Update on PSMA Theranostics

PET AUC & FDG in RPT Eligibility

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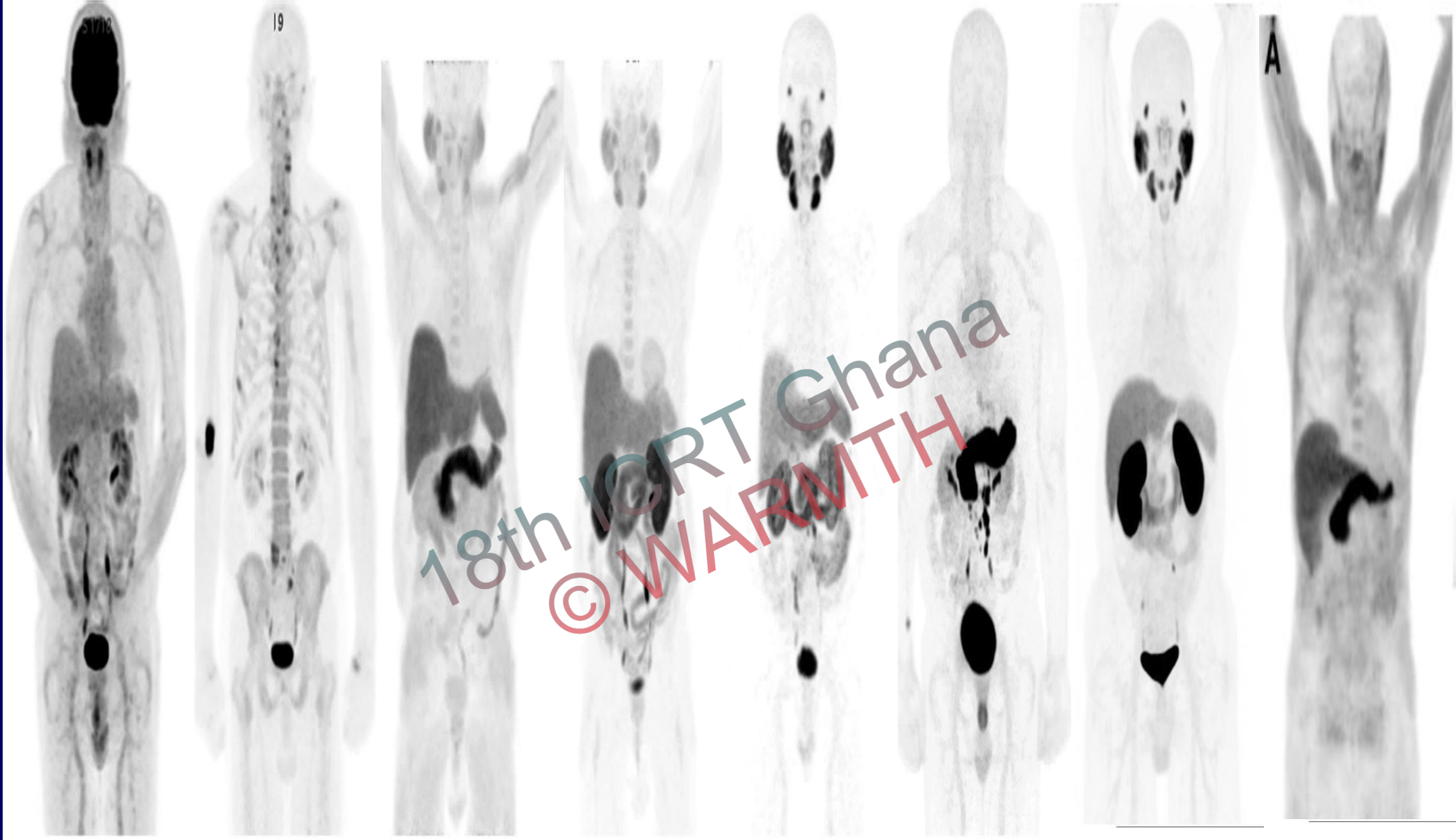


