

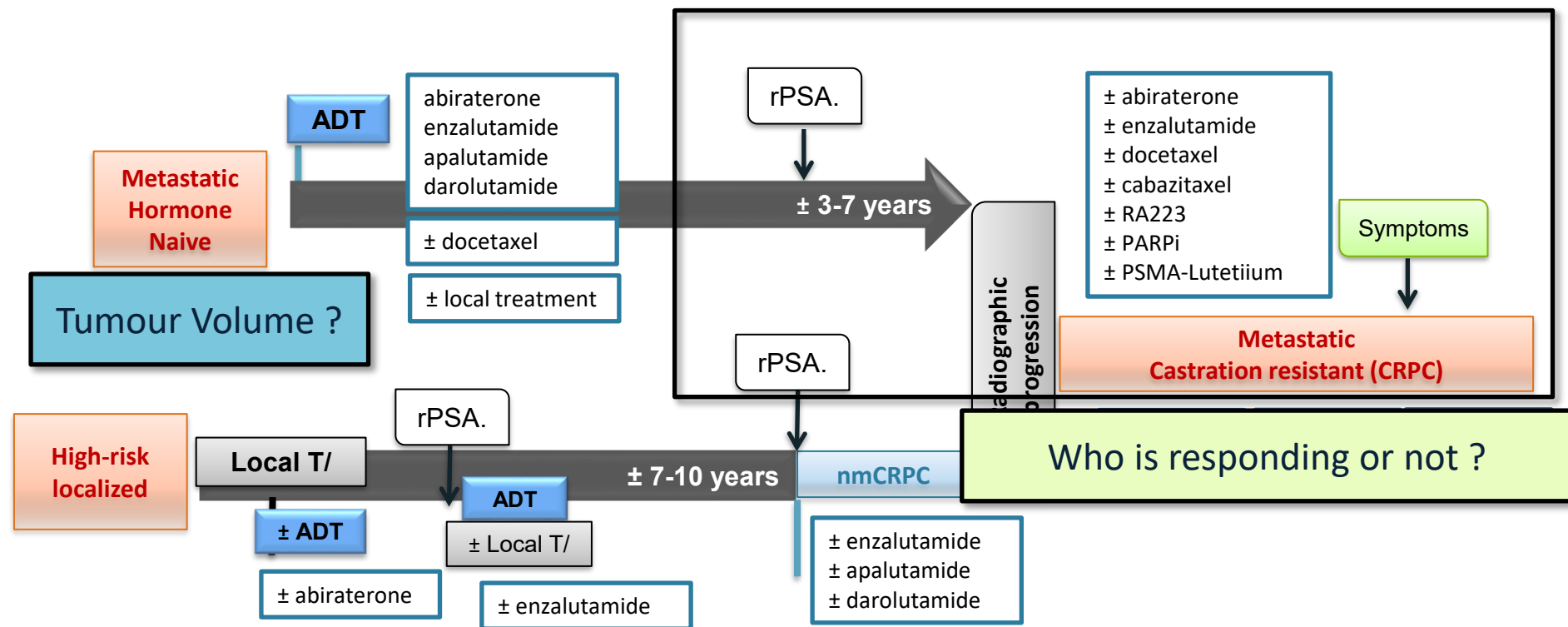
Role of Modern Imaging in the Follow up of Metastatic Prostate Cancer

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Credentials and conflicts of interest

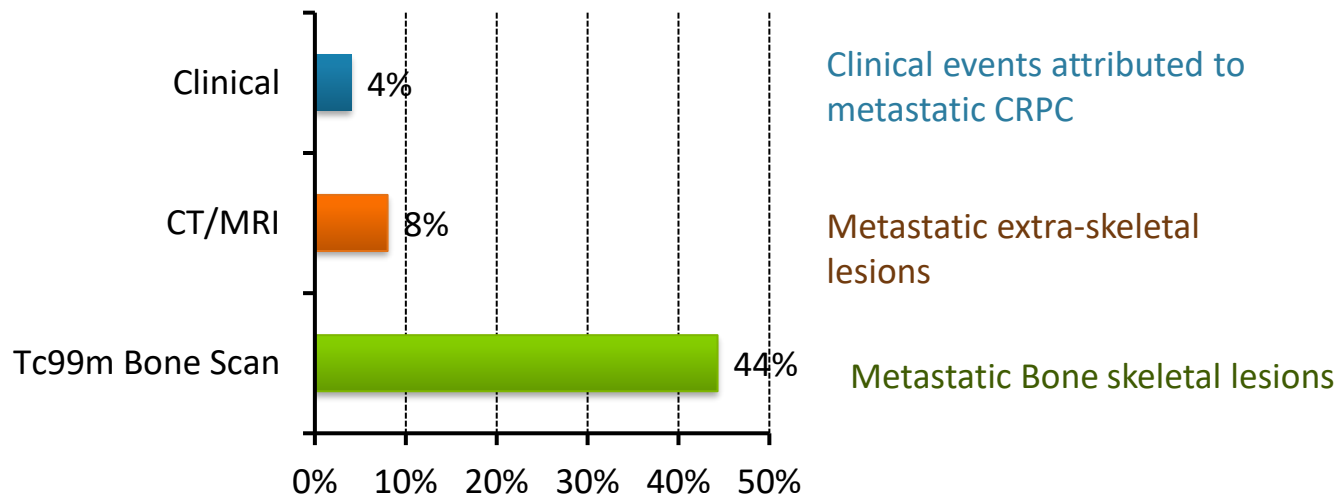
- Honoria as consultant/speaker : Astellas, Bayer, Bristol Myers-Squibb, Janssen, Sanofi, Ipsen, MSD.
- Honoria for scientific advisory Board: Janssen, Ipsen, MSD
- I have no potential conflict of interest related to this topic

