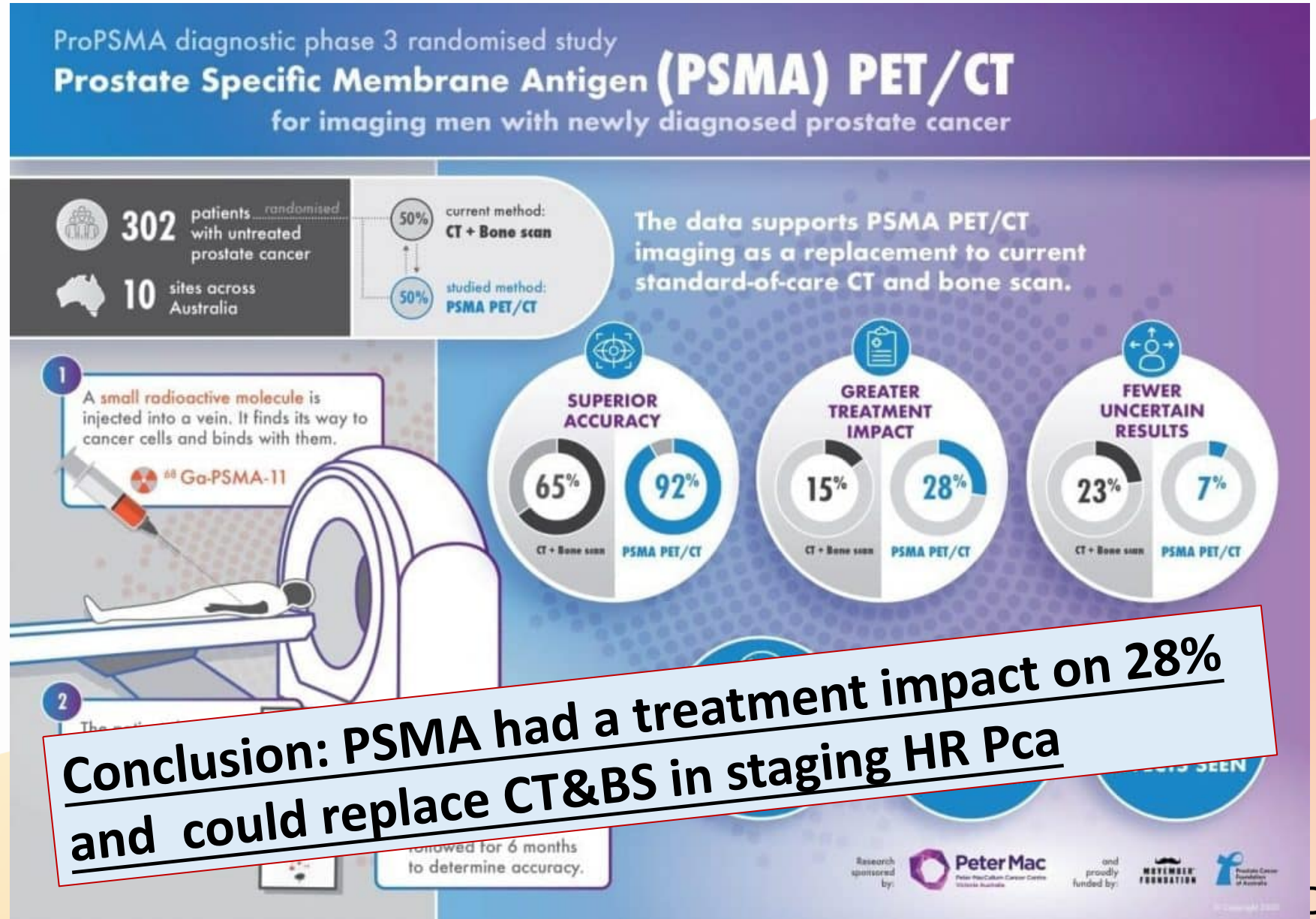
Expression of mPSMA might change during the natural history of the disease and after / during therapies

Summary

- «...critical view....» main limitations of PSMA: expression and heterogeneity
- **PSMA PET in staging localized HR (accuracy & prognosis)**
- *PSMA PET in staging localized HR (influence on treatment decision)*
- *Conclusions*

ProPSMA trial

Hofman et al, Lancet.
2020 Apr
11;395(10231):1208-1216.
doi: 10.1016/S0140-
6736(20)30314-7. Epub
2020 Mar
22.PMID: 32209449
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PSMA in staging High Risk: EAU Guidelines 2020-2025

2020-2021

High-risk localised disease/locally advanced disease

Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	2a	Strong
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Added in 2022-23

High-risk localised disease/locally advanced disease

Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong
When using PSMA PET or whole body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes.	Strong

Added in 2024-25

Intermediate-risk disease

Perform A prostate-specific membrane antigen positron emission tomography (PSMA-PET)/Computed Tomography (CT) if available to increase accuracy.	Weak
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High-risk localised disease/locally advanced disease

Perform metastatic screening using PSMA-PET/CT if available <u>and at least cross-sectional abdominopelvic imaging and a bone-scan.</u>	Strong
---	--------

Pelvic lymph-node staging with ¹⁸F-DCFPyL PET/CT prior to extended pelvic lymph-node dissection in primary prostate cancer - the SALT trial -

B. H. E. Jansen^{1,2,3} • Y. J. L. Bodar^{1,2,3} • G. J. C. Zwezerijnen² • D. Meijer^{1,2,3} • J. P. van der Voorn⁴ • J. A. Nieuwenhuijzen^{1,3} • M. Wondergem⁵ • T. A. Roeleveld^{3,6} • R. Boellaard² • O. S. Hoekstra² • R. J. A. van Moorselaar^{1,3} • D. E. Oprea-Lager² • A. N. Vis^{1,3}

- Prospective, multicentre cohort study in **117 HR PCa** underwent 18F-DCFPyL + (RARP) + ePLND.
- All images were compared with **post-operative histopathologic** results.

Results
Sensitivity: 41.2%
Specificity: 94.0%
NPV: 90.4%
PPV: 53.8%

Patient-based accuracy					
	pN1	pN0	Total	% (95%CI)	
cN1	7	6	13	53.8 (26.1–79.6)	PPV
cN0	10	94	104	90.4 (82.6–95.0)	NPV
Total	17	100	117	14.5	Prevalence
% (95%CI)	41.2 (19.4–66.5)	94.0 (86.9–97.5)			
	Sensitivity	Specificity			
Template-based accuracy					
	pN1	pN0	Total	% (95%CI)	
cN1	8	10	18	44.4 (22.4–68.6)	PPV
cN0	15	435	450	96.6 (94.4–98.0)	NPV
Total	23	445	468	4.9	Prevalence
% (95%CI)	34.7 (17.1–57.1)	97.7 (95.7–98.9)			
	Sensitivity	Specificity			

CI, confidence interval

Eur J. Nucl Med Mol Imaging **2021 Feb**;48(2):509-520.
doi: 10.1007/s00259-020-04974-w. Epub 2020 Aug 12.

A Comprehensive Systematic Review and Meta-analysis of the Role of Prostate-specific Membrane Antigen Positron Emission Tomography for Prostate Cancer Diagnosis and Primary Staging before Definitive Treatment

Elio Mazzone^{a,b,*}, Donato Cannoletta^b, Leonardo Quarta^b, David C. Chen^a, Alice Thomson^a, Francesco Barletta^b, Armando Stabile^b, Daniel Moon^{a,c}, Renu Eapen^{a,c}, Nathan Lawrentschuk^{a,c,d}, Francesco Montorsi^{b,e}, Shankar Siva^{c,f}, Michael S. Hofman^{c,g}, Arturo Chiti^{a,h}, Declan G. Murphy^{a,c}, Alberto Briganti^{b,e}, Marlon L. Perera^{a,d}

18.649 patients High Risk or Intermediate Risk PSMA was positive outside prostate (*weak validation*):