Approved
^{18}F FDG

Approved
^{18}F NaF

^{11}C Acetate

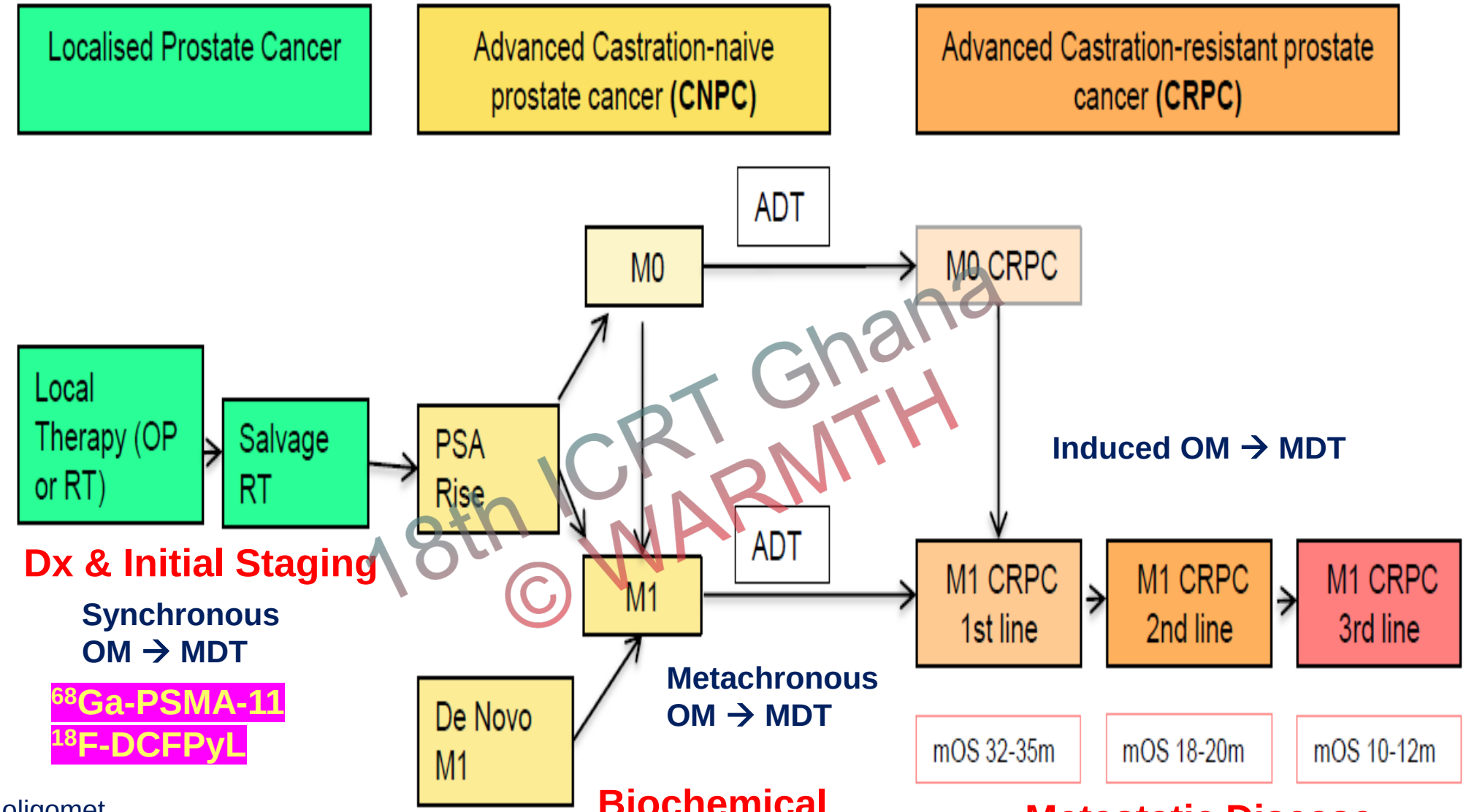
Approved
^{11}C Choline

Approved
^{68}Ga PSMA 11

^{68}Ga RM2

Approved
^{18}F-DCFPyL

Approved
^{18}F-fluciclovine

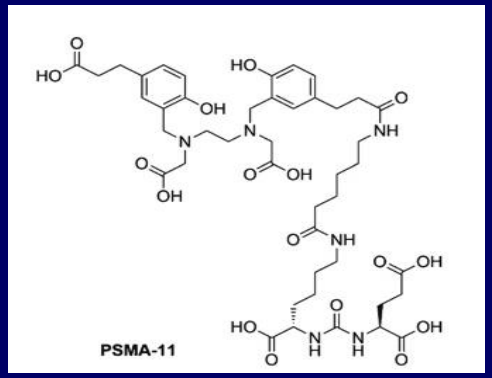


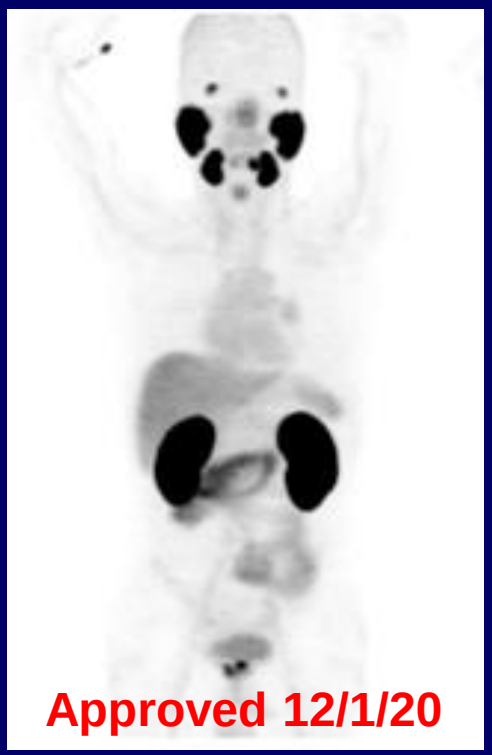
OM: oligomet.
MDT: met-directed Tx
ADT: Androgen deprivation
M0: no evidence of metastatic disease
M1: metastatic disease on imaging