Therapeutic landscape of advanced Pca in 2026

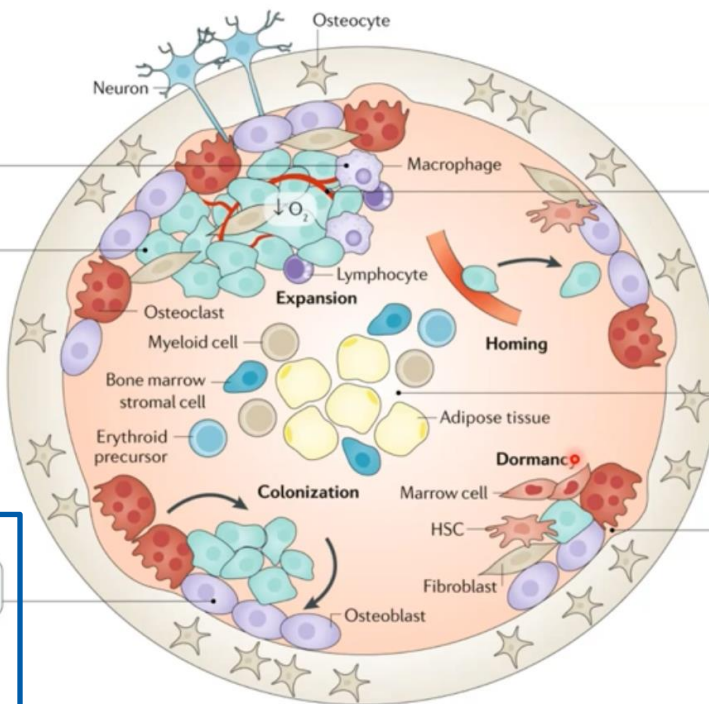


In the later stages of the disease (CRPC), bone is usually the first metastatic site.

Confirmation of progression in non-metastatic CRPC patients
(N = 474, placebo)



Relationship Between Imaging and the Cell Biology of Bone Metastases



Macrophages
FDG

■ PSMA PET/CT

- ✓ SUVmean
- ✓ SUVmax
- ✓ MATV

Tumour cell surface and cytoplasmic receptors (specific)
FDHT, FES, Ga/F-PSMA
HER2/neu PET tracers
Tumour metabolism (non-specific)
FDG, choline, acetate, methionine, fluciclovine
PET tracers

Osteoblasts
Bone scintigraphy, NaF-PET, CT

■ Bone Scintigraphy

Vascularity
DCE MRI

Cell density
DW MRI
Fat water imaging
Dixon MRI, MRS, CT
Metabolism
FCH-PET

■ MRI

- ✓ Fat Fraction
- ✓ ADC
- ✓ TTVolume

Bone trabeculae and osteoclasts
CT scans, UTE MRI, FDG-PET, R2*

The Caveat of historical way of disease monitoring of advanced PCa

PSA: « Clonal Theory »

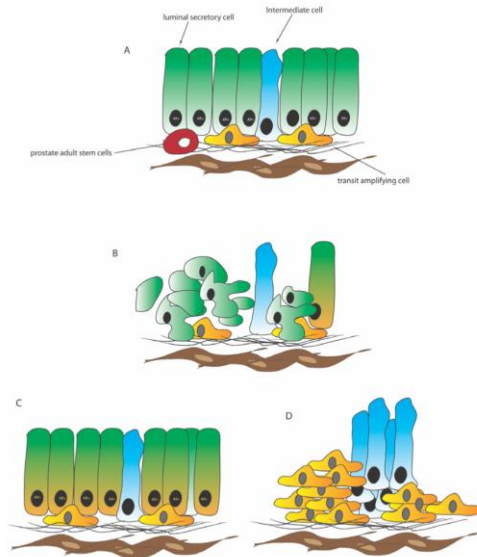


Fig. 1. (A) The prostatic epithelium originates from AR-negative (AR-) prostate adult stem cells (PSA). These generate AR- transit-amplifying (TA) cells and then AR- intermediate cells (I). AR-positive luminal secretory cells are the final adults secreting prostate epithelial cells. (B) Upon suppression of circulating androgen, AR+ luminal cells massively induce apoptosis. (C) The adaptive theory of castration resistance presupposes that some luminal secretory cells adapt their (epi)genetic program to allow growth in absence of androgens. (D) The clonal theory of resistance to castration presupposes that the cancer develops from a pool of AR- cells that is already present in the prostate.