- **High risk 31%**
- **Intermediate risk 15%**

In a subgroup of 7.713 patients where PLND was the standard of reference N+

Sens 54%

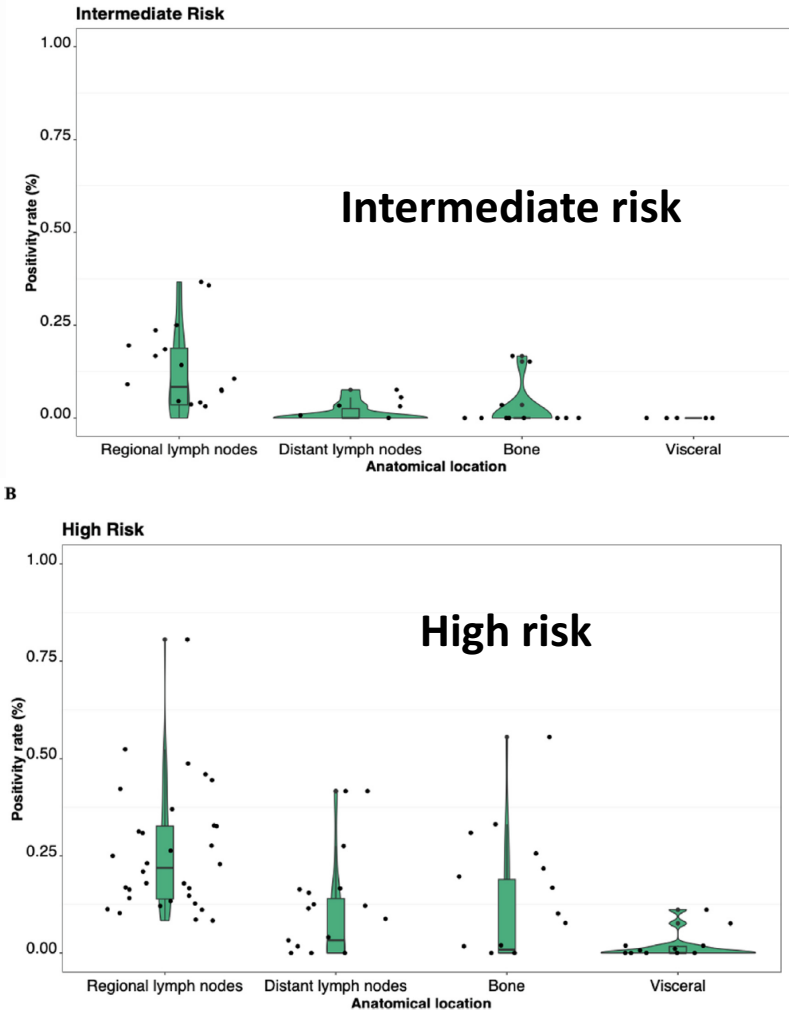
Spec 94%

PPV 77%

NPV 86%

High Specificity in N+ (.. Bias of a selected high risk population)

Conclusions: Models should incorporate PET PSMA to inform treatment decision...



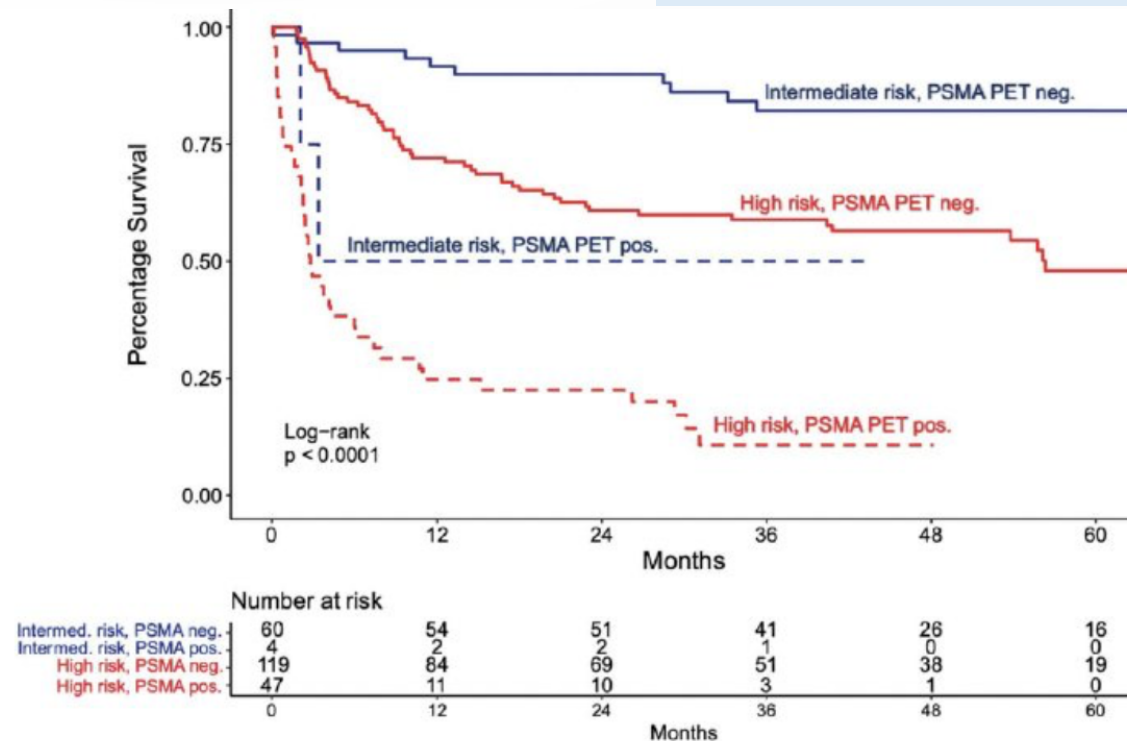
Prognostic value of PSMA PET

Regional Lymph Node Metastasis on Prostate Specific Membrane Antigen Positron Emission Tomography Correlates with Decreased Biochemical Recurrence-Free and Therapy-Free Survival after Radical Prostatectomy: A Retrospective Single-Center Single-Arm Observational Study

Thomas Amiel¹, Christoph Würschimmel^{2,3}, Matthias Heck¹, Thomas Horn¹, Noemi Nguyen¹, Lars Budäus², Sophie Knipper², Mike Wenzel^{3,4}, Isabel Rauscher⁵, Matthias Eiber⁵, Hui Wang⁵, Tobias Maurer^{2,6}

Affiliations + expand
PMID: 33535796 DOI: 10.1097/JU.0000000000001596

230 PCa intermediate and HR received ⁶⁸Ga-PSMA-11 PET followed by RP + PLND



J Urol. 2021 Jun;205(6):1663-1670. doi: 10.1097/JU.0000000000001596. Epub 2021 Feb 4.

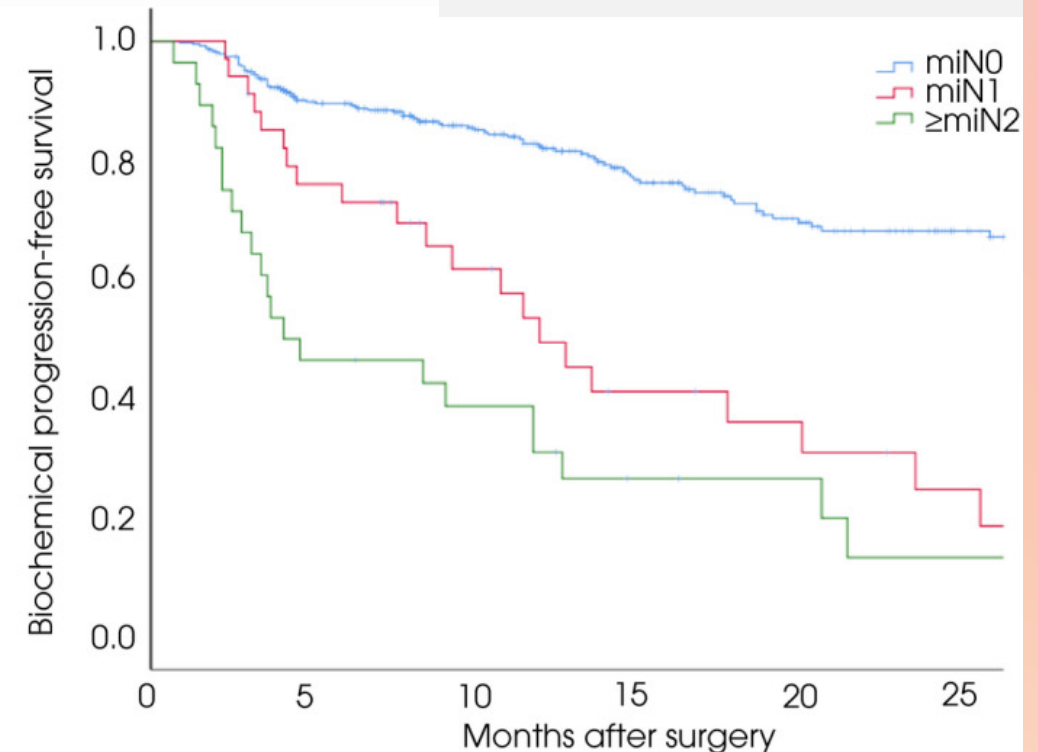
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Predicting early outcomes in patients with intermediate- and high-risk prostate cancer using prostate-specific membrane antigen positron emission tomography and magnetic resonance imaging

Dennie Meijer^{1,2,*}, Pim J van Leeuwen³, Maarten I. Donswijk⁴, Thierry N. Boellaard⁵, Ivo G. Schoots⁵, Henk G. van der Poel³, Harry N. Hendrikse², Daniela E. Oprea-Lager², André N. Vis^{1,3}

► Author information ► Article notes ► Copyright and License information
PMCID: PMC9290881 PMID: 34028165

PSMA in 493 Pca after RARP and ePLND for unfavourable intermediate- or HR PCa.



BJU Int. 2023 Mar;131(3):330-338. doi: 10.1111/bju.15881. Epub 2022 Sep 17.

Prognostic value of PSMA PET

251 High risk pts underwent PSMA PET-CT (**PRO-PSMA trial**), stratified based on PSMA PET-CT nodal status (N0 -n220 or N1-n31) and followed up to 54 mo.