Omlin, 2016 (adapted)

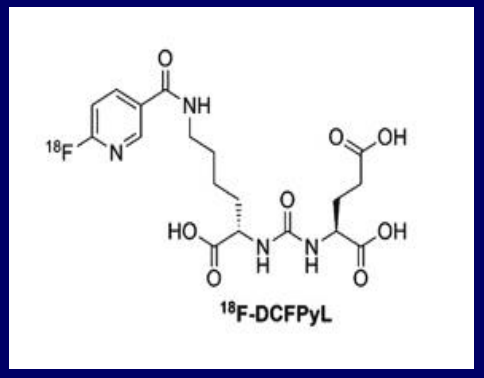
PSMA PET
Appropriate Use Criteria

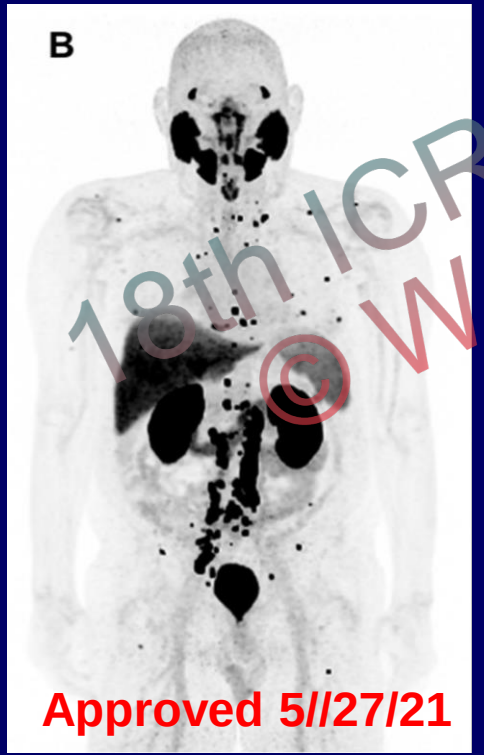
PSMA PET



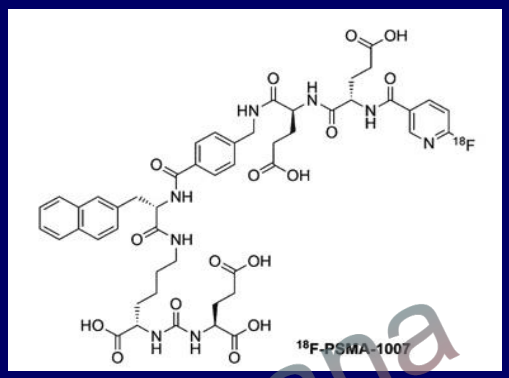


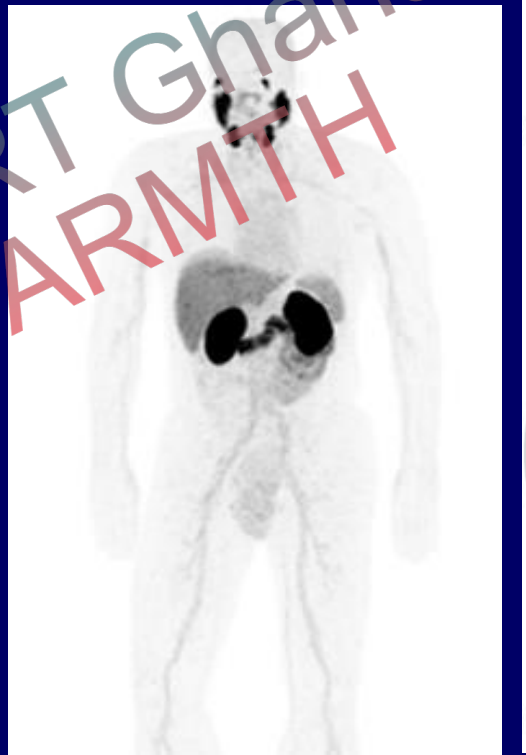
^{68}Ga-PSMA-11
(Locametz; Illuccix)