Tombal et al. Eur J Cancer 2011

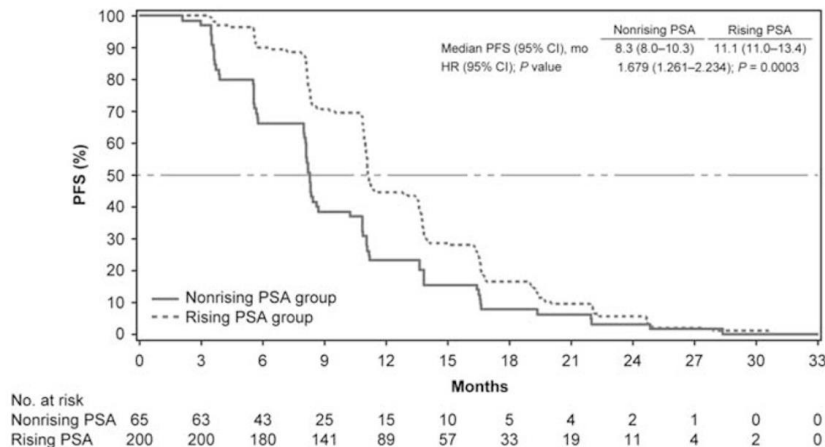
Bone Scan: Lack of Se/Sp



Patients with discordant progression have worse outcomes in mHSPC and mCRPC

PREVAIL

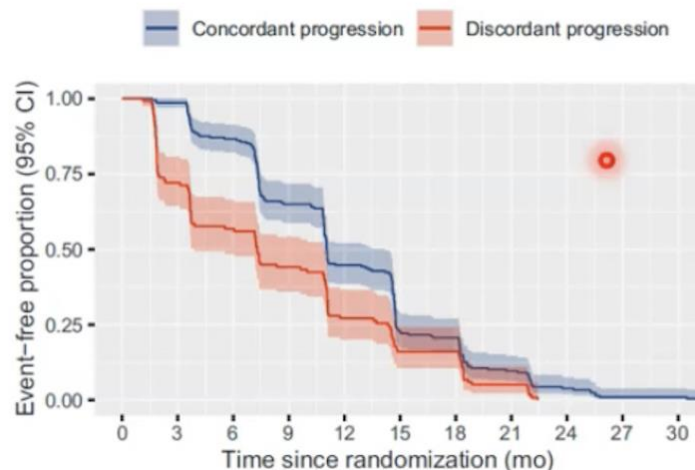
Up to 25 % rPFS with no PSA progression



TITAN

Up to 50 % rPFS with no PSA progression

A rPFS





Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3

Scher et al. J Clin Oncol. 2016 Feb 22;34(12):1402–1418

- Rising PSA
- Progression in Bone
 - Appearance of 2 or more new lesions. Confirm ambiguous results by other imaging modalities (eg, CT or MRI)



New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada.

Therasse P et al. JNCI 2000; 92(3):205-16.

- “Lesions considered to ***be truly non measurable*** include the following: ***bone lesions***, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions”.

Modern Imaging Modalities



From
Tc99m BS
+ CT-Scan
to **Whole
Body MRI**



The Prostate

Original Article | [Full Access](#)

Magnetic resonance imaging of the axial skeleton enables objective measurement of tumor response on prostate cancer bone metastases

Bertrand Tombal , Afshin Rezazadeh, Patrick Therasse, Paul J. Van Cangh, Bruno Vande Berg, Frédéric E. Lecouvet

First published: 09 June 2005 | <https://doi.org/10.1002/pros.20280> | Citations: 71



TABLE I. Patient Characteristics at Entry

	n	%
Number of patients	38	
Positive bone scans	30	78.9
Positive CT-TAP	13	34.2
Lymph nodes	13	34.2
Soft tissue metastasis (liver)	1	2.6
RECIST measurable soft-tissue lesions	11	28.9

TABLE II. Bone Marrow Patterns on Initial MRI Studies

	n	%
No detectable lesions (normal pattern)	5	13.1
Focal lesions (spine ± pelvis)	22	57.9
Diffuse infiltration (spine ± pelvis)	8	21.1
Diffuse infiltration (spine) and focal lesions (pelvis)	3	7.9
Measurable lesions in bone after transposition of RECIST	25	65.7
<10 lesions	20	52.6
>10 lesions	5	13.1

MET-RADS-P RAC categories (bone vs soft tissue)

The MET-RADS-P Response Assessment Categories (RAC) are a 5-point Likert scale applied separately to bone and soft-tissue disease on WB-MRI, from “highly likely responding” (RAC 1) to “highly likely progressing” (RAC 5)

RAC	Short label	Simple description of regional response on WB-MRI*
1	Highly likely responding	Clear imaging improvement vs baseline/nadir (lesions smaller, less conspicuous, diffusion restriction/volume clearly decreased).
2	Likely responding	Probable response with mild–moderate improvements, but not as unequivocal as RAC 1.
3	Stable/indeterminate	No clear change, or minor mixed changes that do not meet response or progression criteria.
4	Likely progressing	Probable progression (some new/worse lesions or diffusion changes) but short of unequivocal progression.
5	Highly likely progressing	Definite progression: new metastatic foci, clear lesion growth or marked worsening of diffusion characteristics within the region.

Association between PSA response and wbMRI response according to MET-RADS-P

mHSPC (n=37)

MET-RADS-P category by group	Patients, n/N (%) No PSA response	PSA response	p value
mHNPC			
RAC 1	2 (9.5)	9 (56.2)	0.012
RAC 2	10 (47.6)	6 (37.5)	
RAC 3	2 (9.5)	1 (6.3)	
RAC 4/5	7 (33.3)	0 (0.0)	0.006
Total	21/37 (56.8)	16/37 (43.2)	

MET-RADS-P = Metastasis Reporting and Data System for Prostate Cancer; mCRPC = metastatic castration-resistant prostate cancer; mHNPC = metastatic hormone-sensitive prostate cancer; PSA = prostate-specific antigen; RAC = response assessment category.

- There is no RX progressor in the group a PSA responder

- 1/3 of the patients with no PSA response are actually progressing in Rx

- 40% of PSA responders have a PR or SD

Association between PSA response and wbMRI response according to MET-RADS-P

mCRPC (n=51)

MET-RADS-P category by group	Patients, n/N (%) No PSA response	PSA response	p value
mCRPC			
RAC 1	0 (0.0)	1 (3.5)	0.450
RAC 2	2 (9.1)	4 (13.7)	
RAC 3	2 (9.1)	5 (17.2)	
RAC 4/5	18 (81.8)	19 (65.5)	0.145
Total	22/51 (43.1)	29/51 (56.9)	

MET-RADS-P = Metastasis Reporting and Data System for Prostate Cancer; mCRPC = metastatic castration-resistant prostate cancer; mHNPc = metastatic hormone-sensitive prostate cancer; PSA = prostate-specific antigen; RAC = response assessment category.

■ 65% of patients have disease progression on WB-MRI with a PSA Response.

■ 65-82% of patients have disease progression independent of the PSA Response.