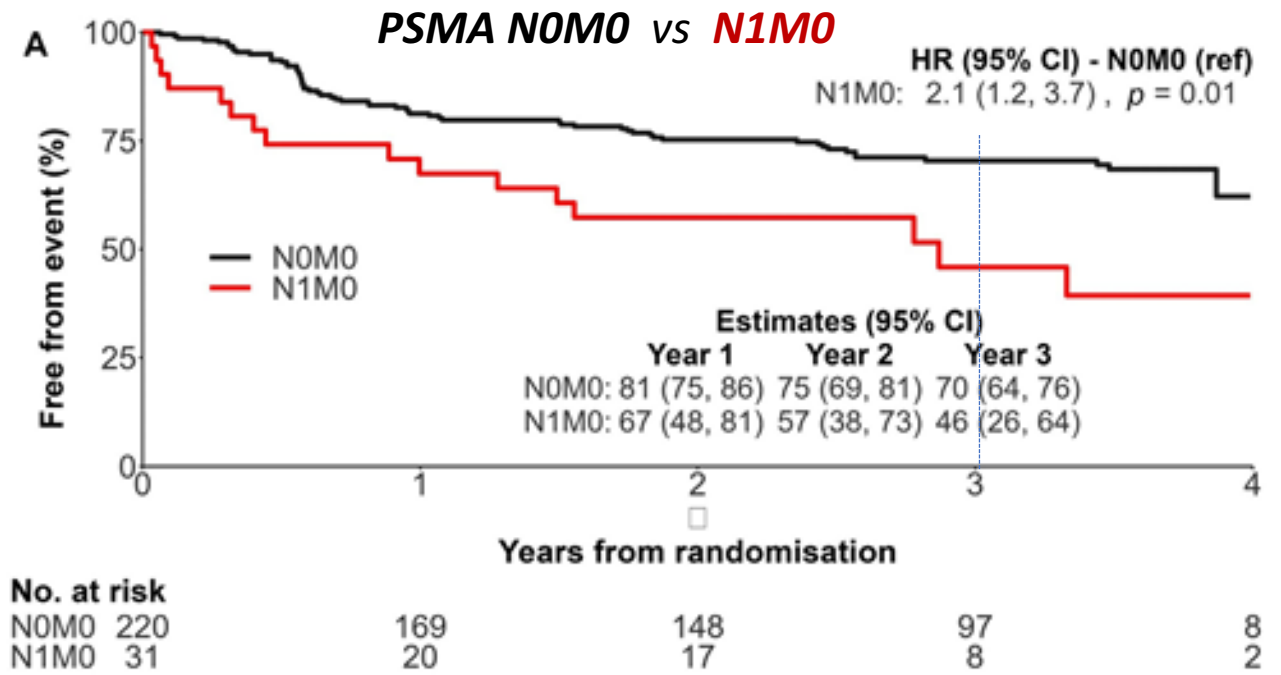
Prognostic value of PSMA in HR

free from BCR was longer in PSMA N0M0 group than the PSMA N1M0 group ($p=0.01$): At 3 years,

70% with N0M0

VS

46% with N1M0.



Summary

- «...critical view....» main limitations of PSMA: expression and heterogeneity
- PSMA PET in staging localized HR (accuracy & prognosis)
- **PSMA PET in staging localized HR (influence on treatment decision)**
- *Conclusions*

RARP... if a PLND is scheduled this should be extended (ePLND)

Recommendations for the first-line treatment of hormone-sensitive metastatic disease*	Strength rating
Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease who are fit for docetaxel.	Strong
Offer ADT combined with prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong

* All the following statements are based on metastatic disease defined by **bone scintigraphy** and **CT scan/MRI**.

...Image Guided RT + ADT

...M1

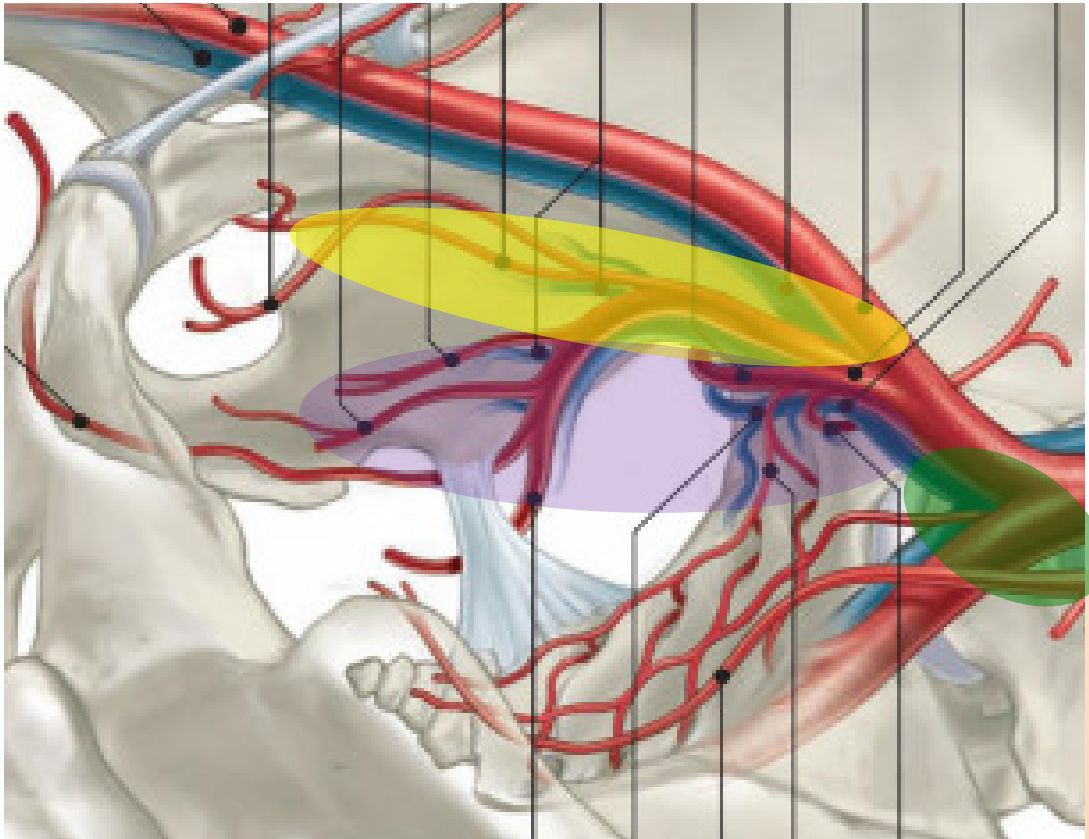
Recommendations for the management of high-risk localised disease*	Strength rating
Expectant management	
Offer watchful waiting to asymptomatic patients with life expectancy < 10 years.	Strong
Radical prostatectomy (RP)	
Offer RP to selected patients as part of potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection (PLND)	
In patients undergoing a lymph node dissection you should perform an extended PLND.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), with a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with long-term androgen deprivation therapy (ADT) (two to three years).	Strong

How a staging PSMA PET can influence treatment decision

- ***T status*** (Seminal Vesicle invasion ? / Guide RT ? In association with MRI)
- ***Identify N1*** (potentially guide (e)PLND and Image Guided RT planning)
- ***Identify M1a or M1b*** (potentially address to systemic treatment and/or guide RT)
- ***Assess the Volume of disease in metastatic de novo M1b-c...address to the “right” treatment***
- ***Prognosticate (!)***

EAU..... *if a PLND is scheduled this should be extended (ePLND)*

ePLND (bilateral obturator, external, internal and common iliac LNs),



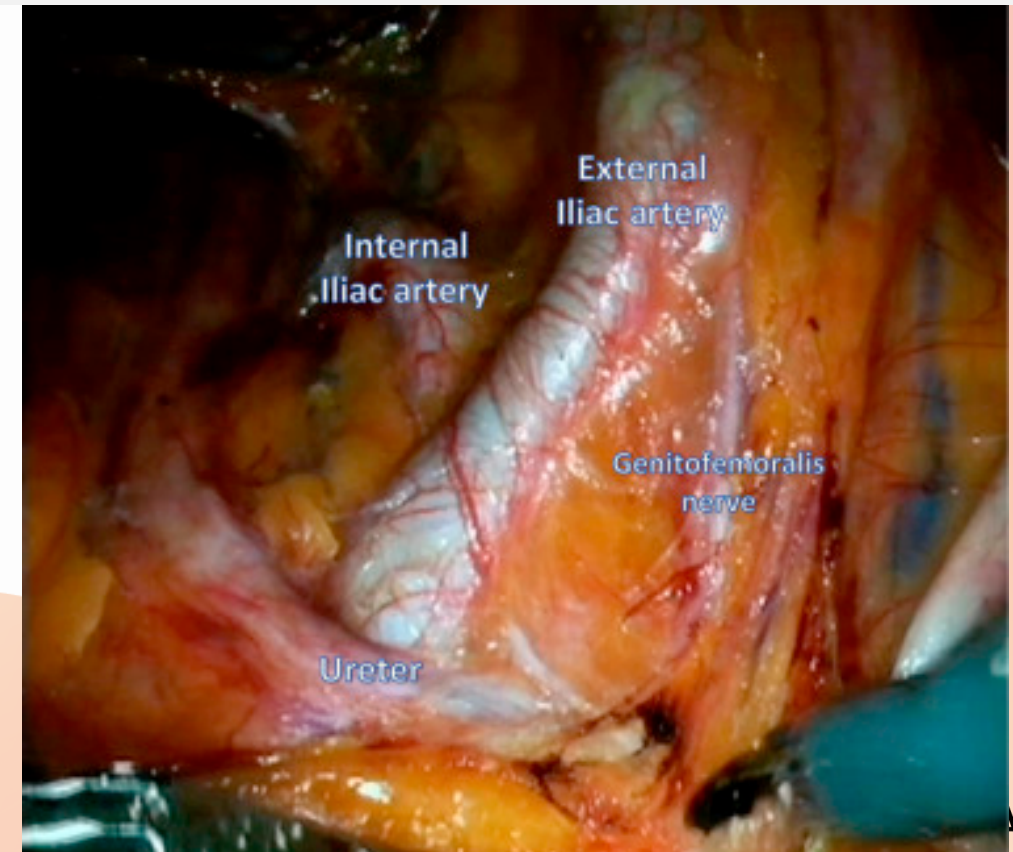
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*Courtesy Prof L..Bianchi
Azienda Ospedaliero Universitaria
IRCCS Bologna Italy*