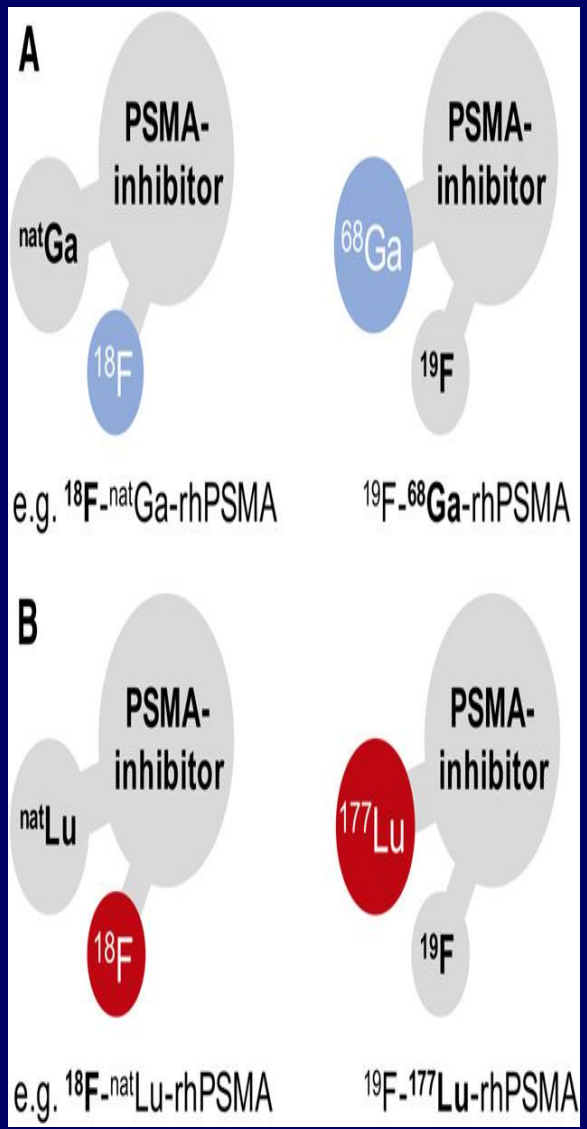


^{18}F-DCFPyL
(Pylarify)





^{18}F-PSMA-1007



^{18}F-rh-PSMA-7.3
(LIGHTHOUSE, SPOTLIGHT)

Jadvar,…..,Hope. J Nucl Med
January 2022

Appropriate Use Criteria for Prostate-Specific Membrane Antigen PET Imaging

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SNMMI, ACNM, ASCO, AUA, EANM, ACP, ANZSNM

NEWSLINE

Updates to Appropriate Use Criteria for PSMA PET

Thomas A. Hope, MD, University of California, San Francisco, CA; and Hossein Jadvar, MD, PhD, MPH, MBA, University of Southern California, Los Angeles, CA

As an indication of how quickly the field of nuclear medicine is advancing, the Appropriate Use Criteria (AUC) for Prostate-Specific Membrane Antigen (PSMA) PET document has been updated (*1*). This is due to the recent U.S. Food and Drug Administration (FDA) approval of ^{177}Lu-PSMA-617 (Pluvicto, ^{177}Lu-vipivotide tetraxetan; Novartis [Basel, Switzerland]/Advanced Accelerator Applications USA, Inc. [Millburn, NJ]) radiopharmaceutical therapy (RPT). Previously the AUC had scored the indication for a posttreatment prostate-specific antigen (PSA) rise in the metastatic castration-resistant prostate cancer (mCRPC) setting as "may be appropriate." This was because no available PSMA-targeted therapies would benefit from imaging using PSMA PET. With the approval of PSMA RPT, the PSMA PET AUC Working Group has split this indication into 2 distinct indications (see supplemental materials, available at http://ow.ly/ABfv30sh3uO). The first is "Posttreatment PSA rise in the mCRPC setting in a patient not being considered for PSMA-targeted radiopharmaceutical therapy," which was again scored as "may be appropriate," because the clinical value of improved tumor localization in grossly metastatic disease is not clear in patients who are not being considered as candidates for PSMA RPT. The second indication is "Evaluation of eligibility for patients being considered for PSMA-targeted radiopharmaceutical therapy," which was scored as "appropriate" given the availability of a PSMA-targeted therapy.

An important point is that the AUC Working Group agreed that both ^{18}F-DCFPyL (Pylarify, ^{18}F-piflufolastat; Lantheus [Billerica, MA]) and ^{68}Ga-PSMA-11 (Illuccix and Locametz, ^{68}Ga-gozetotide; Telix Pharmaceuticals Ltd. [Melbourne, Australia], and Novartis/AAA, respectively) should be considered equivalent for selection of patients for treatment with ^{177}Lu-PSMA-617. In the prescribing information for ^{177}Lu-PSMA-617, the FDA recommended selection of "patients for treatment using Locametz or an approved PSMA-11 imaging agent based on PSMA expression in tumors." However, given the near equivalency of ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL, either of these radiotracers can be used for patient selection.

