OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

Facts and Myths of Next Generation Imaging in Prostate Cancer

Matteo Bauckneht

Nuclear Medicine Unit
University of Genoa
IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Facts:

PSMA PET offers greater diagnostic accuracy than conventional imaging

PSMA PET offers greater accuracy than conventional imaging in the **primary staging**

Study (year)	Tracer	Patients	Study phase, design, arms, reference standard	Results
proPSMA (2020)	68Ga-PSMA-11	302 high-risk Pca	Phase III, two-arm (conventional imaging vs. PSMA PET), randomized. Reference standard: composite	Conventional imaging vs. PSMA PET: - **Overall accuracy: 65% vs. 92%** - Accuracy for pelvic nodal mets: 59% vs. 91% - Accuracy for distant mets: 74% vs. 95%
Hope et al. JAMA Oncol (2021)	68Ga-PSMA-11	764 intermediate to high-risk PCa (36% submitted to EPLND)	Phase III, single-arm. Reference standard: histopathology	**SENS, SPEC**, PPV, and NPV for pelvic nodal mets: **40%, 95%,** 75%, and 81%.
OSPREY cohort A (2021)	18F-DCFPyL	252 high risk PCa	Phase II/III, single-arm, multi-reader. Refrence standard: histopathology	Median **SENS, SPEC**, PPV, and NPV among 3 readers for pelvic nodal mets: **40.3%, 97.9%**, 86.7%, and 83.2%.

Wording of **clinical guidelines** about PSMA PET

EAU 2022 “more accurate”

ESMO 2020 “better sensitivity and specificity than CT or bone scan”

ASCO 2020 “consider”

NCCN 2021 “equally effective if not more effective compared to conventional imaging”

PSMA PET offers greater accuracy than conventional imaging (and choline PET) in PCa **restaging**

Study (year)	Tracer	Patients	Study phase, design, arms, reference standard	Results
CONDOR (2021)	18F-DCFPyL	208 BCR men (median PSA 0.8 ng/mL) with **negative or equivocal conventional imaging**	Phase III, single-arm, multi-reader. Refrence standard: composite	**Correct Localization Rate (CLR)** among 3 readers: **84.8%-87.0%**.
OSPREY cohort B (2021)	18F-DCFPyL	93 BCR men (median PSA 11.3 ng/ml) with **suspected recurrent PCa on conventional imaging**	Phase II/III, single-arm, multi-reader. Refrence standard: histopathology	Median **SENS** and **PPV** among 3 readers for extraprostatic lesions: **95.8%** and **81.9%**
Olivier et al. J Nucl Med (2022)	18F-PSMA-1007	190 BCR men (median PSA 1.7 ng/ml)	Phase III open-label, multi-reader, randomized, cross-over study (18F-PSMA-1007 vs. 18F-Fluorocholine PET/CT). Refrence standard: composite after 6-months FU	**CLR: 82% vs. 65% for PSMA vs. Fluorocholine** (77% vs. 57% when considering undetermined findings as negative for malignancy).

Wording of **clinical guidelines** about PSMA PET

EAU 2022 “perform”

ESMO 2020 “replacing conventional imaging”

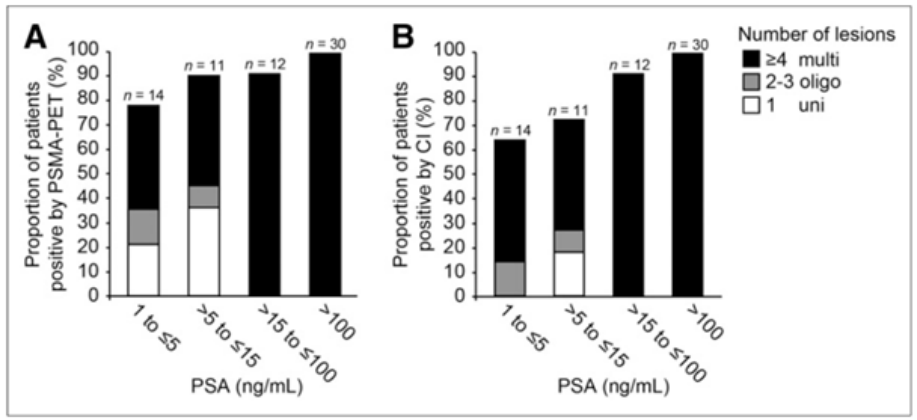
ASCO 2020 “should be offered”

NCCN 2021 “equally effective if not more effective compared to conventional imaging”

PSMA PET is accurate and reproducible even in **castration-resistant prostate cancer**

Compared to conventional imaging
PSMA-PET better identifies the true extent of CRPC

setting	positivity rate	patients	author
mØCRPC	0.98	200	Fendler et al.
	0.7	37	Wang et al.
	0.74	55	Weber et al.
	0.9	30	Forquet et al.
mCRPC	0.83	18	Zang et al.
	1	26	Kallur et al.
	1	16	Rowe et al.
	1	40	Pyka te al.
	1	10	Soydal et al.



Weber et al. Eur Urol Focus 2021; Farolfi et al. J Nucl Med 2021

Optimum Imaging Strategies for Advanced Prostate Cancer: ASCO Guideline

Edouard J. Trabulsi, MD[1]; R. Bryan Rumble, MSc[2]; Hossein Jadvar, MD, PhD[3]; Thomas Hope, MD[4]; Martin Pomper, MD, PhD[5]; Baris Turkbey, MD[6]; Andrew B. Rosenkrantz, MD[7]; Sadhna Verma, MD[8]; Daniel J. Margolis, MD[9]; Adam Froemming, MD[10]; Aytekin Oto, MD[11]; Andrei Purysko, MD[12]; Matthew I. Milowsky, MD[13]; Heinz-Peter Schlemmer, MD[14]; Matthias Eiber, MD[15]; Michael J. Morris, MD[16]; Peter L. Choyke, MD[6]; Anwar Padhani, MD[17]; Jorge Oldan, MD[13]; Stefano Fanti, MD[18]; Suneil Jain, NMD[19]; Peter A. Pinto, MD[6]; Kirk A. Keegan, MD[20]; Christopher R. Porter, MD[21]; Jonathan A. Coleman, MD[16]; Glenn S. Bauman, MD[22]; Ashesh B. Jani, MD[23]; Jeffrey M. Kamradt, MD[24]; Westley Sholes, MPA; and H. Alberto Vargas, MD[16]

Accepted on October 25, 2019 and published at ascopubs.org/journal/jco on January 15, 2020: DOI https://doi.org/10.1200/JCO.19.02757

Metastatic CRPC

Recommendation 4.9. PSA progression. As recommended by the Prostate Cancer Working Group 3 consensus statements, PSA progression alone for men on treatment of metastatic CRPC should not be the sole reason to change therapy. Conventional imaging can be used for initial evaluation of PSA progression and should be continued to facilitate changes/comparisons and serially to assess for development of radiographic progression (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.10. The use of NGI in this cohort is unclear, with a paucity of prospective data. When a change in clinical care is contemplated, in an individualized manner, and there is a high clinical suspicion of subclinical metastasis despite negative conventional imaging, the use of NGI could be contemplated, especially in the setting of a clinical trial (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: insufficient; Strength of recommendation: weak).

Systemic Therapy Update on ^{177}Lutetium-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer: ASCO Rapid Recommendation

Rohan Garje, MD[1]; R. Bryan Rumble, MSc[2]; and Rahul A. Parikh, MBBS, PhD[3]

Accepted on August 17, 2022 and published at ascopubs.org/journal/jco on September 16, 2022: DOI https://doi.org/10.1200/JCO.22.01865

Evidence-Based Medicine Committee approval: August 8, 2022

UPDATED RECOMMENDATIONS

Updated Recommendation 1.1

The panel recommends the use of ^{177}Lu-PSMA-617 IV once every 6 weeks for 4-6 cycles as a treatment option in patients with PSMA PET/CT–positive mCRPC who have progressed on one prior line of androgen receptor pathway inhibitor and at least one line of prior chemotherapy (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

Updated Recommendation 1.2.1

The panel recommends that patients should be selected with PSMA PET (Type: Evidence-based; benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

AGENDA

Facts:

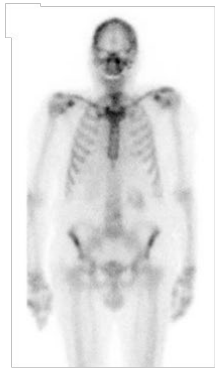
PSMA PET offers greater diagnostic accuracy than conventional imaging

Myths:

PSMA-guided treatment selection: greater accuracy means greater clinical outcome?