Uncommon localization (extra-template) of pelvic LNs

Presacral Pararectal Aortic bifurcation

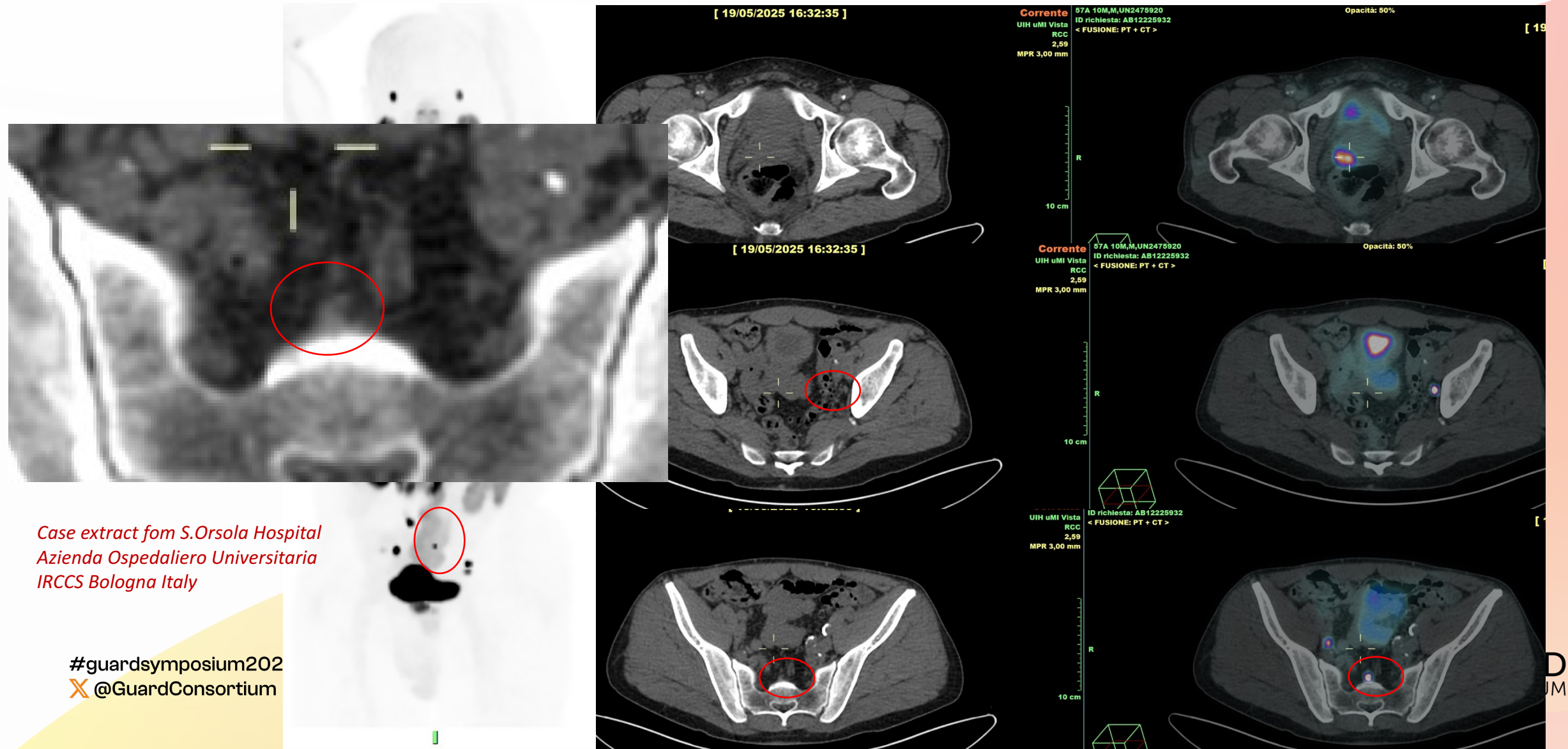
**risk of inadequate PLND (even with extended template)
and PSA persistence and early recurrence**



ARD
CONSORTIUM

63 yo; Gs 3+4; PSA 16ng/ml; PI-RADS 5 candidate to RP
Ga PSMA PET CT shows diffuse intense uptake in the prostate,
Three LNs in left and right ext Iliac and one in presacal outside the stadard template for ePLND

Staging Intermediate
Un-favourable risk



67 yo iPSA 13ng/ml

PET PSMA with ^{18}F -DCFPyl

MRI T2 NO M0

ISUP 3 (GS 3+4) Cribriform

Intermediate un-favourable risk (EAU 2025)

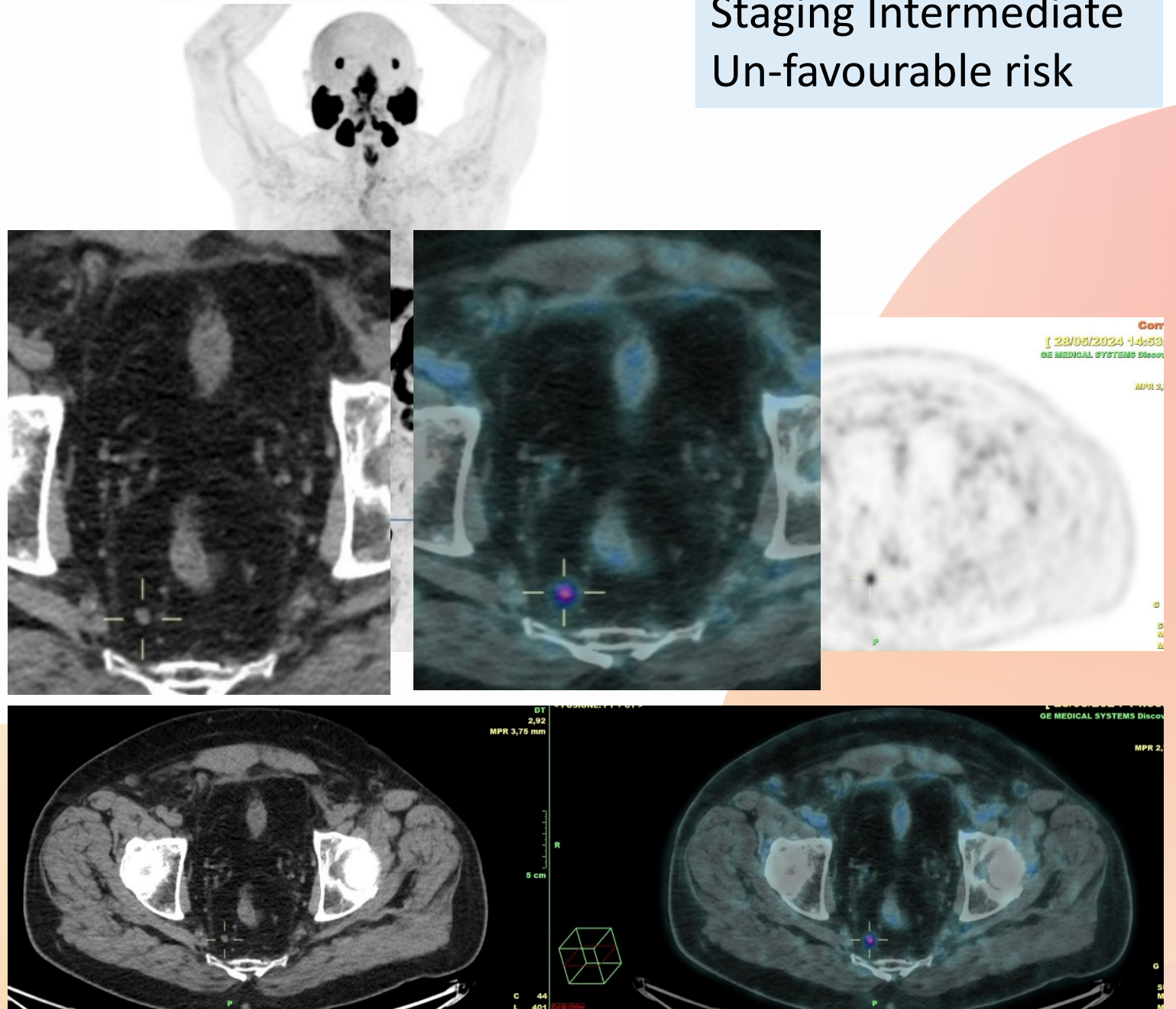
PET PSMA pararectal LN outside the standard template for ePLND