Another consideration for patient selection is what cutoff should make a patient eligible. Two randomized trials have evaluated ^{177}Lu-PSMA-617 therapy: the VISION and TheraP trials. Optimal PSMA PET criteria for patient selection are not yet well established. In the VISION trial, eligibility required uptake in disease greater than that in the liver, and no measurable disease with uptake less than that in the liver (*2*). Eligibility in the TheraP study required an SUV ≥20 at 1 site of disease, an SUV ≥10 at measurable soft tissue sites, and no ^{18}F-FDG–positive PSMA-negative sites of disease (*3*). It should be noted that, in general, the higher the uptake on PSMA PET, the better patients respond to treatment (*4,5*). PSMA PET is not only a prognostic biomarker but was shown to be predictive in the TheraP trial, with patients who had an SUV_{mean} ≥10 having a higher likelihood of PSA response compared to chemotherapy (cabazitaxel) (*6*). Although the decision in the VISION trial was binary, uptake may be used to help weigh various treatment options. The debate as to whether ^{18}F-FDG PET/CT should also be used to screen patients prior to PSMA RPT is outside of the scope of the PSMA PET AUC, although ^{18}F-FDG PET may provide additional value in identifying ^{18}F-FDG–positive/PSMA-negative sites of disease (*3*).

PSMA PET plays a significant role in the appropriate selection of patients for PSMA RPT. With the approval and availability of 2 PSMA PET agents, this imaging study should be widely available. Overall, these 2 imaging agents are considered equivalent for patient selection.

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Hope & Jadvar. J Nucl Med
May 2022

Table 2

Clinical Scenarios for PSMA PET

Scenario no.	Description	Appropriateness	Score
1	Patients with suspected prostate cancer (e.g., high/rising PSA levels, abnormal digital rectal examination results) evaluated for targeted biopsy and detection of intraprostatic tumor	Rarely appropriate	3
2	Patients with very low, low, and favorable intermediate-risk prostate cancer	Rarely appropriate	2
3	Newly diagnosed unfavorable intermediate, high-risk, or very high-risk prostate cancer	Appropriate	8
4	Newly diagnosed unfavorable intermediate, high-risk, or very high-risk prostate cancer with negative/equivocal or oligometastatic disease on conventional imaging	Appropriate	8
5	Newly diagnosed prostate cancer with widespread metastatic disease on conventional imaging	May be appropriate	4
6	PSA persistence or PSA rise from undetectable level after radical prostatectomy	Appropriate	9
7	PSA rise above nadir after definitive radiotherapy	Appropriate	9
8	PSA rise after focal therapy of the primary tumor	May be appropriate	5
9	nmCRPC (M0) on conventional imaging	Appropriate	7
10	Posttreatment PSA rise in the mCRPC setting in a patient not being considered for PSMA-targeted radioligand therapy	May be appropriate	5
11	Evaluation of eligibility for patients being considered for PSMA-targeted radioligand therapy	Appropriate	9
12	Evaluation of response to therapy	May be appropriate	5

PSMA PET AUC
Initial Staging

- *Scenario 1: Patients with suspected prostate cancer to evaluate for targeted biopsy and detection of intraprostatic tumor (Score 3 – Rarely Appropriate)*
  - Limited evidence; PSMA expression heterogeneous and may be negative in both primary tumor and metastases (5-10%)
  - May be considered when mpMRI is inconclusive (~13% miss rate for csPC) or prior biopsy results are negative
  - **PRIMARY:** multicenter prospective phase II imaging trial (n=296) to provide evidence on added value of PSMA PET to mpMRI for detecting csPC (ISUP≥2) and reduction in unnecessary bx – Emmett, Eur Eurol 2021
    - PSMA PET+mpMRI improved sensitivity over mpMRI alone (97% v. 83%, p<0.001) at cost of reduced specificity (40% v. 53%, p=0.011)
    - 19% with neg. PSMA PET+mpMRI could avoid bx at risk of delaying csPC detection in 3.1%

PSMA PET AUC
Initial Staging

- *Scenario 2: Patients with very low, low, and favorable intermediate-risk prostate cancer (Score 2 – Rarely Appropriate)*
  - NCCN guidelines risk stratification
  - Imaging generally not indicated
  - Initial management often observation or active surveillance
  - Paucity of evidence, morbidity and financial cost associated with screening for clinically insignificant prostate cancer

PSMA PET AUC
Initial Staging

- *Scenario 3: Newly diagnosed unfavorable intermediate-, high-, or very high-risk prostate cancer (Score 8 – Appropriate)*
  - NCCN guidelines risk stratification
  - Supportive evidence for PSMA PET as more informative than conventional imaging
  - **proPSMA:** ^{68}Ga-PSMA-11, randomized trial comparing PSMA PET and CI for staging high-risk prostate cancer - Hofman, Lancet 2020
    - PSMA > CI -- accuracy, impact
    - PSMA < CI -- equivocal findings, radiation, cost
  - **OSPREY:** ^{18}F-DCFPyL, Cohort A, high-risk, pelvic LN involvement: specificity 97.9%,sensitivity 40.3% - Pienta, J Urol 2021