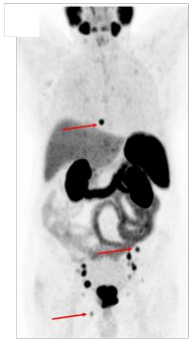
Need to raise the bar of evidence for next-generation imaging modalities

Conventional imaging M0



Treatment options:
RP
RT+/ADT

PSMA PET low/high volume M1



Treatment options:
ADT + RT (low volume only)
ADT + ARPI
ADT + Docetaxel

Risk of *undertreatment*?

modified from Ost APCCC 2021

Zacho et al. EJNMMI Res 2020; Durack et al. ASCO 2021; Sundahl et al. Eur Urol 2021

Reducing false positive results… isn't it stage migration?

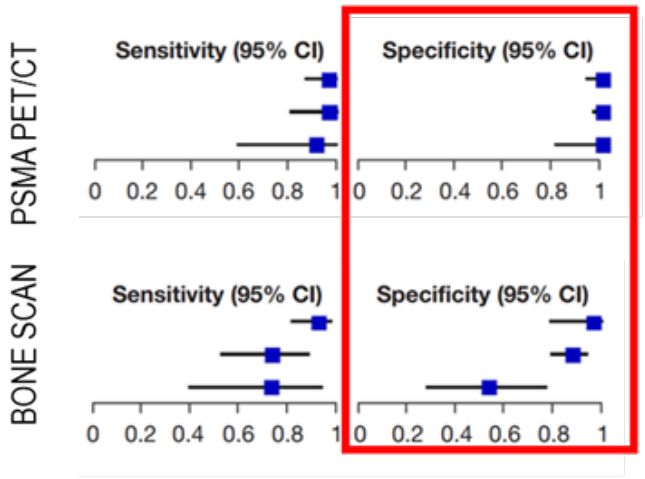
Systematic review and meta-analysis including 3 studies (n = 215)

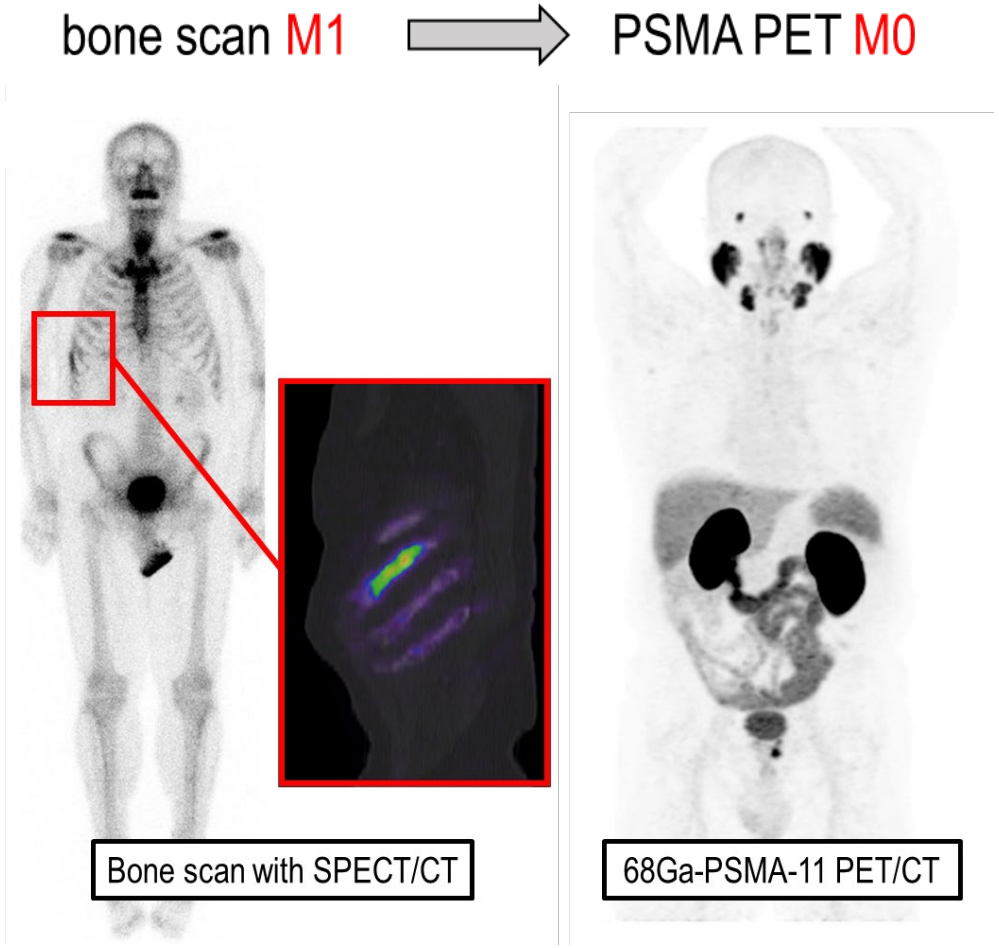
PSMA PET/CT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kumar A 2018	49	0	2	53	0.96 [0.87, 1.00]	1.00 [0.93, 1.00]
Lengana T 2018	25	0	1	87	0.96 [0.80, 1.00]	1.00 [0.96, 1.00]
Uslu-Besli L 2019	10	0	1	17	0.91 [0.59, 1.00]	1.00 [0.80, 1.00]

BONE SCAN

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kumar A 2018	47	1	4	22	0.92 [0.81, 0.98]	0.96 [0.78, 1.00]
Lengana T 2018	19	11	7	76	0.73 [0.52, 0.88]	0.87 [0.79, 0.94]
Uslu-Besli L 2019	8	8	3	9	0.73 [0.39, 0.94]	0.53 [0.28, 0.77]