Case extract fom S.Orsola Hospital
Azienda Ospedaliero Universitaria
IRCCS Bologna Italy

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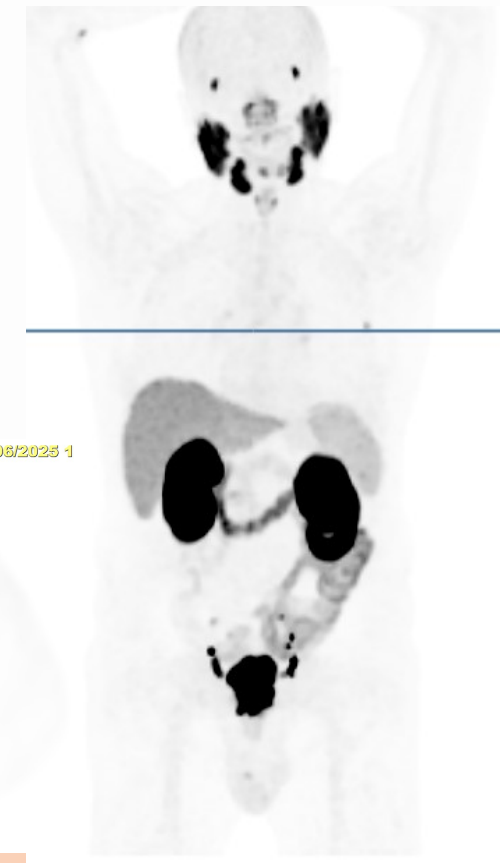
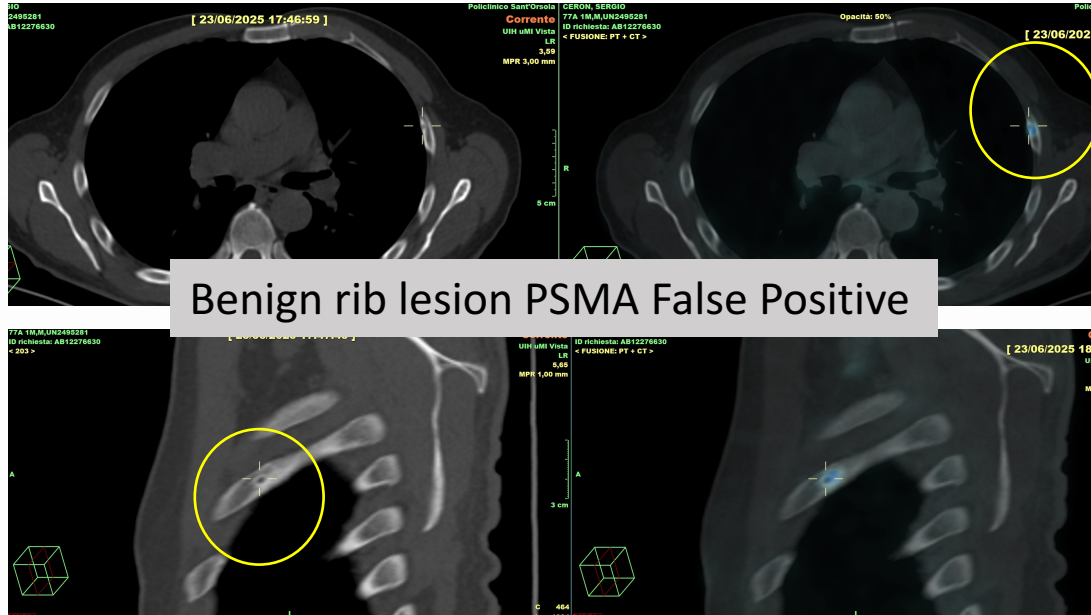
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Staging Intermediate
Un-favourable risk



73 yo; Gs 5+4; PSA 9ng/ml; PI-RADS 5 candidate to RP
 Ga PSMA PET CT shows diffuse intense uptake in the prostate,
Multiple LNs in lthe pelvis and one in the common iliac left chain behind the
vase outside the stadard template for ePLND T3aN1M1a

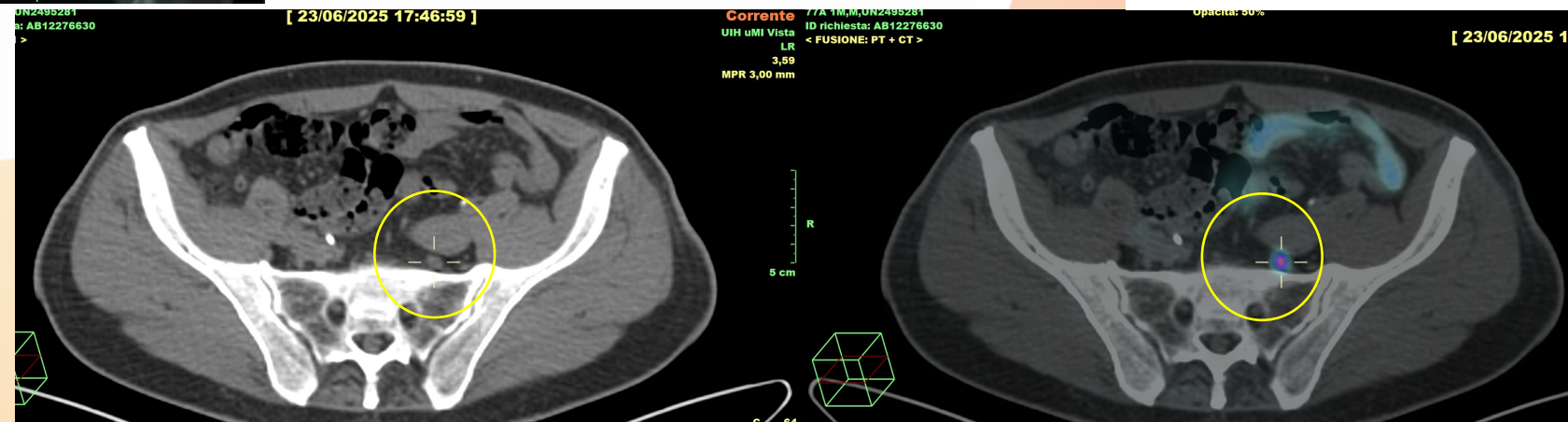
Staging High risk



After **PET PSMA** addressed to
 RT + ADT

*Case extract fom S.Orsola Hospital
 Azienda Ospedaliero Universitaria
 IRCCS Bologna Italy*

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65yo; Gs 5+4; PSA 47ng/ml; candidate

- **BS neg**
- **MRI PIRADS 5; T3, N+**
- **Ga PSMA PET CT** shows diffuse inte uptake in the prostate, large LNs in and retroperitneneum and 8 bone l
- **PET STAGING T3N1M1b(diss)**

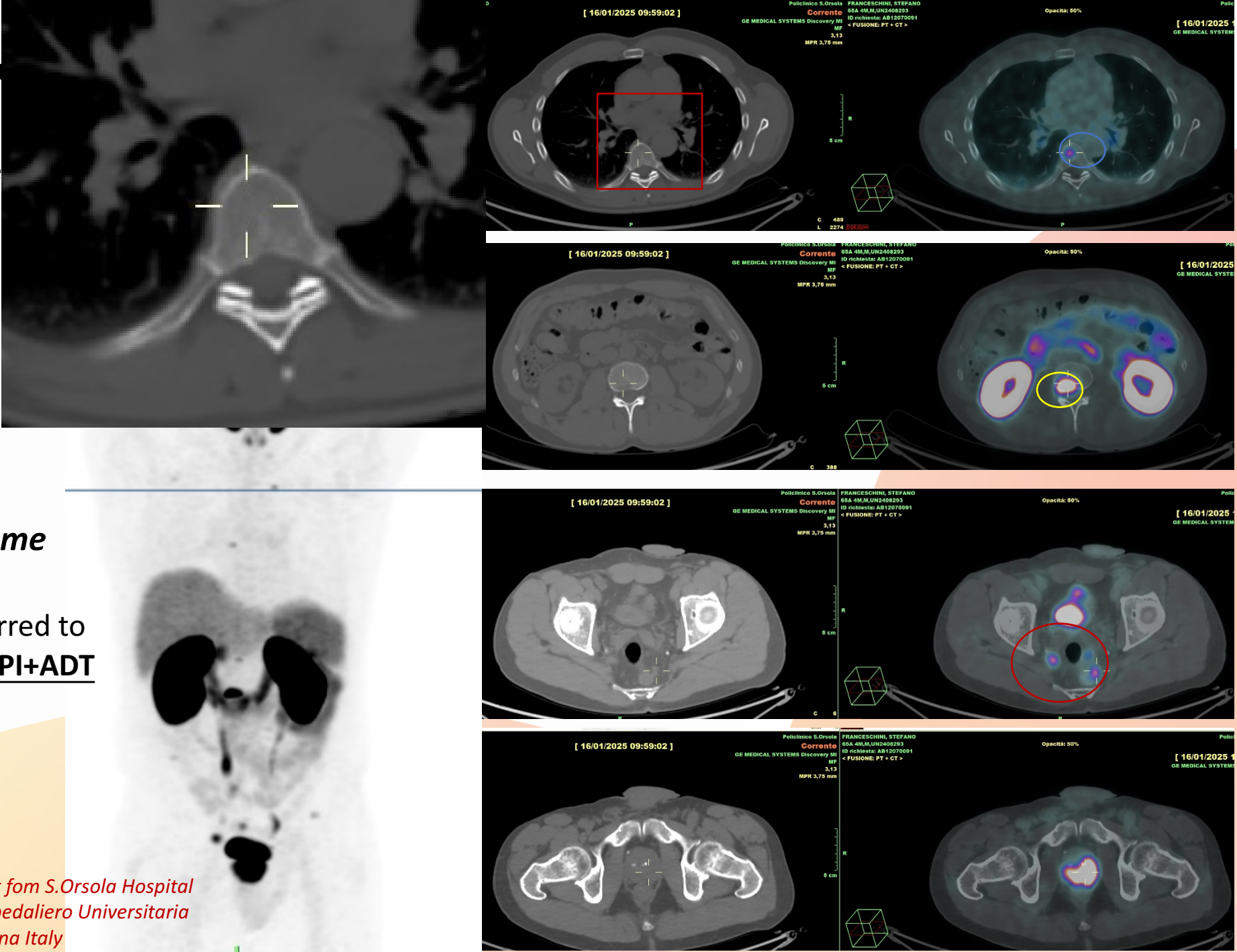
What next ??