Sankey diagrams showing the concordance and discordance between response assessment via PSA and via WB-MRI using the MET-RADS-P.

mHSPC



mCRPC

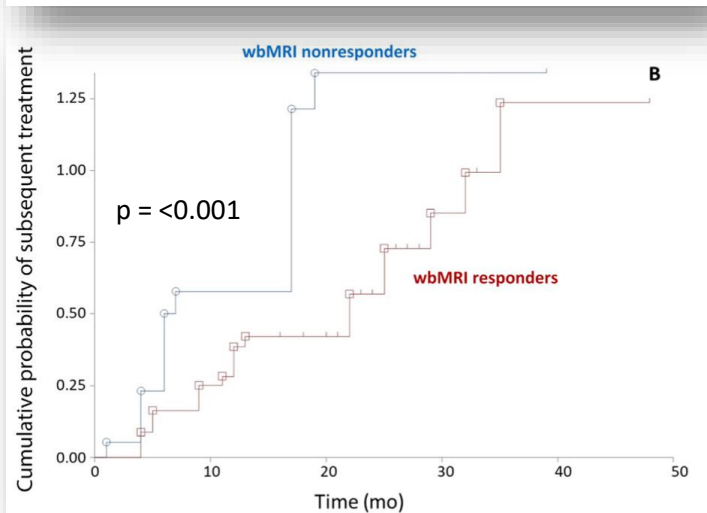
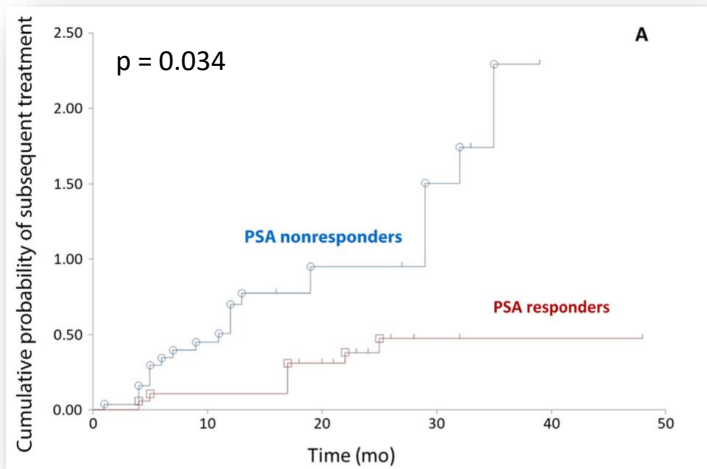


Cox regression results for the association between a positive response and the probability of subsequent treatment

Response type	Events, n/N (%)	HR (95% CI)	p value
mHNPc			
PSA response	14/37 (37.9%)	0.36 (0.14–0.93)	0.034
wbMRI response		0.13 (0.05–0.37)	<0.001
mCRPC			
PSA response	49/51 (96.1%)	0.64 (0.36–1.14)	0.129
wbMRI response		0.65 (0.35–1.22)	0.184

HR = hazard ratio; CI = confidence interval; mCRPC = metastatic castration-resistant prostate cancer; mHNPc = metastatic hormone-sensitive prostate cancer; PSA = prostate-specific antigen; wbMRI = whole-body magnetic resonance imaging.

Cumulative probability of subsequent treatment according to Cox regression for patients with mHNPc by (A) PSA response (≤ 0.2 ng/ml vs not) and (B) a wbMRI response according to MET-RADS-P.



Cox regression results for the association between a positive response and the probability of OS.

Response category	HR (95% CI)	p value
mHNPC		
No PSA response ^a	2.77 (0.61–12.6)	0.189
wbMRI progression	8.59 (2.27–32.5)	0.002
PSA response and wbMRI response	0.36 (0.08–1.65)	0.189
wbMRI progression and PSA response	–	–
mCRPC		
No PSA response	1.25 (0.71–2.21)	0.444
wbMRI progression	1.28 (0.68–2.40)	0.446
PSA response and wbMRI response	0.79 (0.39–1.60)	0.516
wbMRI progression and PSA response	1.30 (0.59–2.88)	0.520
HR = hazard ratio; CI = confidence interval; mCRPC = metastatic castration-resistant prostate cancer; mHNPC = metastatic hormone-sensitive prostate cancer; PSA = prostate-specific antigen; wbMRI = whole-body magnetic resonance imaging.		

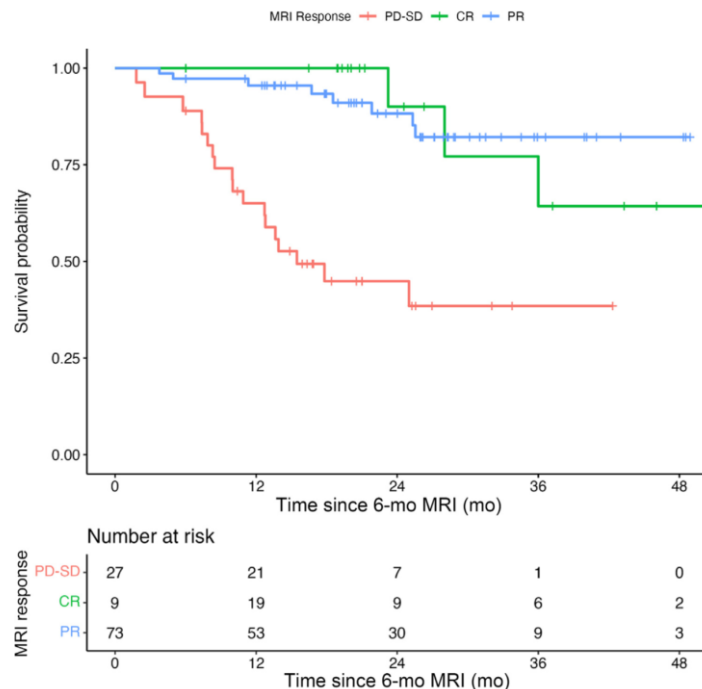
Whole-body Diffusion-weighted Magnetic Resonance Imaging for Assessment of the Bone Response Rate in Patients with Metastatic Hormone-sensitive Prostate Cancer Receiving Enzalutamide (BONENZA trial)