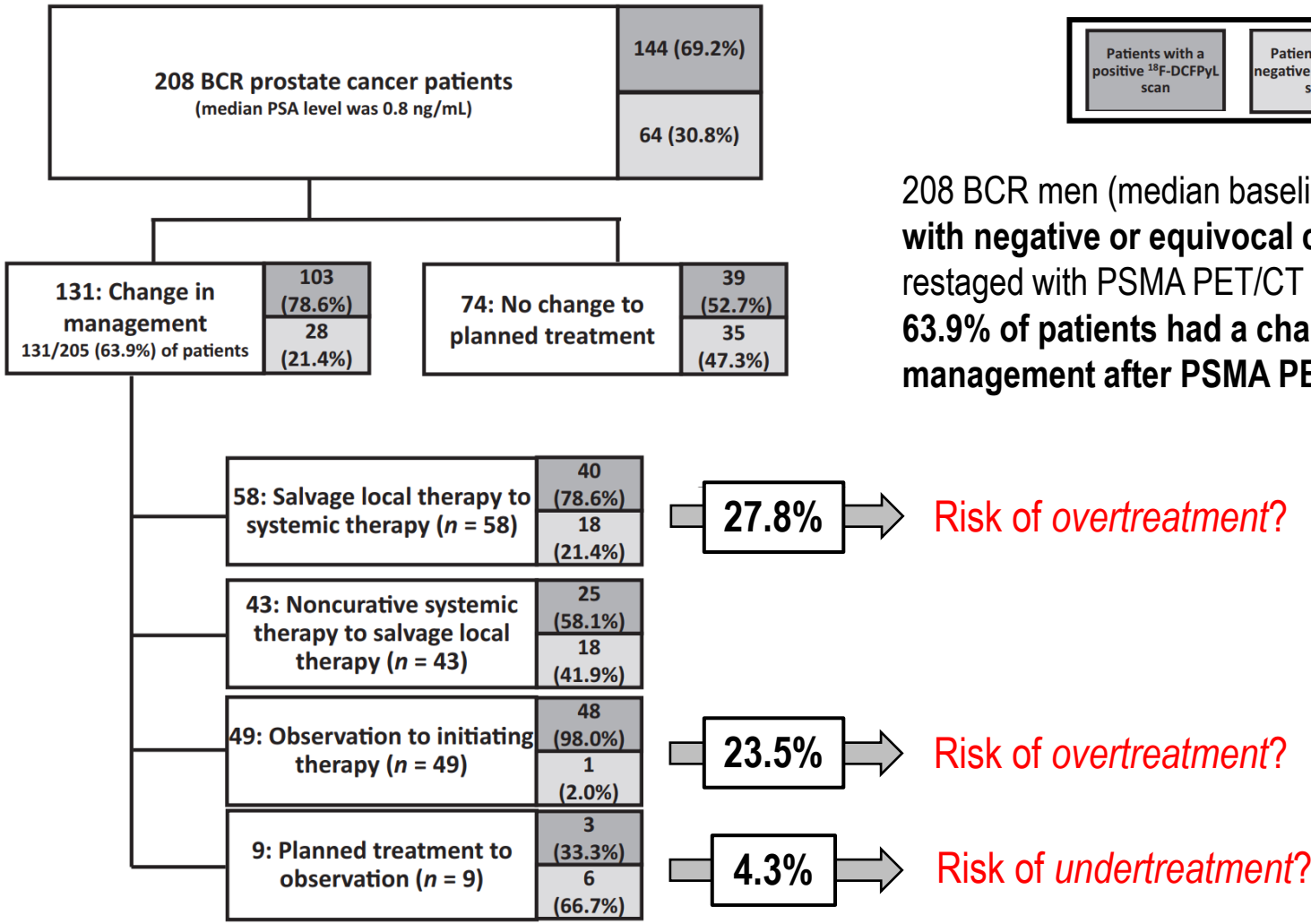




Risk of undertreatment *when using conventional imaging*?

Wang et al. Transl Androl Urol 2021; Durack et al. ASCO 2021; Ayati et al. Eur Urol 2022

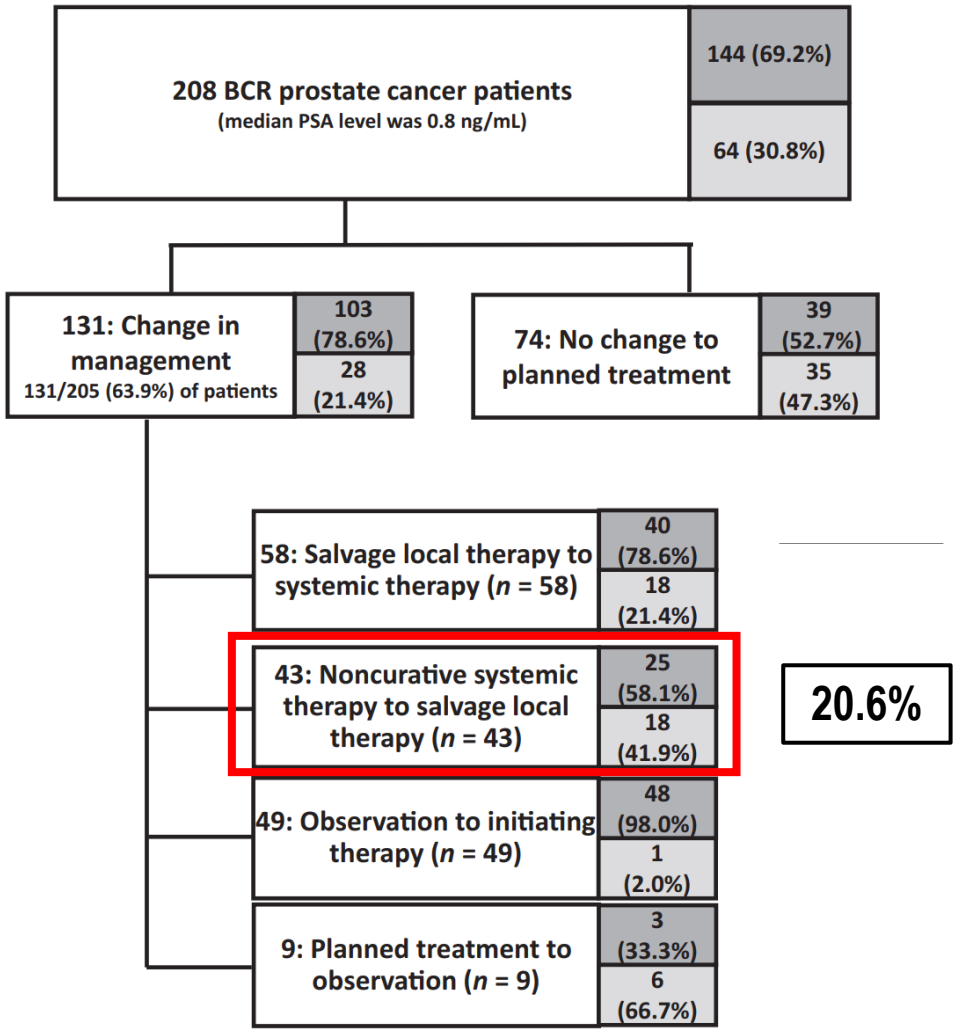
Need to raise the bar of evidence for next-generation imaging modalities
a prospective multicenter, multi-reader, open-label, single arm, phase III trial (**CONDOR**)



208 BCR men (median baseline PSA=0.8 ng/mL)
with negative or equivocal conventional imaging
restaged with PSMA PET/CT
63.9% of patients had a change in intended management after PSMA PET/CT.

Morris et al. Clin Canc Res 2021

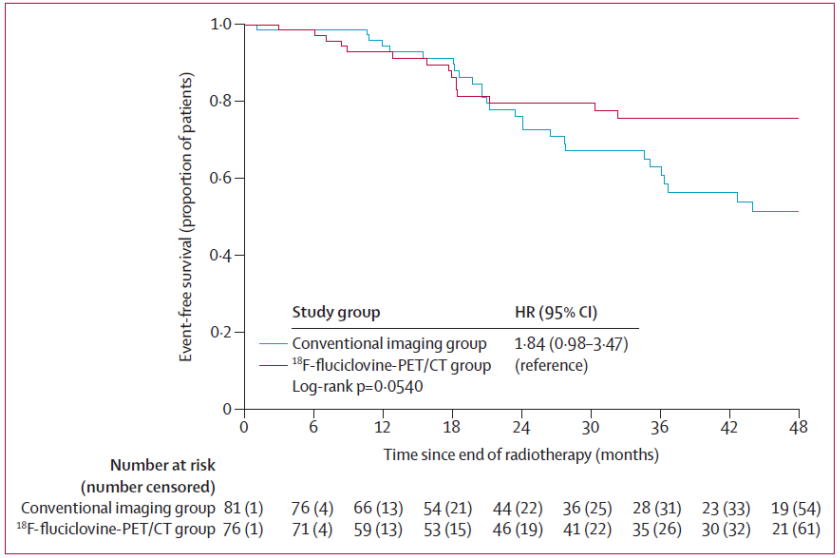
Need to raise the bar of evidence for next-generation imaging modalities
a prospective multicenter, multi-reader, open-label, single arm, phase III trial (**CONDOR**)



20.6%

^{18}F-fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial

Lancet 2021; 397: 1895-904



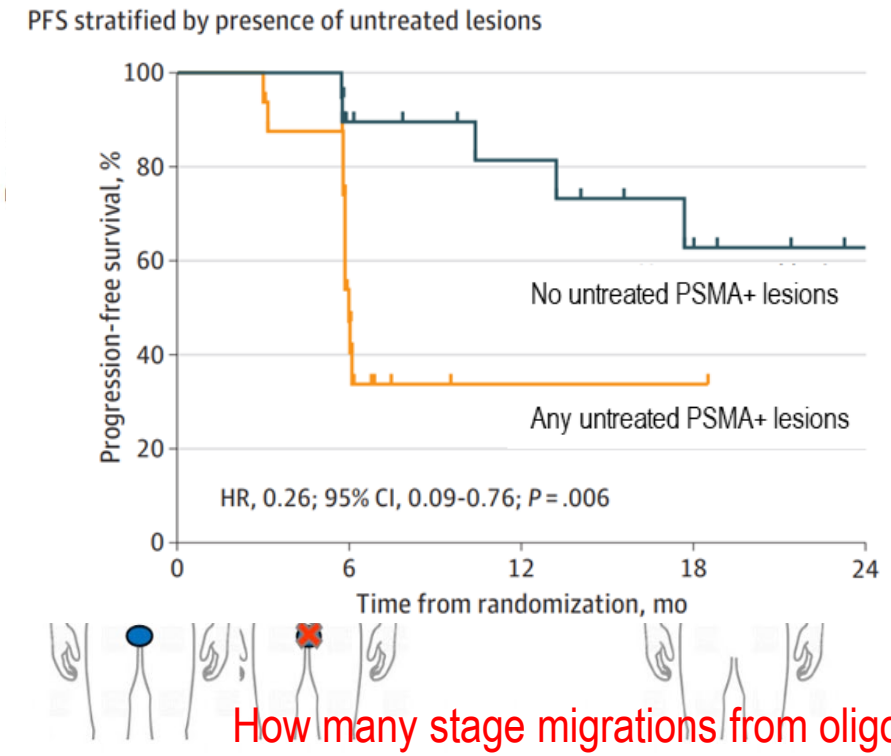
In 165 patients with BCR or PSA persistence and negative conventional imaging after RP, the incorporation of next-generation imaging into post-surgery RT decision-making and planning was associated with a significant improvement in bRFS and PSA persistence-free survival.