After PET PSMA staged as
Metastatic de novo high volume

major impact: patient was referred to
systemic treatment Docetax +ARPI+ADT

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Case extract fom S.Orsola Hospital
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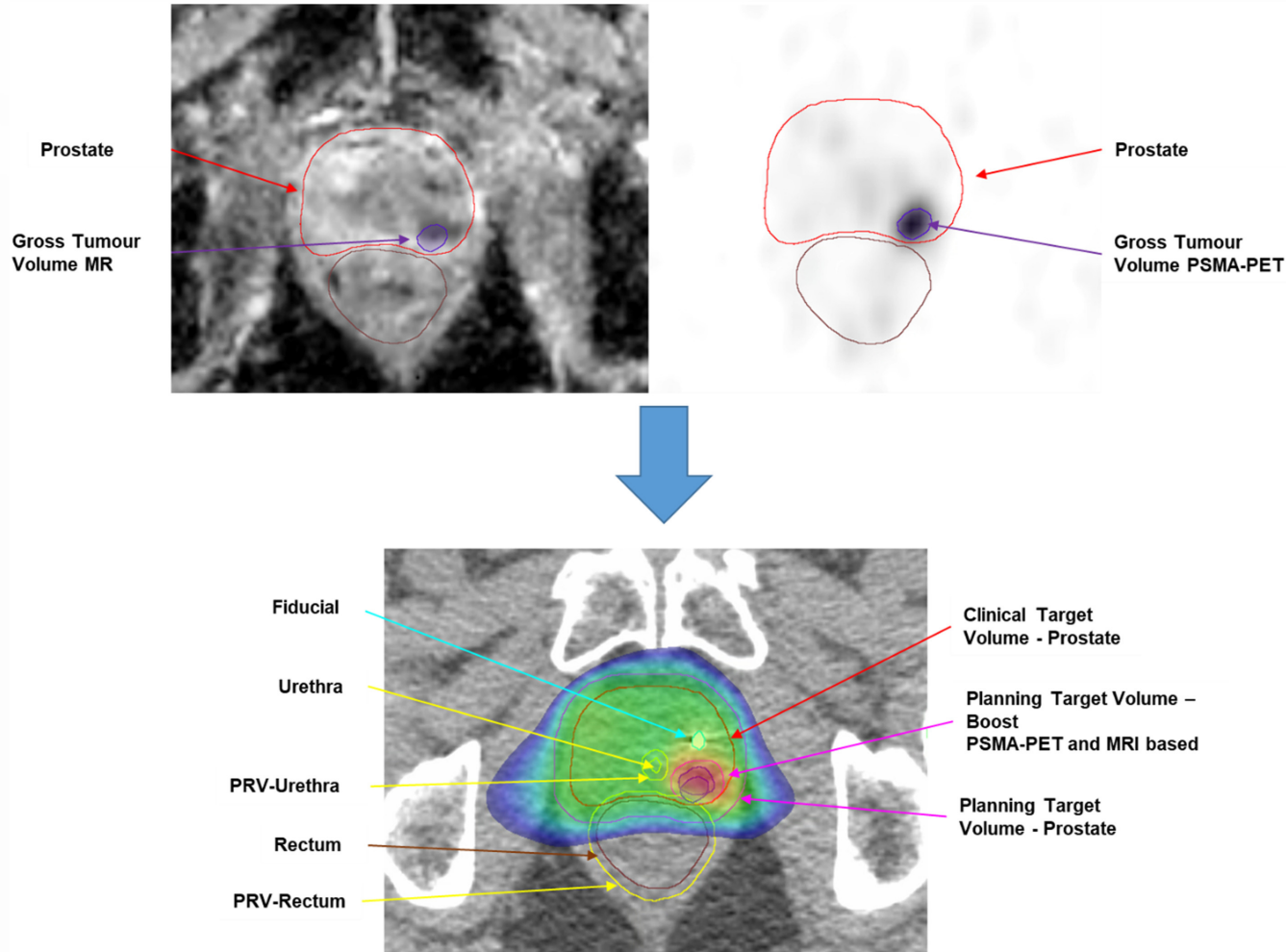
...Image Guided RT + ADT

Recommendations for the management of high-risk localised disease*	Strength rating
<i>Expectant management</i>	
Offer watchful waiting to asymptomatic patients with life expectancy < 10 years.	Strong
<i>Radical prostatectomy (RP)</i>	
Offer RP to selected patients as part of potential multi-modal therapy.	Strong
<i>Extended pelvic lymph node dissection (PLND)</i>	
In patients undergoing a lymph node dissection you should perform an extended PLND.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
<i>Radiotherapeutic treatment</i>	
Offer intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), with a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with long-term androgen deprivation therapy (ADT) (two to three years).	Strong

Impact of PSMA PET on Radiation Oncology Planning

Simon K.B. Spohn, MD,^{†,§} and Anca-L. Grosu, MD^{†,§}

Seminars in
NUCLEAR
MEDICINE



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MRI and PSMA Image Guided RT in T

PSMA-PET and mpMRI based focal dose escalated SBRT. Upper left picture shows a representative slide of the apparent diffusion coefficient map images with the **gross tumor volume** defined in purple and the prostate in red. The upper right picture shows a representative slide of the corresponding PSMA-PET scan. Based on these co-registered images, radiotherapy target volumes are defined.

PSMA Image Guided RT in N

PEARLS – A multicentre phase II/III trial of extended field radiotherapy for androgen sensitive prostate cancer patients with PSMA-avid pelvic and/or para-aortic lymph nodes at presentation

Julia Murray^{a,b,*}, Clare Cruickshank^b, Thomas Bird^c, Philip Bell^d, John Braun^e,