Phase 2 randomized clinical trial

Primary endpoint : bone response rate measured via WB-DW-MRI in 126 mHSPC patients treated with Enza + ADT , with or without zoledronic acid

Evaluation of treatment response was adapted from MET-RAS-P

- In comparison to WB-DW-MRI while PSA responses were more consistent (78.5%).
- CR (RAC 1) : 20/126 patients (15.9%)
- PR (RAC 2) : 68/126 (53.9%)
- SD (RAC 3): 9/ 126 (7.1%)
- PD (RAC 4-5) : 12/126 (9.5%)

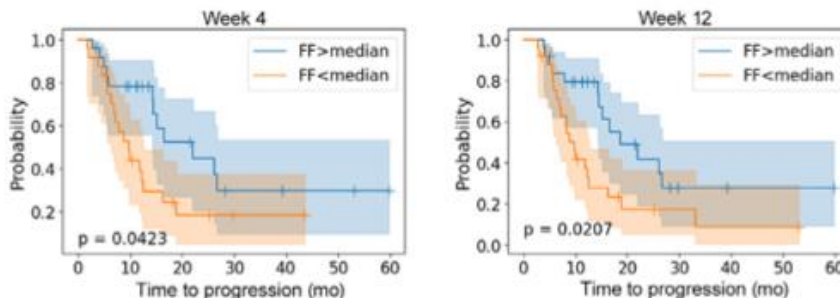
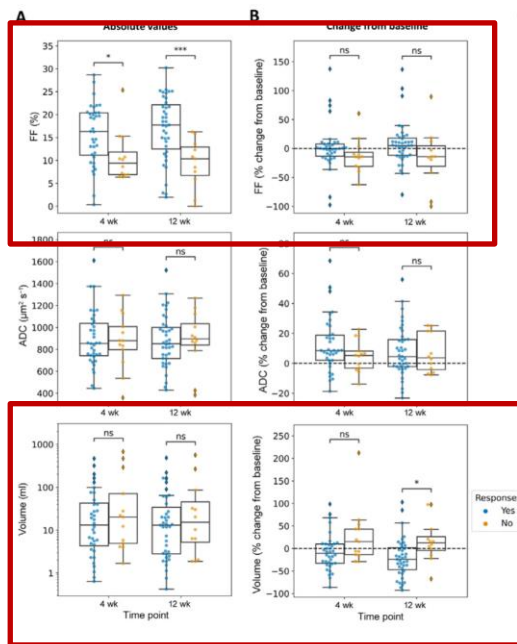


Whole-body Magnetic Resonance Imaging as a Treatment Response Biomarker in Castration-resistant Prostate Cancer with Bone Metastases: The iPROMET Clinical Trial

55 mCRPC

Assessed the correlation of imaging biomarkers to response and time to progression

Response was defined as RECIST v1.1 response and/or a 50% decrease in prostate-specific antigen (PSA50) from baseline

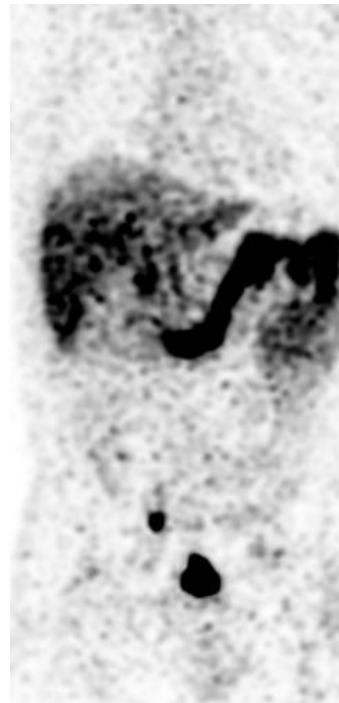
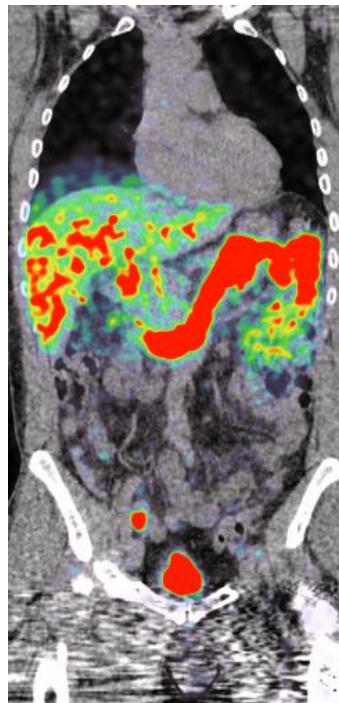


- In addition, the 12-mo probability of progression varied significantly across the groups:
 - ✓ no patients progressed in the RAC 1
 - ✓ 40% in the RAC 2 group
 - ✓ 66% in the RAC 3 group
 - ✓ 67% in the RAC 4–5 group.