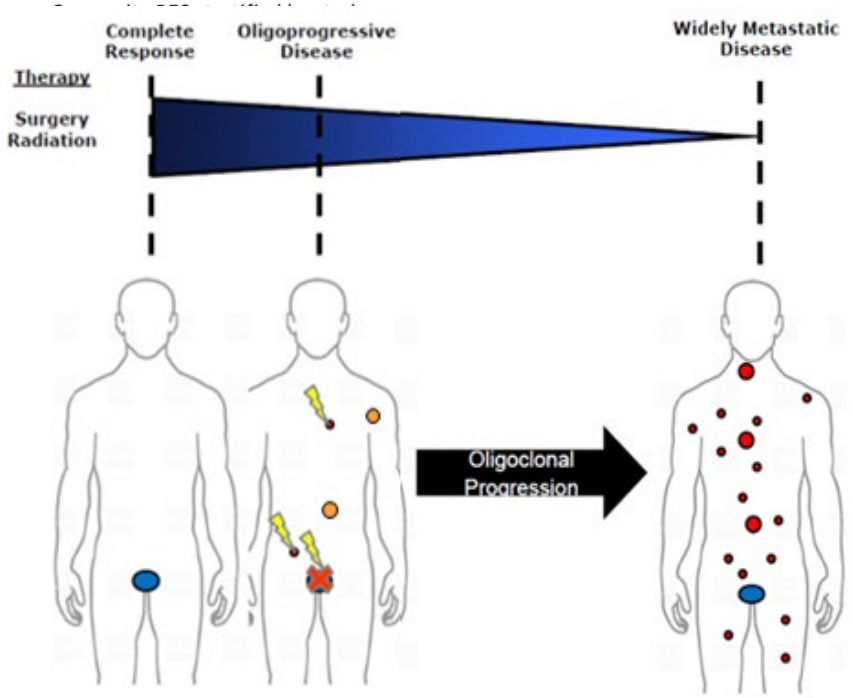
Morris et al. Clin Canc Res 2021

Need to raise the bar of evidence for next-generation imaging modalities in the oligometastatic setting: a prospective phase II randomized clinical trial (**ORIOLE**)

54 recurrent hormone-sensitive PCa men with 1-3 mets *detectable by conventional imaging* who had not received ADT, randomized (2:1) to receive SABR or observation.
Primary outcome: progression at 6 months.

METASTASES DIRECTED THERAPY





19% SABR vs. 61% observation

How many stage migrations from oligometastatic to disseminated M1?

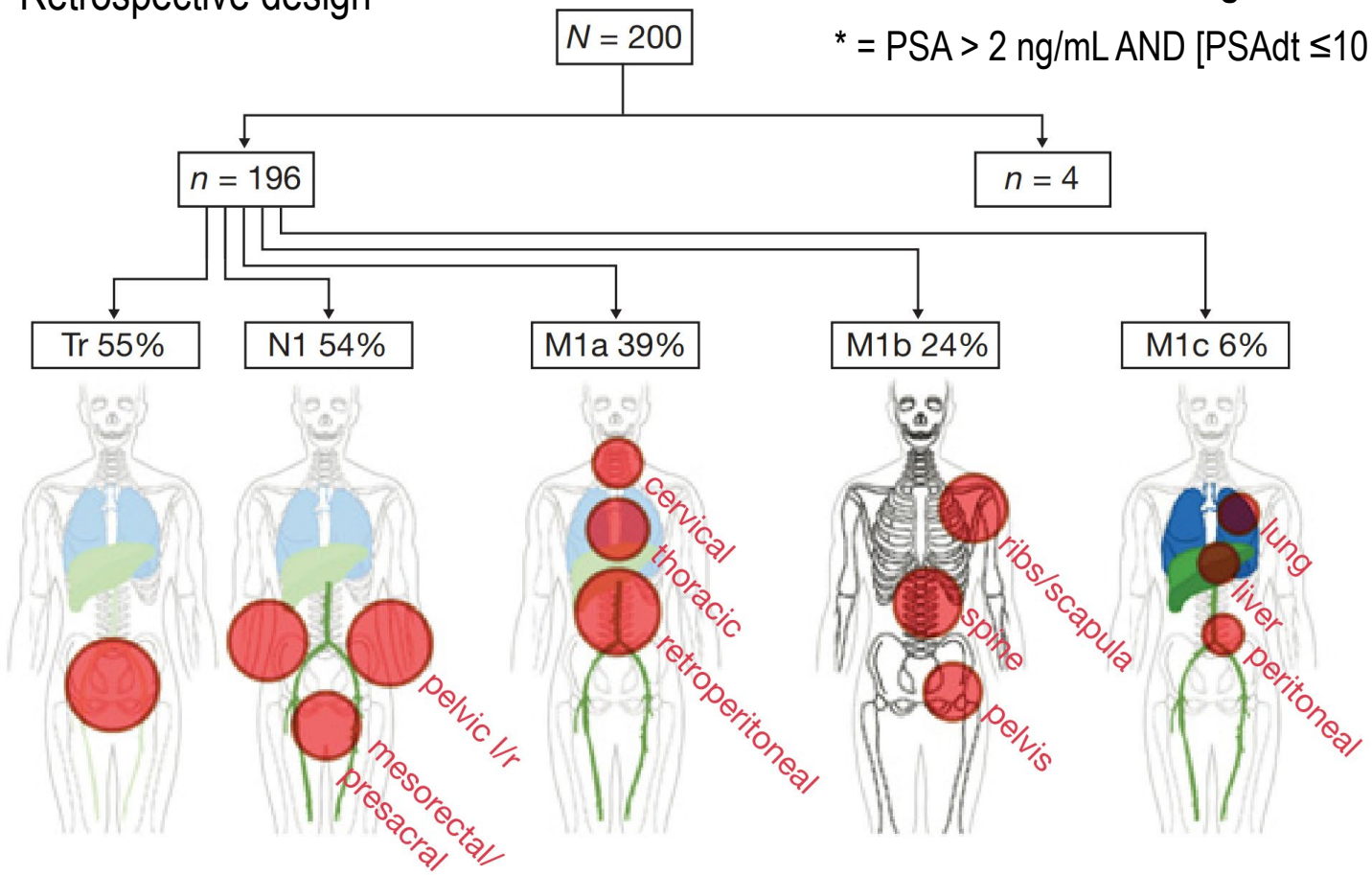
Philips et al. JAMA Oncol 2020

Need to raise the bar of evidence for next-generation imaging modalities in the mØCRPC setting: a virtual space in the era of PSMA PET imaging?