PSMA PET AUC
Initial Staging

- *Scenario 4: Newly diagnosed unfavorable intermediate-, high-, or very high-risk prostate cancer with negative/equivocal or oligometastatic disease on conventional imaging (Score 8 – Appropriate)*
  - NCCN guidelines risk stratification
  - Some clinicians may continue to use CI initially; will take time before adoption of PSMA PET
  - PSMA PET may identify sites of disease not detected on CI including oligometastatic disease amenable to MDT
  - Oligometastatic disease on CI may be polymetastatic disease on PSMA PET

PSMA PET AUC
Initial Staging

- *Scenario 5: Newly diagnosed prostate cancer with widespread metastatic disease on conventional imaging (Score 4 – May Be Appropriate)*
  - Little evidence that PSMA PET adds additional value or have management impact
  - Until approval of PSMA RLT, scored as “may be appropriate”

PSMA PET AUC
Biochemical Recurrence

- *Scenario 6: PSA persistence or PSA rise from undetectable level after radical prostatectomy (Score 9 – Appropriate)*
  - Supportive evidence with impact on clinical management
    - Calais, Lancet Oncol 2019 (^{18}F-Fluciclovine vs. ^{68}Ga-PSMA-11)
    - Fendler, JAMA Oncol 2019 (^{68}Ga-PSMA-11)
    - **CONDOR:** ^{18}F-DCFPyL, phase 3, uninformative CI, 49.5% post-RP - Morris, Clin Cancer Res 2021
    - **OSPREY:** ^{18}F-DCFPyL, Cohort B - Pienta, J Urol 2021
  - Trials underway whether change in management improves patient outcome
    - **PSMA-SRT:** randomized phase 3, PSMA- vs. CI-guided salvage RT planning for recurrent prostate cancer - Calais, Eur Urol Focus 2021
  - *No PSA threshold defined*; other risk factors; disease detection & salvage Rx below AUA definition of BCR

PSMA PET AUC
Biochemical Recurrence

- *Scenario 7: PSA rise above nadir after definitive radiotherapy (Score 9 – Appropriate)*
  - Supportive evidence with impact on clinical management similar to Scenario 6
  - Panel consensus not to limit utility of PSMA PET to only BCR defined by ASTRO-Phoenix criteria
  - Treatment often occurs before BCR threshold
  - Other factors than PSA may play role (e.g., PSADT)

PSMA PET AUC
Biochemical Recurrence

- *Scenario 8: PSA rise after focal therapy of primary tumor (Score 5 – May Be Appropriate)*
  - Scarce data
  - Unclear definition of BCR after focal therapy
  - Focal therapy often used in low-grade primary tumor
  - Refer to Scenario 2

PSMA PET AUC
Castration-Resistant Prostate Cancer

- *Scenario 9: nmCRPC (M0) on conventional imaging (Score 7 – Appropriate)*
  - M0 on CI is often positive on PSMA PET
  - All drugs approved for M0 CRPC space are also approved for metastatic setting
  - Oligometastatic disease may be amenable to MDT with some supportive data on effectiveness
    - **STOMP:** choline, observation vs. MDT - Ost, J Clin Oncol 2018
    - **POPSTAR:** ^{18}F-NaF, 48% ADT-free surv. with MDT - Siva, Eur Urol 2018
    - **ORIOLE:** PSMA, 95% 6-mo PFS vs. 62% with CI-guided MDT - Phillips, JAMA Oncol 2020

PSMA PET AUC
Castration-Resistant Prostate Cancer

- *Scenario 10: Posttreatment PSA rise in the mCRPC setting in a patient not being considered for PSMA-targeted radioligand therapy (Score 6 – May Be Appropriate)*
  - Unclear how improved staging with PSMA PET over CI improves management of patients with mCRPC
  - PSMA RLT combination therapy may still have a role in individual patients

PSMA PET AUC
Castration-Resistant Prostate Cancer

- *Scenario 11: Evaluation of eligibility for patients being considered for PSMA-targeted radioligand therapy (Score 9 – Appropriate*)
  - **LuPSMA:** PSA50 of 57% - Hofman, Lancet Oncol 2018
  - **TheraP:** PSMA RLT vs. cabazitaxel - Hofman, Lancet 2021
    - higher PSA50, longer PFS, fewer Gr 3/4 AEs than cabazitaxel
  - **VISION:** PSMA RLT vs. BSC - Sartor, NEJNM 2021
    - rPFS: 8.7 m vs. 3.4 m (HR 0.40)
    - OS: 15.3 vs. 11.3 m (HR 0.62)
    - FDA approval of ^{177}Lu-vipivotide tetraxetan *(Pluvicto)*