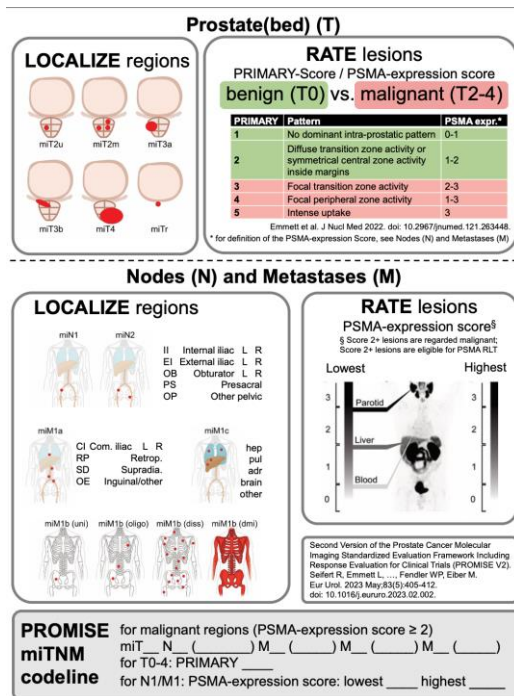
Modern Imaging modalities



From
Tc99m BS
+ CT-Scan
to **PSMA-
PET/CT**



PROMISE: miTNM



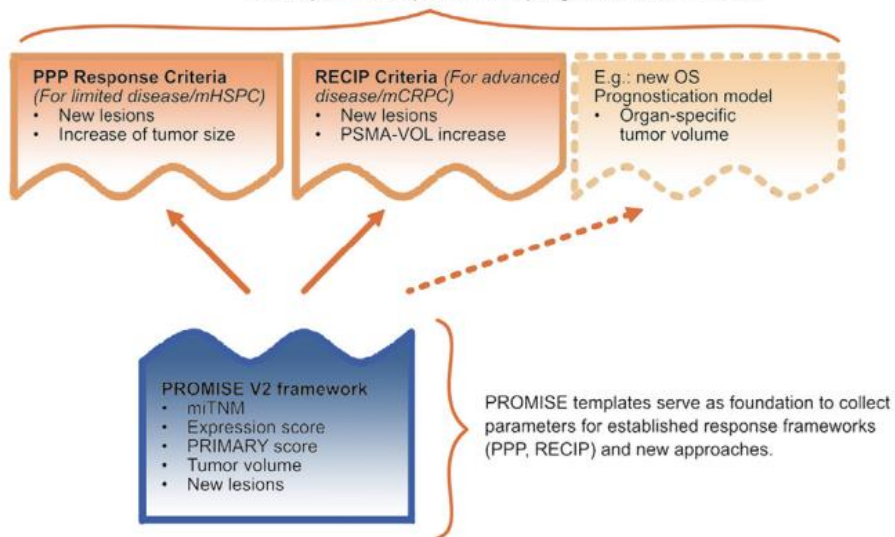
Summary of PSMA-RADS Version 1.0 for Reporting Findings on PSMA-Targeted PET Imaging

Category	Findings
PSMA-RADS-1 (benign)	
PSMA-RADS-1A	Benign lesion characterized by biopsy or pathognomonic finding on anatomic imaging and without abnormal uptake (Fig. 1).
PSMA-RADS-1B	Benign lesion characterized by biopsy or pathognomonic finding on anatomic imaging and with focal radiotracer uptake (Fig. 2).
PSMA-RADS-2 (likely benign)	Equivocal (focal, but low level such as blood pool) uptake in soft-tissue site atypical of PCA involvement (e.g., axillary or hilar lymph nodes) (Fig. 3); equivocal uptake in bone lesion atypical of PCA involvement (e.g., uptake fused to bone lesion and strongly suspected of being degenerative or another benign etiology) (Fig. 4).
PSMA-RADS-3 (equivocal*)	
PSMA-RADS-3A	Equivocal uptake in soft-tissue site typical of PCA involvement (e.g., pelvic or retroperitoneal lymph nodes). If targetable for biopsy (up to and including excision), biopsy may help confirm diagnosis. Alternatively, follow-up imaging (either anatomic or PSMA-targeted PET/CT) showing progression can confirm diagnosis. We recommend initial follow-up period of 3-6 mo (Fig. 5).
PSMA-RADS-3B	Equivocal uptake in bone lesion not definitive but also not atypical of PCA on anatomic imaging (i.e., pure marrow-based lesion with little if any surrounding bony reaction, lytic or infiltrative lesion, or classic osteoblastic lesion (Fig. 6)). Comparison to bone scan, Na ¹⁸ F PET, or tumor-protocol MR images may be helpful, and bone biopsy may have a role. Alternatively, follow-up imaging (either anatomic or PSMA-targeted PET/CT) with evidence of progression may confirm diagnosis. We recommend initial follow-up period of 3-6 mo.
PSMA-RADS-3C	Intense uptake in site highly atypical of all but advanced stages of PCA. Likelihood of nonprostatic malignancy or other benign tumor is high (Fig. 7). Biopsy to confirm diagnosis histologically is often preferred, although organ-specific follow-up imaging may be done (e.g., liver-protocol MRI to evaluate possible primary hepatocellular carcinoma).
PSMA-RADS-3D	Lesion suggestive of malignancy on anatomic imaging but lacking uptake (Fig. 8). Differential considerations include nonprostatic malignancy, neuroendocrine PCA, and an uncommon case of prostate adenocarcinoma that fails to express PSMA. Biopsy to confirm diagnosis histologically is often preferred, although organ-specific follow-up imaging may be done.
PSMA-RADS-4 (PCA highly likely)	Intense uptake in site typical of PCA but lacking definitive findings on conventional imaging (Fig. 9). Given the high specificity of PSMA agents in all reported series, it is unlikely that biopsy confirmation will be needed, although obtaining tissue for genomic analysis or other purposes may be useful.
PSMA-RADS-5 (PCA almost certainly present)	Intense uptake in site typical of PCA and having corresponding findings on conventional imaging (Fig. 10). Given the high specificity of PSMA agents in all reported series, it is unlikely that biopsy confirmation will be needed, although obtaining tissue for genomic analysis or other purposes may be useful.

*Further work-up can be considered.

Standardisation of tumor response assessment : PROMISE V2, PPP, RECIP1.0

Task-specific response and prognostication models



Criteria	Definition
PPP	
PD	1. Volume increase of any metastasis $\geq 30\%$ and consistent clinical/lab data Or 2. Two or more new PSMA-positive lesions Or 3. One new PSMA-positive lesion and consistent clinical/lab data
Non-PD	All other
RECIP	
PD	Total tumor volume increase $\geq 20\%$ and new lesions
PR	Total tumor volume decrease $\geq 30\%$ without new lesions
CR	Absence of any PSMA uptake on PET
SD	All other
CR = complete remission; CT = computed tomography; PD = progressive disease; PET = positron emission tomography; PPP = PSMA-PET progression; PR = partial remission; PSMA = prostate-specific membrane antigen; RECIP = Response Evaluation Criteria in PSMA-PET/CT; SD = stable disease.	