Retrospective design

"SPARTAN-like" **high-risk mØCRPC***

* = PSA > 2 ng/mL AND [PSAdt ≤10 mo OR GS ≥8]



Fendler et al. Clin Cancer Res 2019

Apalutamide provides benefit in the presence of features predicting PSMA-M1

7 clinical variables associated with PSMA-PET M1

Table 4. Multivariable analysis of odds for PSMA-PET M1 disease ($n = 200$)

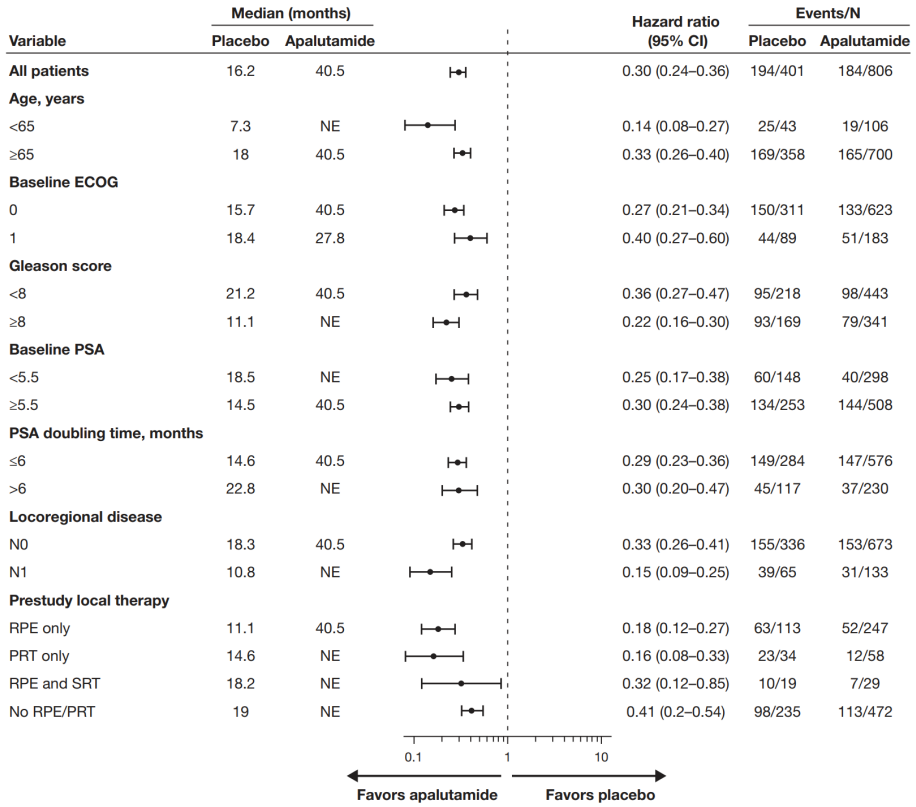
Variable	*n* (%)	OR	95% CI	*P*
Age ≥65 years	151 (76)	0.6	0.3–1.3	0.23
Gleason score of ≥8	151 (76)	1.1	0.5–2.3	0.80
PSA ≥5.5 ng/mL	97 (49)	2.0	1.1–3.6	0.03[a]
PSADT of ≤6 months ($n = 132$[b])	85 (43)	1.6	0.8–3.3	0.22
Locoregional disease pN1	45 (23)	2.7	1.3–6.0	0.01[a]
RPE and SRT	40 (20)	4.6	2.0–11.0	<0.01[a]
PRT	64 (32)	3.1	1.5–6.1	0.02[a]

Abbreviations: PRT, primary radiotherapy; RPE, radical prostatectomy; SRT, salvage radiotherapy.

[a]$P < 0.05$.

[b]On the basis of univariate analysis.

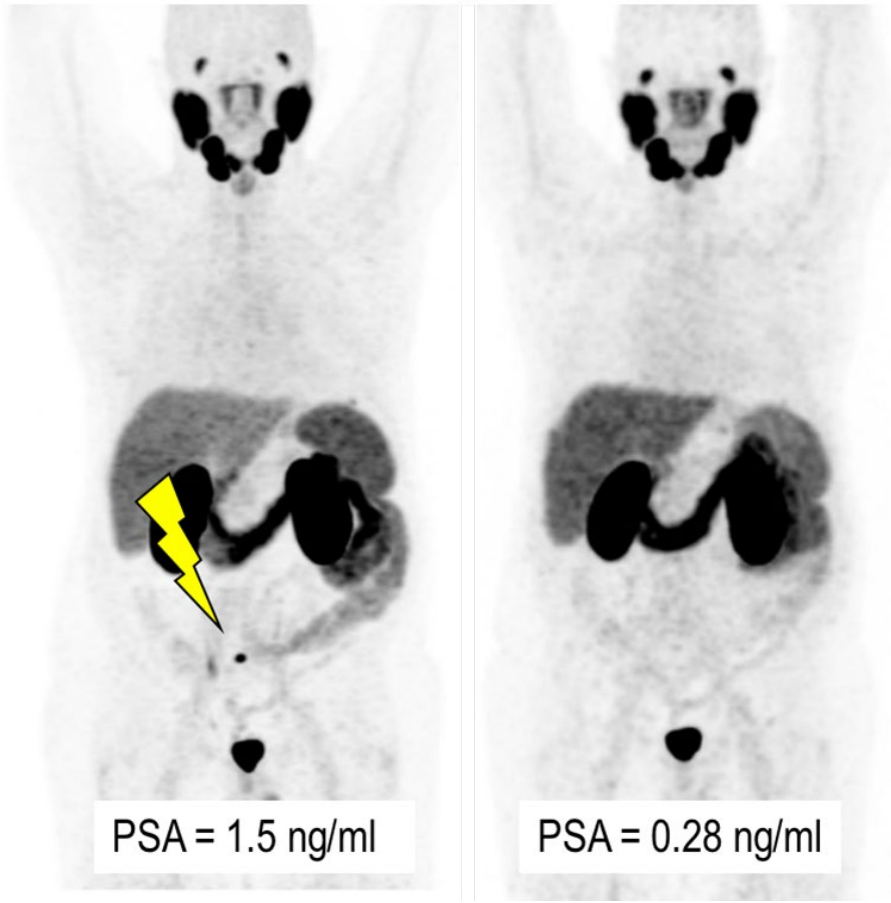
Evaluation of the above predictors of PSMA-M1 disease in post hoc SPARTAN subgroup analyses of MFS

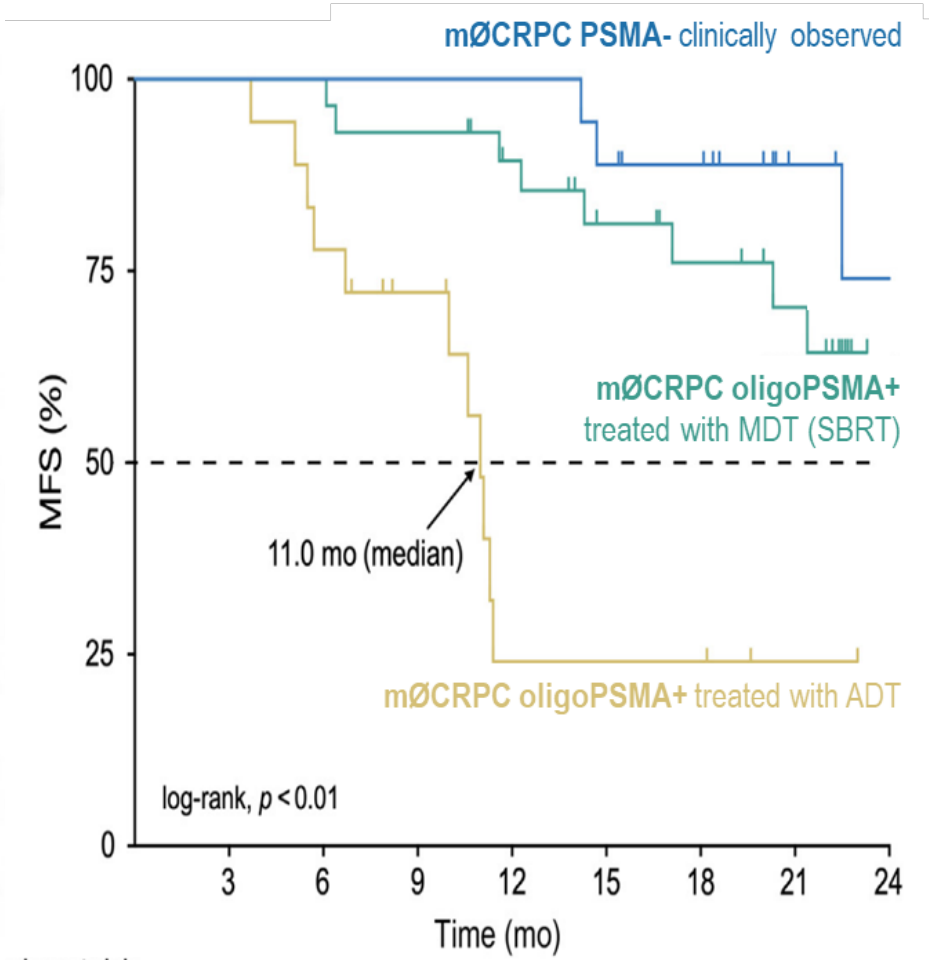


Apalutamide provided significant benefit in all clinically relevant subgroups of patients, including those with disease characteristics predictive of M1 disease

Fendler et al. Clin Cancer Res 2019

Know the true disease extent: a chance to increase the local control rate?





mØCRPC resulting oligoPSMA+ show similar MFS compared to mØCRPC PSMA- if treated with MDT (SBRT)