PSMA PET AUC
Castration-Resistant Prostate Cancer

- *Scenario 12: Evaluation of response to therapy (Score 5 – May Be Appropriate)*
  - Limited data and not validated in clinical trials
  - Androgen axis targeting drugs may affect PSMA expression which may not correlate with response
  - Effect of various other current and emerging therapies on PSMA expression needs additional studies
  - May be useful in PSMA RLT response assessment

PSMA Radiopharmaceutical Therapy

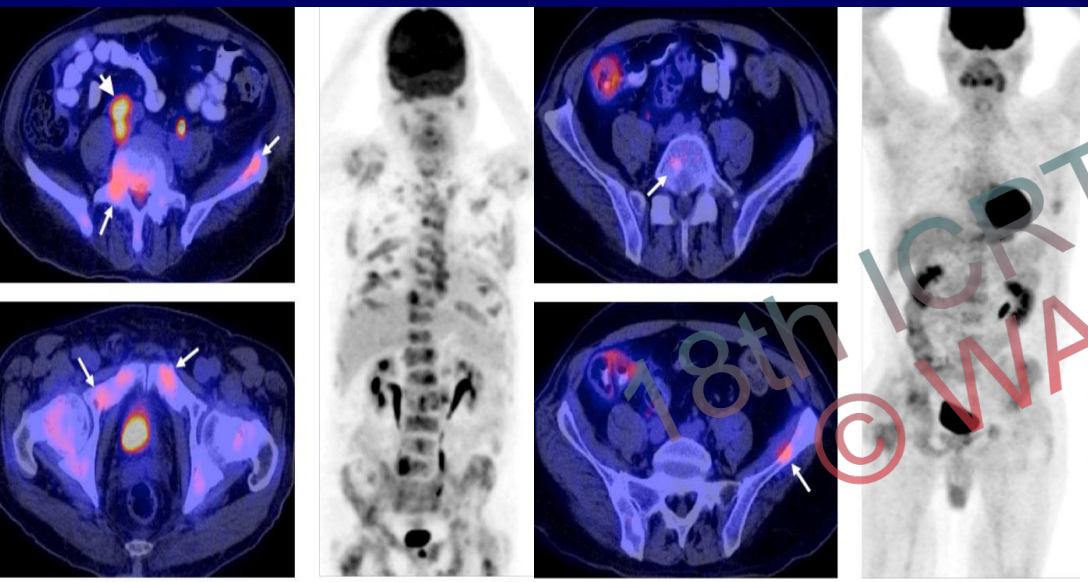
Role of FDG

Metastatic Castrate-Sensitive Prostate Cancer

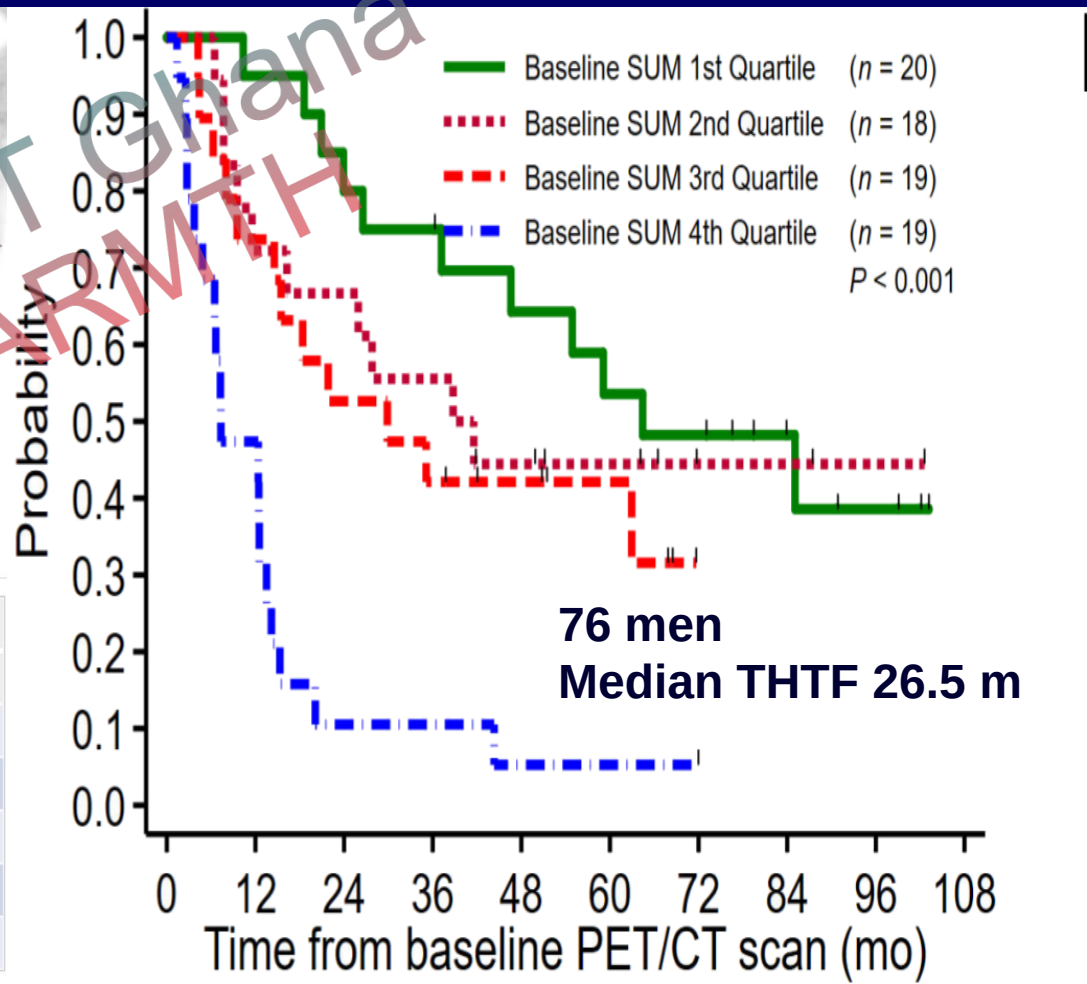
Sum of SUVmax (SUM) as Predictor of THTF (time to change from ADT to chemoRx or death)