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European Association of Urology



Original Article – Editor's choice

Editorial by Erik Briers on pp. 275–276 of this issue

SPARC: The Standardised Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Analysis and Reporting Consensus: A Delphi Analysis

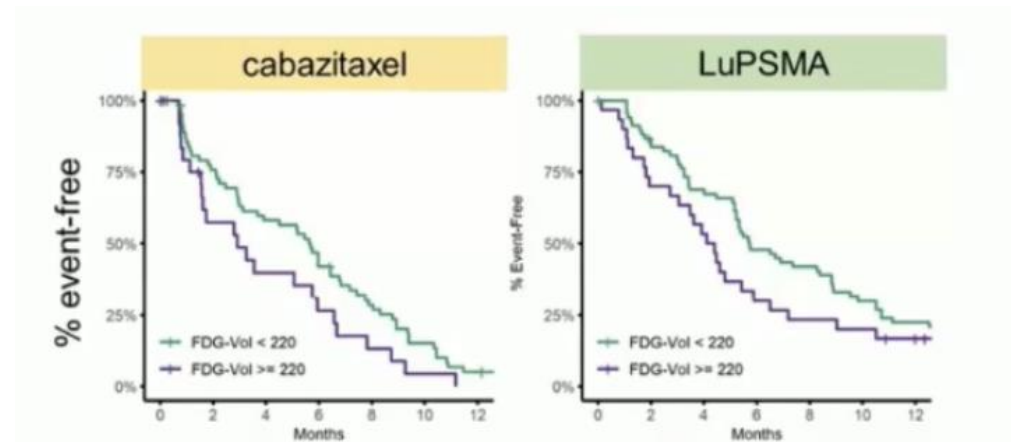
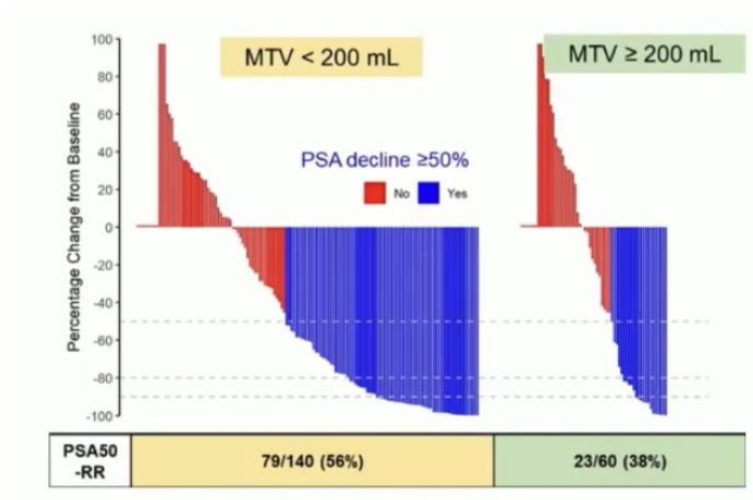
Ken Herrmann^{a,b}, Jochen Walz^c, Steven MacLennan^d, Alberto Briganti^e, Philip Cornford^f, Johannes Czernin^g, Matthias Eiber^{h,i}, Stefano Fanti^j, Wolfgang P. Fendler^{a,b}, Karim Fizazi^k, Andrei Gafita^l, Silke Gillesen^{m,al}, Karolien Goffin^{n,ak}, Boris Hadaschik^{b,o}, Michael S. Hofman^{p,q}, Thomas A. Hope^r, Tobias Maurer^s, Alicia K. Morgans^t, Michael J. Morris^u, Declan G. Murphy^v, Daniela E. Oprea-Lager^w, Piet Ost^{x,y}, Joe M. O'Sullivan^z, Olivier Rouvière^{aa}, Shahneen Sandhu^q, Oliver Sartor^{ab}, Mike Machaba Sathekge^{ac,ad}, Clare Tempany^{ae}, Wim Witjes^{af}, Louise Emmett^{ag,ah}, Anders S. Bjartell^{ai,aj,*}

Trial Design and Objectives for Patients With Prostate Cancer: Recommendations From the Prostate Cancer Working Group 4