Pan et al. Eur Urol Oncol 2022

AGENDA

Facts:

PSMA PET offers greater diagnostic accuracy than conventional imaging

Myths:

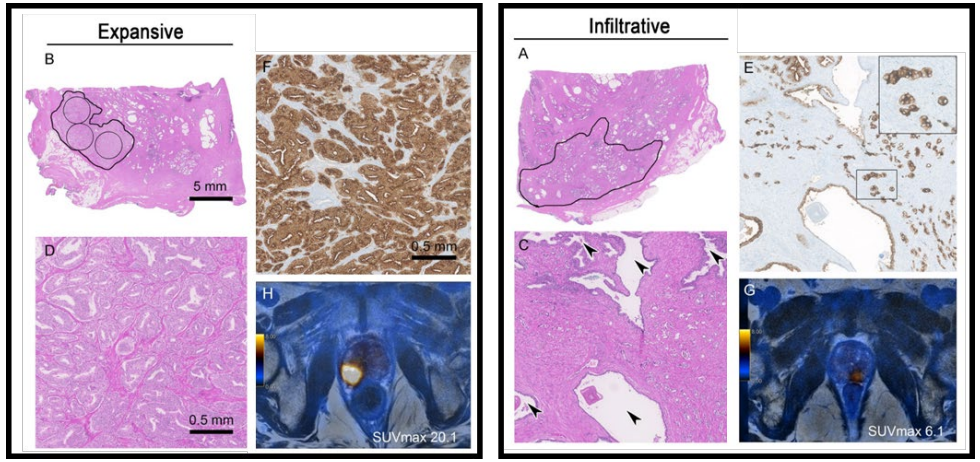
PSMA-guided treatment selection: greater accuracy means greater clinical outcome?

Implications of PSMA expression heterogeneity: one imaging fits all?

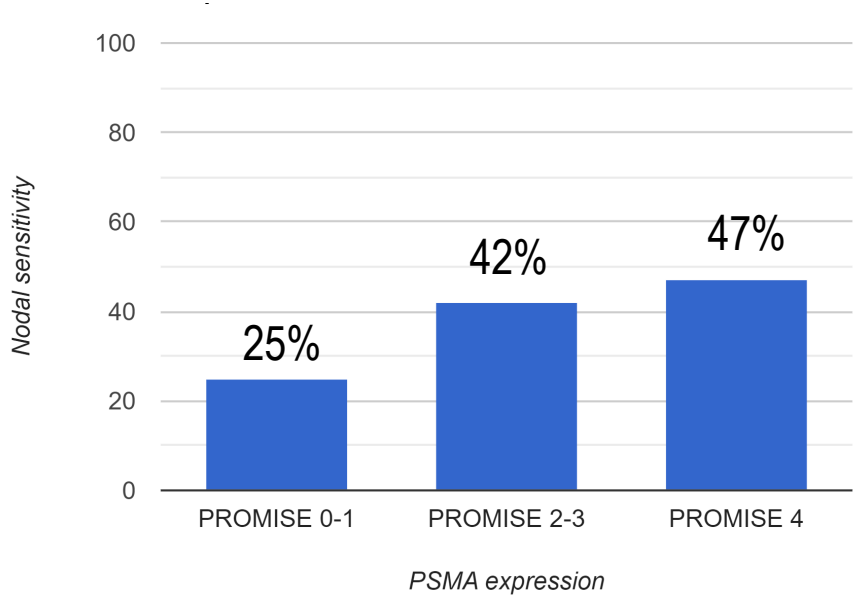
PSMA PET/CT cannot detect about 5-10% of PCa due to the low or lack of PSMA expression

Determinants of PSMA-positive disease at HHC:

- PSA serum levels
- Gleason score
- Expansive/infiltrative growth pattern
- Tumor size



Impact of PSMA expression on PSMA PET sensitivity for nodal staging in intermediate to high-risk prostate cancer submitted to extended pelvic lymph node dissection



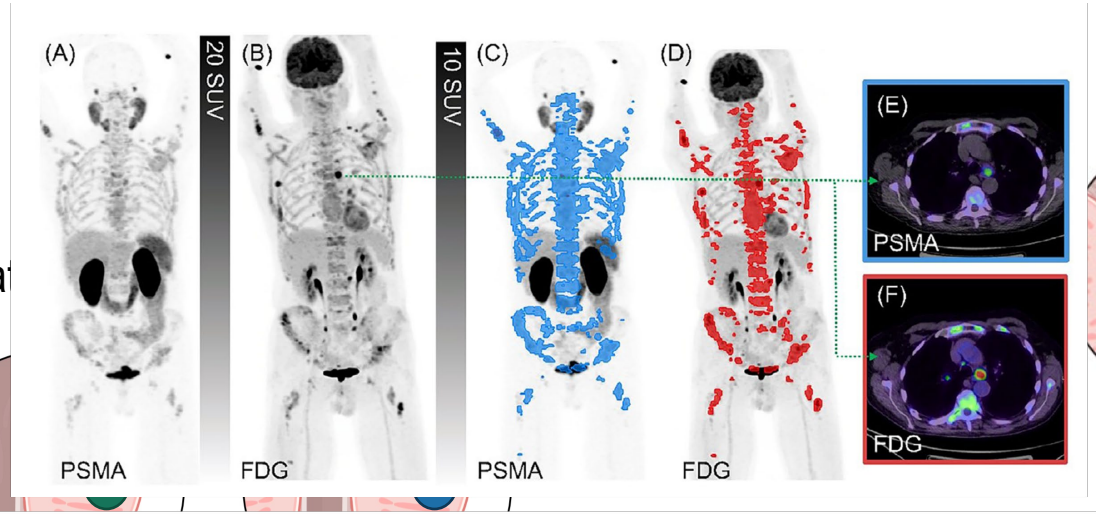
Rüschoff et al. Eur J Nucl Med Mol Imaging 2021; Hope et al. JAMA Oncol 2021; Hope et al. JAMA Oncol 2022

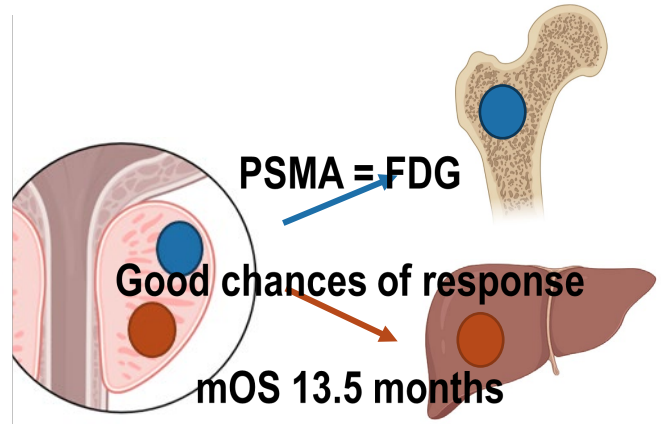
IMPLICATIONS OF PSMA HETEROGENEITY

Heterogeneity in PSMA expression within the primary or between primary and metastases

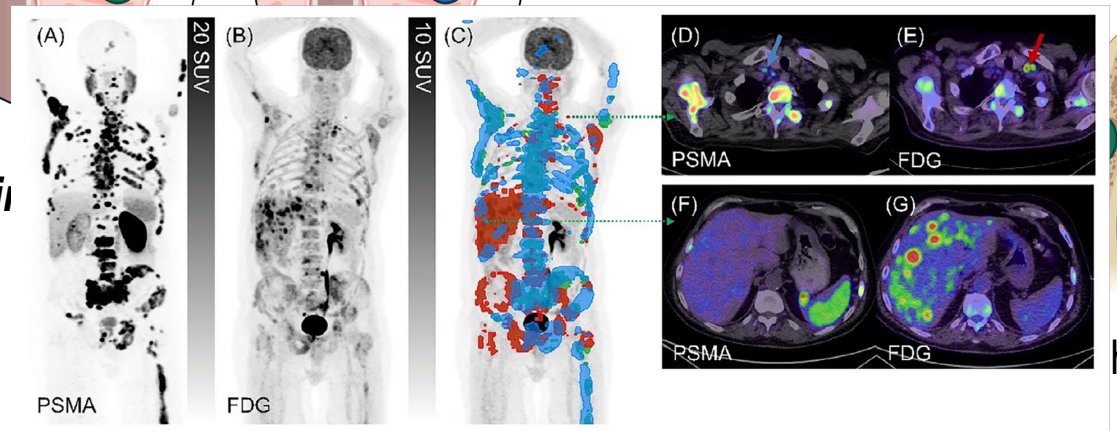
Complementary role of FDG PET imaging in CRPC patients receiving PSMA-based RLT