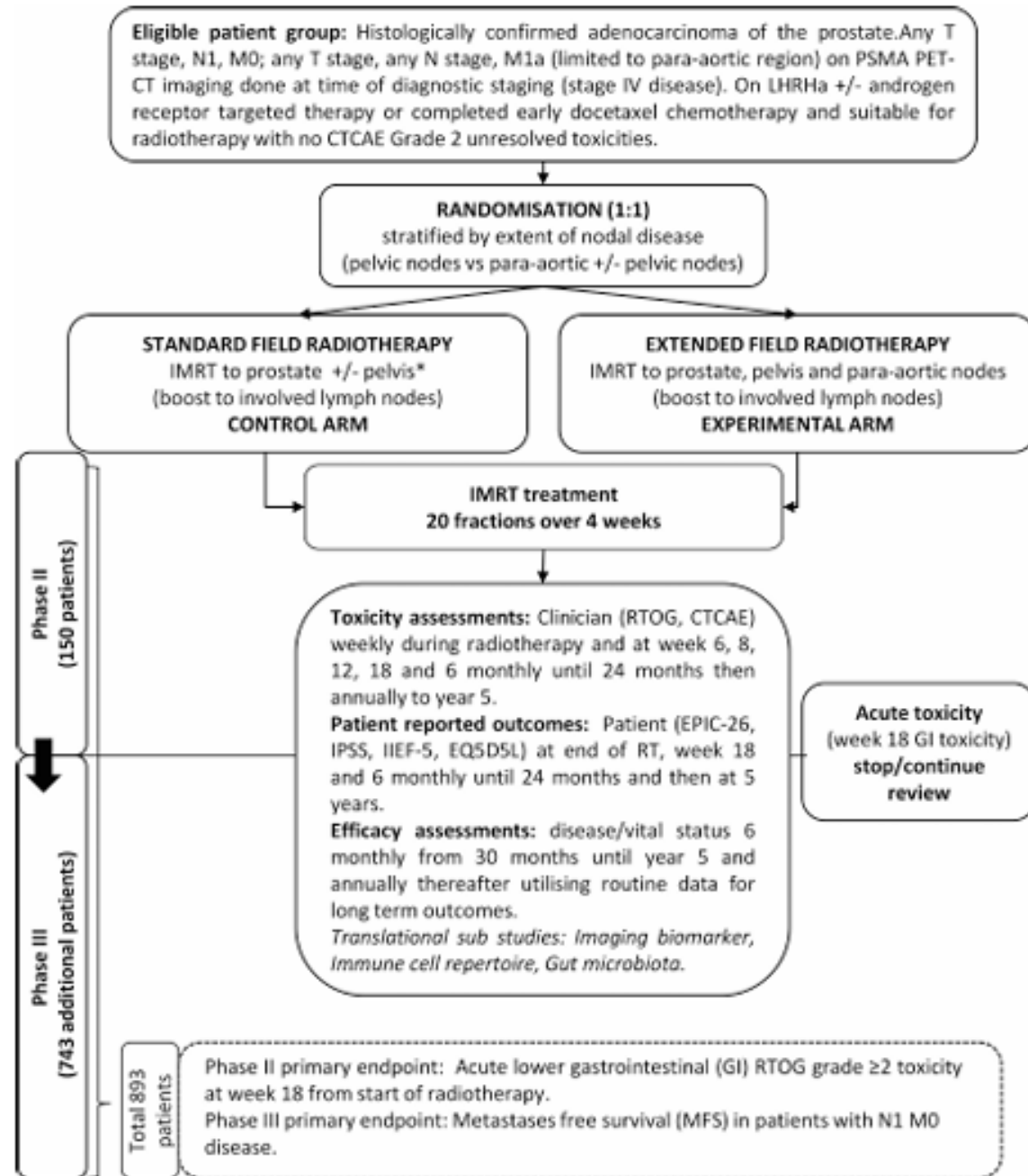


PEARLS trial includes patients with **PSMA-PET-positive (N1 or M1a) pelvic and/or paraaortic lymph node metastases.**

PSMA-PET-positive lymph nodes receive dose escalation of up to 51 Gy in 20 fractions.

Results from these trials will demonstrate whether **maximizing local control with hypofractionated RT regimens in the PSMA-PET era** will be a favorable treatment option.

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PSMA PET in the current clinical managament «today»....In the NL

Intermediate Favourable

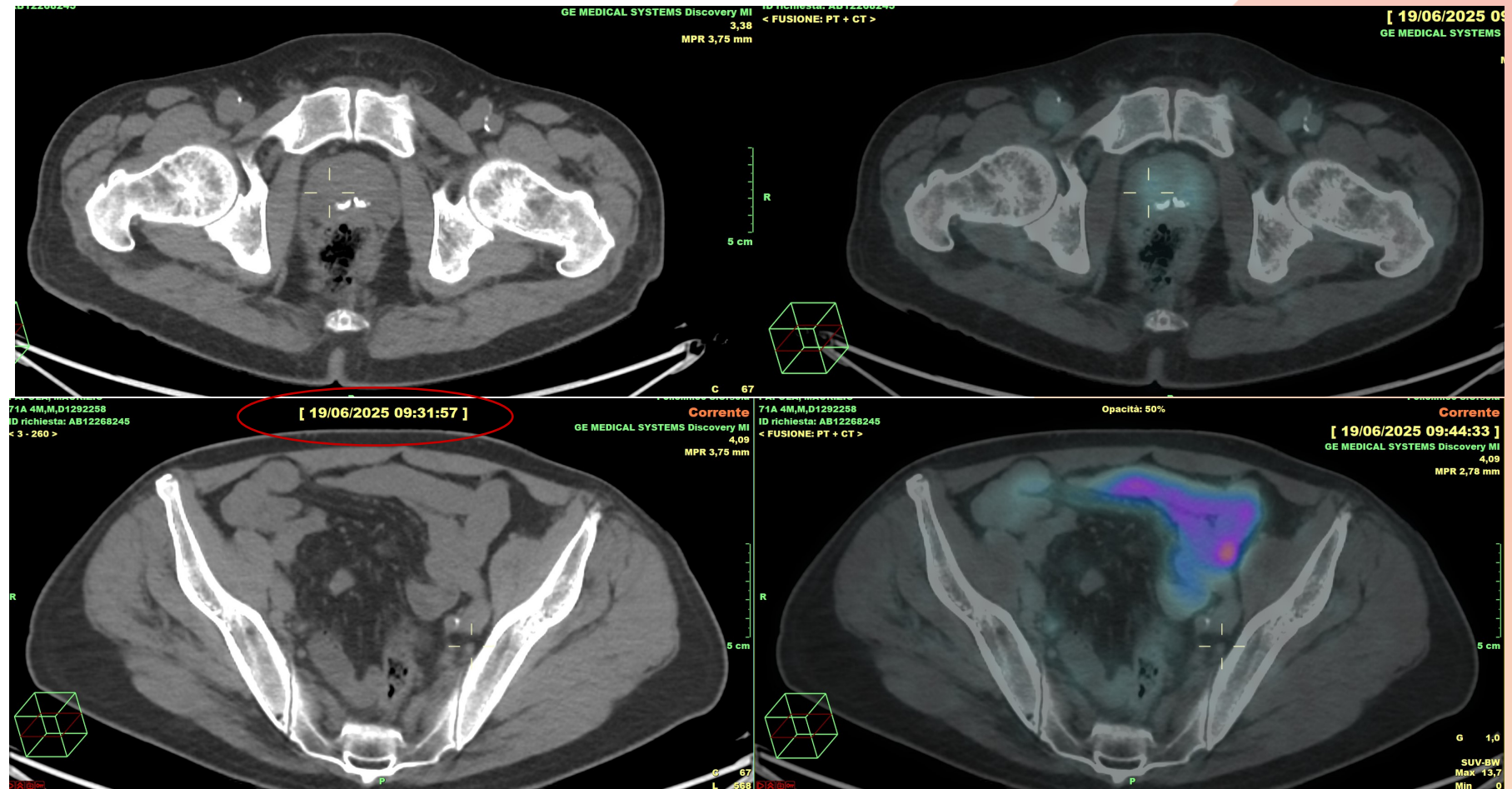
Intermediate Un-favourable

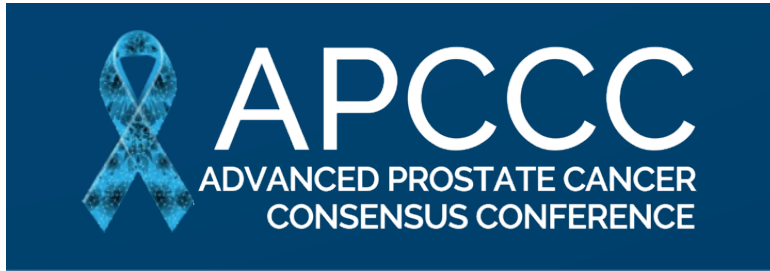
High Risk

Table 1 – Panel results on the appropriateness of different imaging modalities for primary staging (detection of metastases) in PCa (N = 40 panellists)^a

Question	Panellists (%) ^{a,b}	Cannot judge (%)
Which imaging modality do you consider most appropriate in the current, average Dutch practice for primary staging (detection of metastases) for favourable-risk intermediate PCa?		18
Bone and CT scan	3	
PSMA-PET/CT or PSMA-PET/MRI	12	
Whole-body MRI	0	
No imaging for metastatic screening	85	
Which imaging modality do you consider most appropriate in the current, average Dutch practice for primary staging (detection of metastases) for unfavourable-risk intermediate PCa?		5
Bone and CT scan	0	
PSMA-PET/CT or PSMA-PET/MRI	97	
Whole-body MRI	0	
No imaging for metastatic screening	3	
Which imaging modality do you consider most appropriate in the current, average Dutch practice for primary staging (detection of metastases) for high-risk PCa?		3
Bone and CT scan	0	
PSMA-PET/CT or PSMA-PET/MRI	100	
Whole-body MRI	0	
No imaging for metastatic screening	0	

71yo: STAGING ; Gs 4+4 (3+/12); iPSA 6.4 ng/ml; PI-RADS 4 (right lobe) ; No significant comorbidities
PSMA PET negative in the prosate and LNs... what next ??
PLND ? ePLND ? NO PLND ?

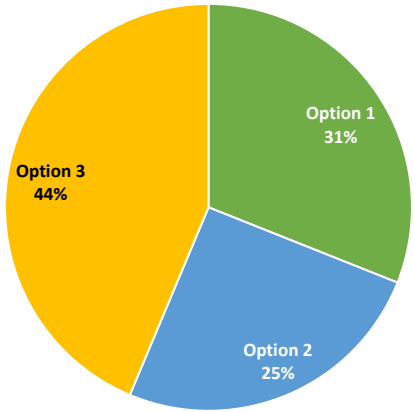




APCCC 2024

12. In patients with unfavourable intermediate-risk localised prostate cancer (NCCN definition) for whom radical prostatectomy is planned, and who have a negative PSMA PET (N0 M0), do you recommend an extended pelvic lymphadenectomy (ePLND)?