TABLE 6. Synthesis of Delay/Prevent Outcomes by Imaging Modality

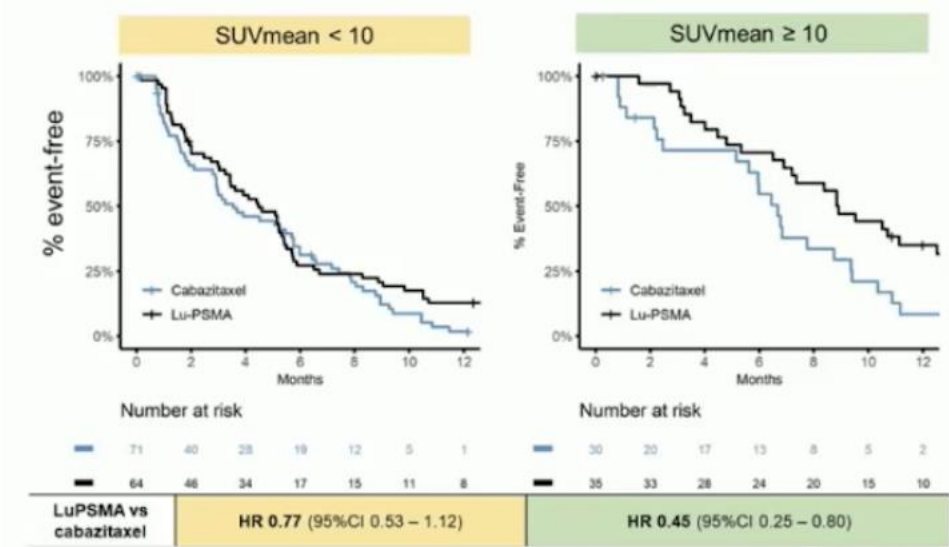
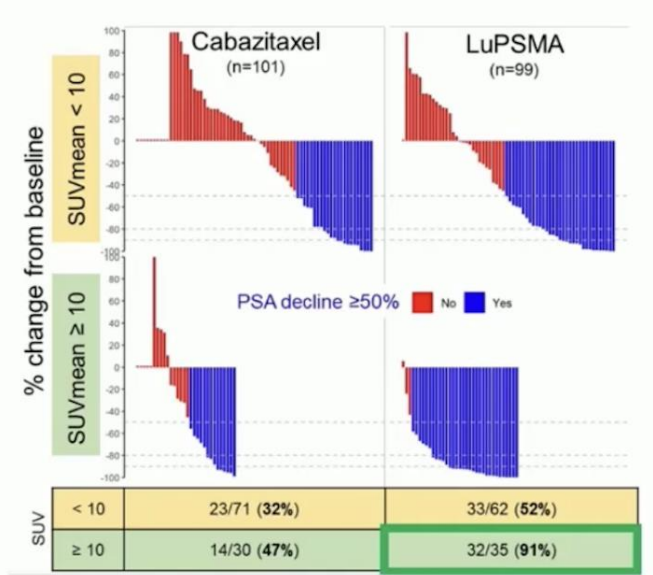
Imaging Modality	Pretreatment Scan	On-Treatment Scan 1 (≥week 8)	On-Treatment Scan 2	All Subsequent Scans
Bone scintigraphy				
	Comparator for on-treatment scan 1	Comparator for all subsequent scans POD only if ≥2 new lesions confirmed on the subsequent scan (2 + 2) ^a	POD: ≤5 new lesions: PCWG3 criteria 2 new lesions that are confirmed on a subsequent scan (2 + 0) ^a Or ≥6 new lesions	Same as on-treatment scan 2
CT/MRI				
Any measurable disease	Comparator	PCWG3/RECIST	PCWG3/RECIST	PCWG3/RECIST
PSMA-PET				
Bones and lymph nodes and lung metastases (non-RECIST qualifying by + on PET only)	Comparator	POD: ≤5 new lesions: 2 new lesions that are confirmed on a subsequent scan ≥6 new lesions	Same as on-treatment scan 1	Same as on-treatment scan 1
Liver parenchyma and nonpulmonary viscera	Comparator	POD: Any single new lesion that represents disease	Same as on-treatment scan 1	Same as on-treatment scan 1

PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [177Lu]Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): a biomarker analysis from a randomised, open-label, phase 2 trial



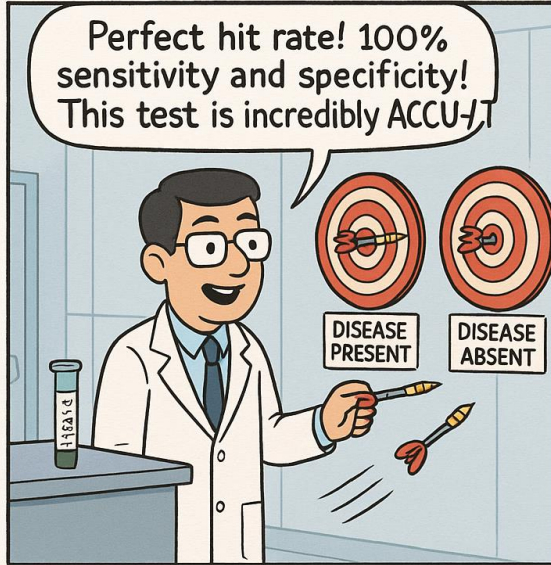
High FDG-PET metabolic tumour volume (MTV) of 200 mL or higher was associated with lower responses regardless of randomly assigned treatment

PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [177Lu]Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): a biomarker analysis from a randomised, open-label, phase 2 trial



High PSMA expression (SUVmean ≥ 10) was predictive of a higher likelihood of favorable response to 177Lu-PSMA than cabazitaxel

THE RADIOLOGIST vs. THE CLINIC



Diagnostic Accuracy

The test's ability to correctly identify the condition.



Clinical Utility

The test's actual benefit in managing patient's health and improving outcomes

A tale of diagnostic accuracy **vs.** clinical utility.

Association between PSA response and wbMRI response according to MET-RADS-P

mHSPC

MET-RADS-P category by group	Patients, n/N (%)		p value
	No PSA response	PSA response	
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MET-RADS-P = Metastasis Reporting and Data System for Prostate Cancer; mCRPC = metastatic castration-resistant prostate cancer; mHNPc = metastatic hormone-sensitive prostate cancer; PSA = prostate-specific antigen; RAC = response assessment category.

Should we escalate or consolidate, e.g., with MDT, these patients?

Challenges and Key Questions in Modern Imaging

Challenges	Key Questions / Implications
➤ Lack of evidence for improvement in oncological outcomes for therapeutic assessment by NGI	✓ Need for prospective studies
➤ Uncertain prognosis for metastases detected by modern imaging	✓ Is the prognosis of a CT(-) PSMA(+) patient the same as that of a CT(+) PSMA(+) patient?
➤ Dilemma in the treatment of metastatic patients	✓ Differences in treatment based on tumor burden
➤ Risk of overtreatment	✓ Does the increased sensitivity of modern imaging lead to over-detection of clinically insignificant lesions?
➤ Bias: change in risk category (stage migration)	✓ Treatment intensification or omission of local therapy

Thank You

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