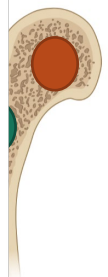
Pat





intermetastatic heterogeneity





PSMA ≠ FDG

Poor chances of response

mOS 2.5 months

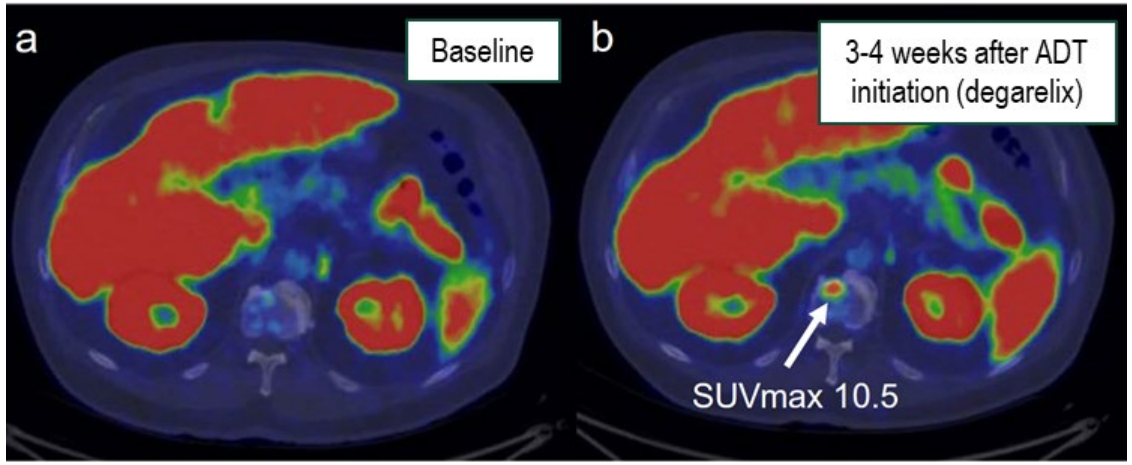
heterogeneity

Created in BioRender.com

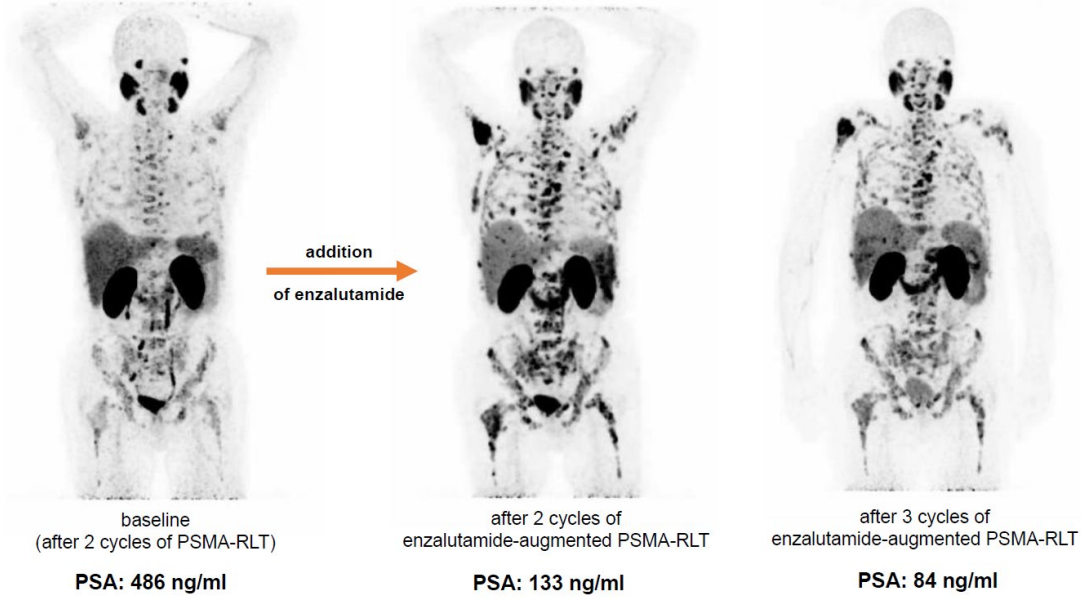
Thang et al. Eur Urol Oncol 2019; Seifert et al. Theranostics 2020; Chen J Nucl Med 2022

Heterogeneity in PSMA expression after treatment: is there a synergistic potential?

Changes in PSMA uptake after short-term ADT in **HSPC**



Changes in PSMA uptake after darolutamide or enzalutamide in **CRPC**



Hammer et al. Clin Cancer Res 2021; Rosars et al. Cancers 2022; Malaspina et al. Eur J Nucl Med Mol Imaging 2022

AGENDA

Facts:

PSMA PET offers greater diagnostic accuracy than conventional imaging

Myths:

PSMA-guided treatment selection: greater accuracy means greater clinical outcome?

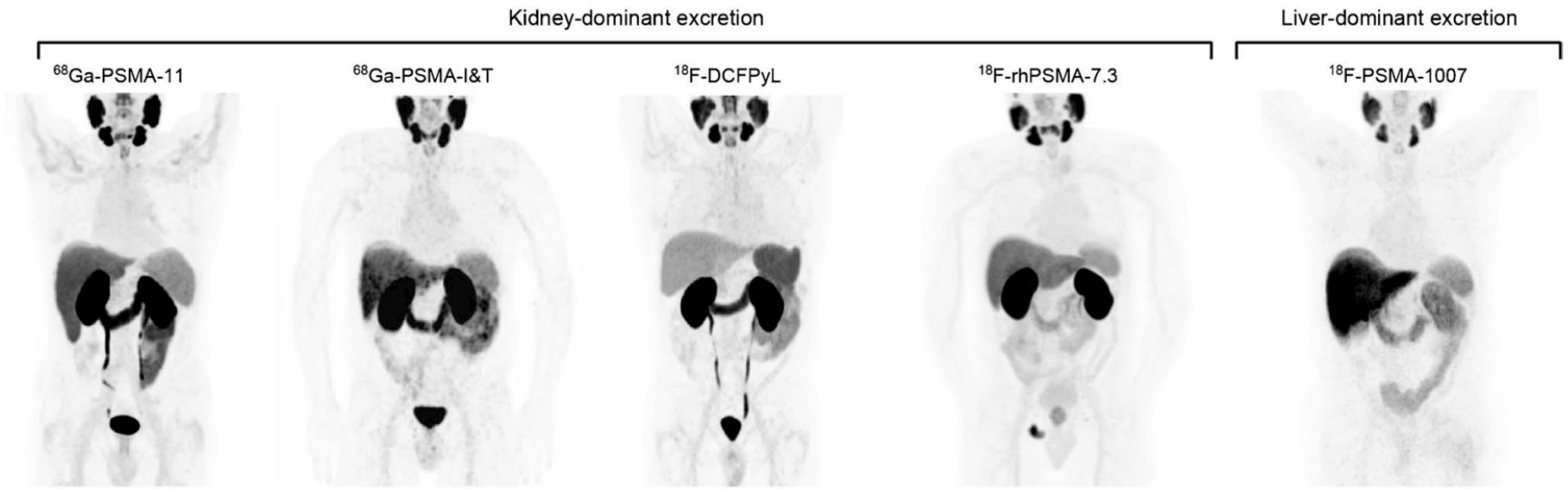
Implications of PSMA expression heterogeneity: one imaging fits all?

68Ga- and 18F-labelled PSMA targeted tracers: the one like the other?

PSMA AS A BASKET CONCEPT

Differences in:

costs, **logistics**, **availability**, **patentability** and (perhaps) **diagnostic accuracy**



Need to measure the clinical impact of using different PSMA-targeted tracers, eventually identifying specific patients-, lesions- and reader-based scenarios that might benefit from the tracer choice.