1. Yes, in the majority of patients
2. Yes, but only in selected patients
3. No
4. Abstain/unqualified to answer

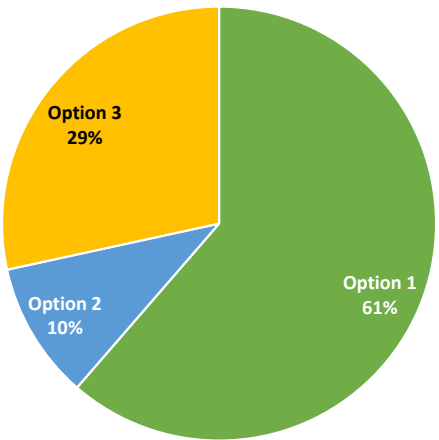


Option	Votes
Option 1	27
Option 2	22
Option 3	38
Abstain	19

Supplementary material to the full-text publication: <https://doi.org/10.1016/j.eururo.2024.09.017>

13. In patients with high-risk localised prostate cancer (NCCN definition) for whom radical prostatectomy is planned, and who have a negative PSMA PET (N0 M0), do you recommend an extended pelvic lymphadenectomy (ePLND)?

1. Yes, in the majority of patients
2. Yes, but only in selected patients
3. No
4. Abstain/unqualified to answer



Option	Votes
Option 1	54
Option 2	9
Option 3	25
Abstain	18

perform ePLND if PSMA is negative ?

- **30% No in HR**
- **44% No in Intermediate Un-favourable**

Conclusions: PET PSMA in *High Risk Pca*

PSMA is not specific for Pca, PSMA expression is Heterogeneous, possible FP in the bones...

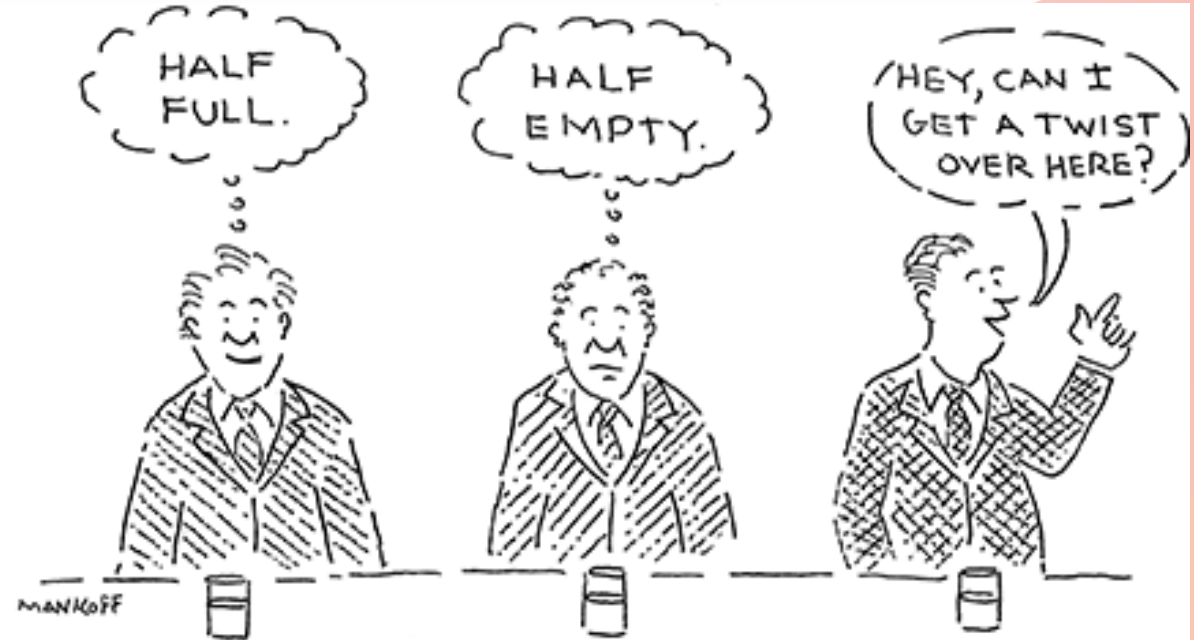
Low sensitivity in N+

BUT

Nowadays it is (by far) the method of choice in Pca especially in staging **High Risk Pca**

WHY

It has an **impact on treatment strategy** and a significant **prognostic value**.



-  OPTIMIST
-  PESSIMIST
-  PRAGMATIST

Grazie per l'attenzione!

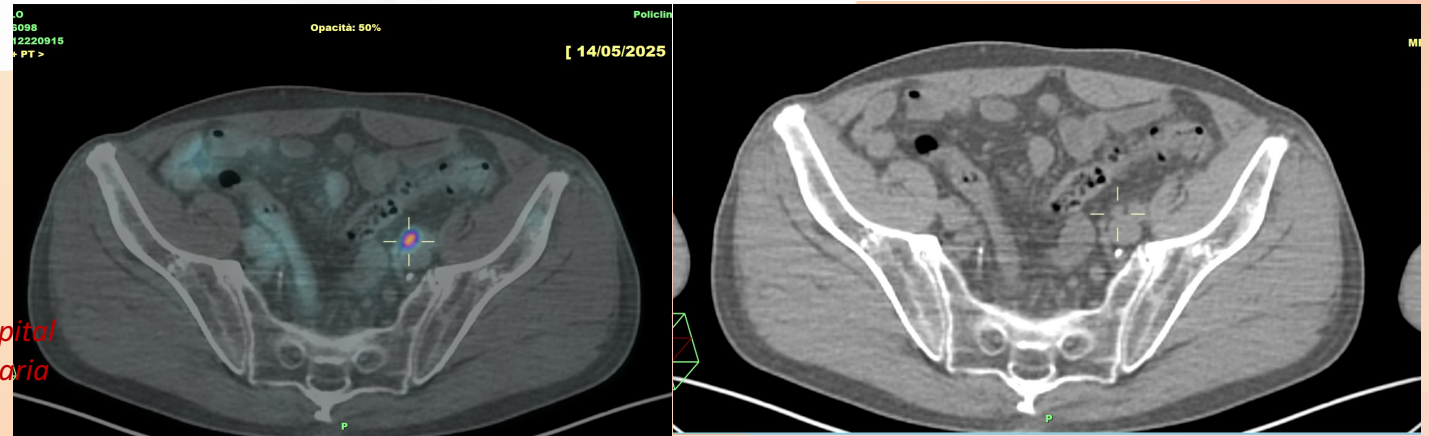
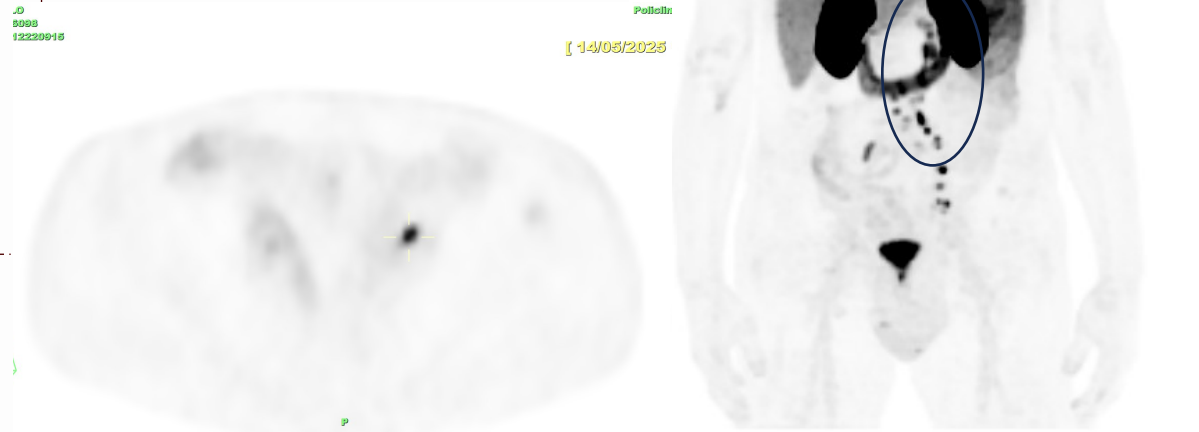
74yo: STAGING ; Gs 4+4 ; iPSA 14 ng/ml; PI-RADS 4;
No significant comorbidities

- **Staged with CT & BS** Negative
- **RARP Surgery as primary treatment;**
- **T3a pN1(1/8) M0**

PSA persistence

6 weeks after surgery PSA 10ng/ml
PET PSMA performed

... Avoid this nightmare



**Multiple small (< 10mm) LNs
pelvic and retroperitoneal
easily detected by PSMA**

Conclusion

PSMA PET in High risk ...

- ***High specificity/low sensitivity in detecting N1 (potentially guide ePLND); there are not enough data to avoid ePLND in negative PSMA (if scheduled according to the risk and clinical status)***
- ***Exclude from surgery patients already N1-2 (?)/M1a/M1b....***
- ***Image Guided RT in T & N as primary treatment***
- ***Volume of disease in metastatic de novo to address the right treatment***
- ***Prognostic info***
- ***Intermediate un-favourable risk could benefit from PSMA PET in patients scheduled for surgery***