Thank you for your attention and a special thank to:

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

Uro-Oncology Disease Management Team of the IRCCS Ospedale Policlinico San Martino Genoa, Italy

Oncologists
Giuseppe Fornarini
Elisa Zanardi
Laura Tomasello

Radiation Oncologists
Salvina Barra
Michela Marcenaro
Giorgia Timon

Radiologists
Veronica Giasotto
Jeries Zawaideh

Urologists
Carlo Terrone
Marco Borghesi
Guglielmo Mantica
Daniele Panarello

Pathologists
Bruno Spina
Nataniele Piol

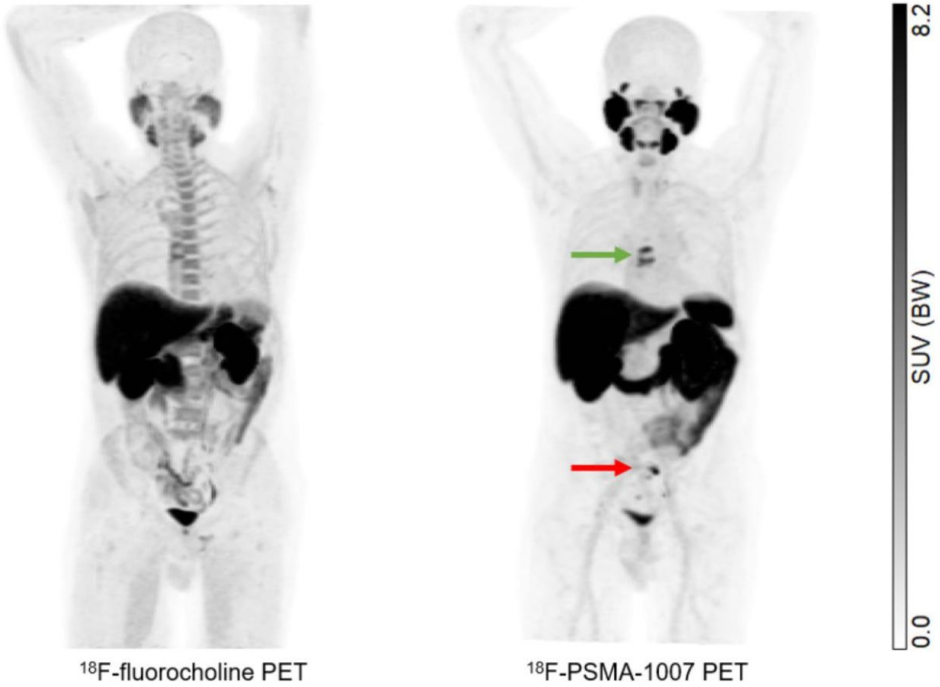
matteo.bauckneht@unige.it

UNSPECIFIC BONE UPTAKES (UBU)

Phase III open-label, multi-reader, randomized, cross-over study (18F-PSMA-1007 vs. 18F-Fluorocholine PET/CT)
190 BCR men (median PSA 1.7 ng/ml). Reference standard: composite after 6-months FU

Undetermined findings: 3.2-6.3% vs. 5.3-11.1% for 18F-PSMA-1007 PET/CT vs. 18F-Fluorocholine PET/CT

Correct Localization Rate (CLR, primary endpoint) for 18F-PSMA-1007 PET/CT vs. 18F-Fluorocholine PET/CT:



^{18}F-fluorocholine PET

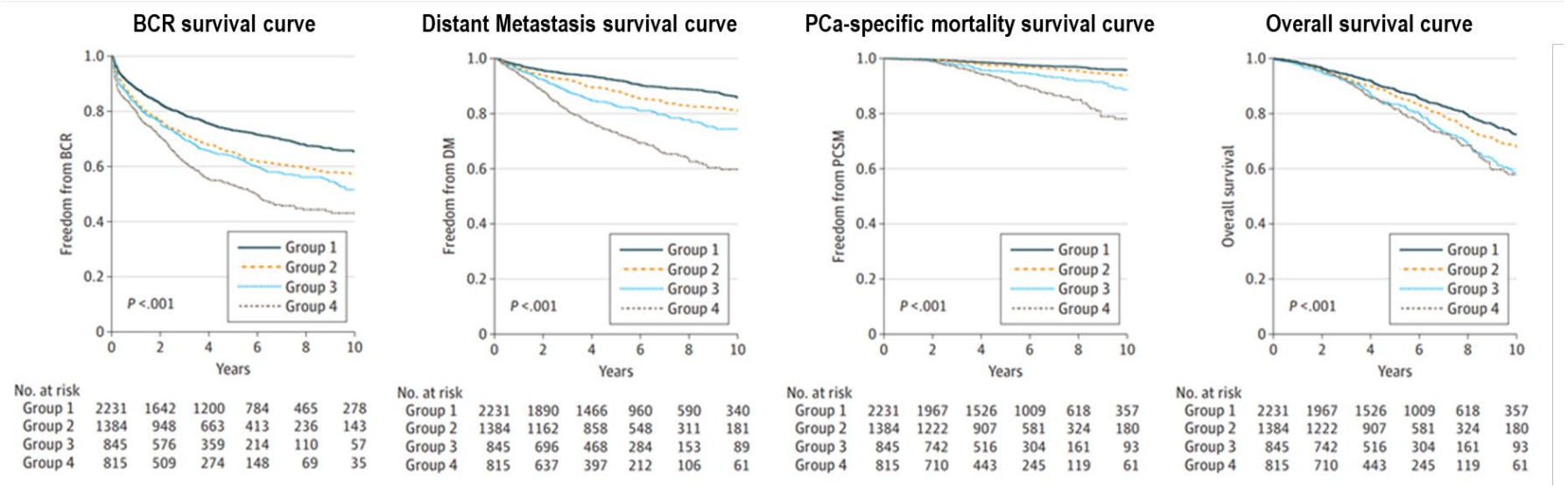
^{18}F-PSMA-1007 PET

	^{18}F-PSMA-1007	^{18}F-fluorocholine	
Undetermined lesions considered as **positive** for prostate cancer recurrence in the analysis			
Proportion	0.82 [0.78-0.86]	0.65 [0.60-0.71]	
Difference in proportion	0.16 [0.11-0.22]		p<0.0001
Odds ratio	2.40 [1.79-3.21]		p<0.0001
Positive predictive value	0.96 [0.93-0.99]	0.96 [0.93-0.99]	
Difference in positive predictive value	0.002 [0.031-0.035]		p=0.90
Odds ratio	0.95 [0.42-2.15]		p=0.90
Undetermined lesions considered as **negative** for prostate cancer recurrence in the analysis			
Proportion	0.77 [0.72-0.82]	0.57 [0.51-0.62]	
Difference in proportion	0.21 [0.15-0.26]		p<0.0001
Odds ratio	2.61 [1.97-3.46]		p<0.0001
Positive predictive value	0.95 [0.92-0.99]	0.97 [0.95-1.00]	
Difference in positive predictive value	0.02 [0.01-0.05]		p=0.25
Odds ratio	0.58 [0.22-1.55]		p=0.27

Olivier et al. J Nucl Med 2022

PSMA PET-detectable nonlocalized disease may be a key driver of outcome

Significance of the **UCLA PSMA prediction nomogram** (and, by proxy, PSMA PET/CT itself) applied to a **multi-institutional cohort of 5275 high risk PCa patients** on long-term, clinically meaningful endpoints.



PSMA upstage *probability* is prognostic of all clinically meaningful endpoints

Results were validated in two large registry-based cohorts from the Surveillance, Epidemiology, and End Results database (SEER, n=23.989 patients) and the National Cancer Database (NCDB, n= 88.909 patients).

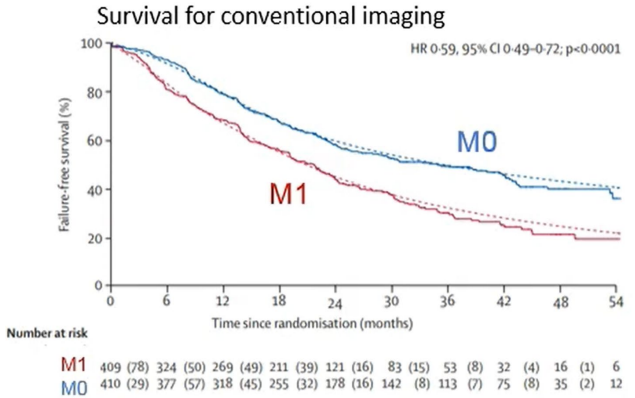
Ting MA, et al. Eur Urol Oncol 2021; Xiang et al. JAMA Netw Open 2021

THE STAGE MIGRATION

Need to raise the bar of evidence for next-generation imaging modalities

Conventional imaging (CT + bone scan)

No M disease M0 µM disease M1



Next generation imaging (PSMA PET/CT)

No M disease µM disease M1