Jadvar, JNM 2019

NIH R01-CA111613



PSA (ng/mL)	296.2	PSA (ng/mL)	489
Avg liver SUV	1.5	Avg liver SUV	1.6
Sum	89.9	Sum	12.9
Max	6.5	Max	2.4
Avg	3	Avg	1.4
No. of lesions	30	No. of lesions	9
THTF (mo)	1.3	THTF (mo)	None at 108 mo

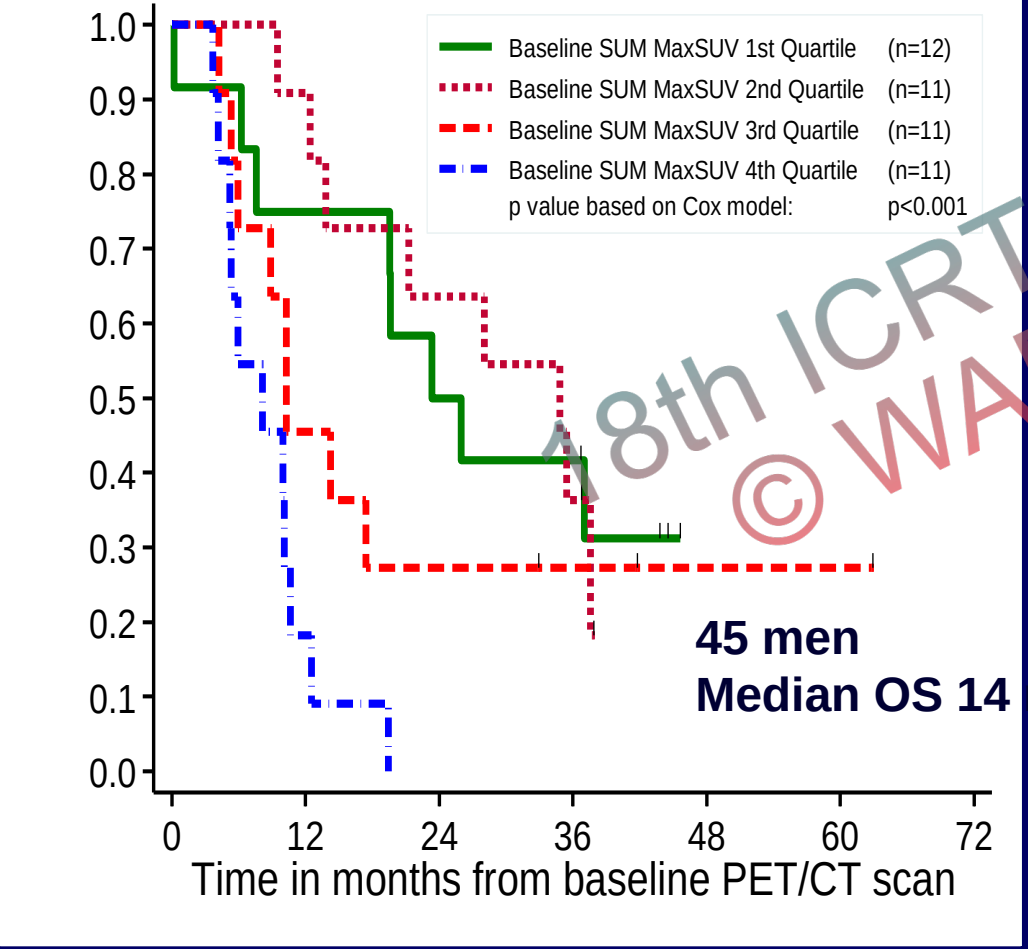


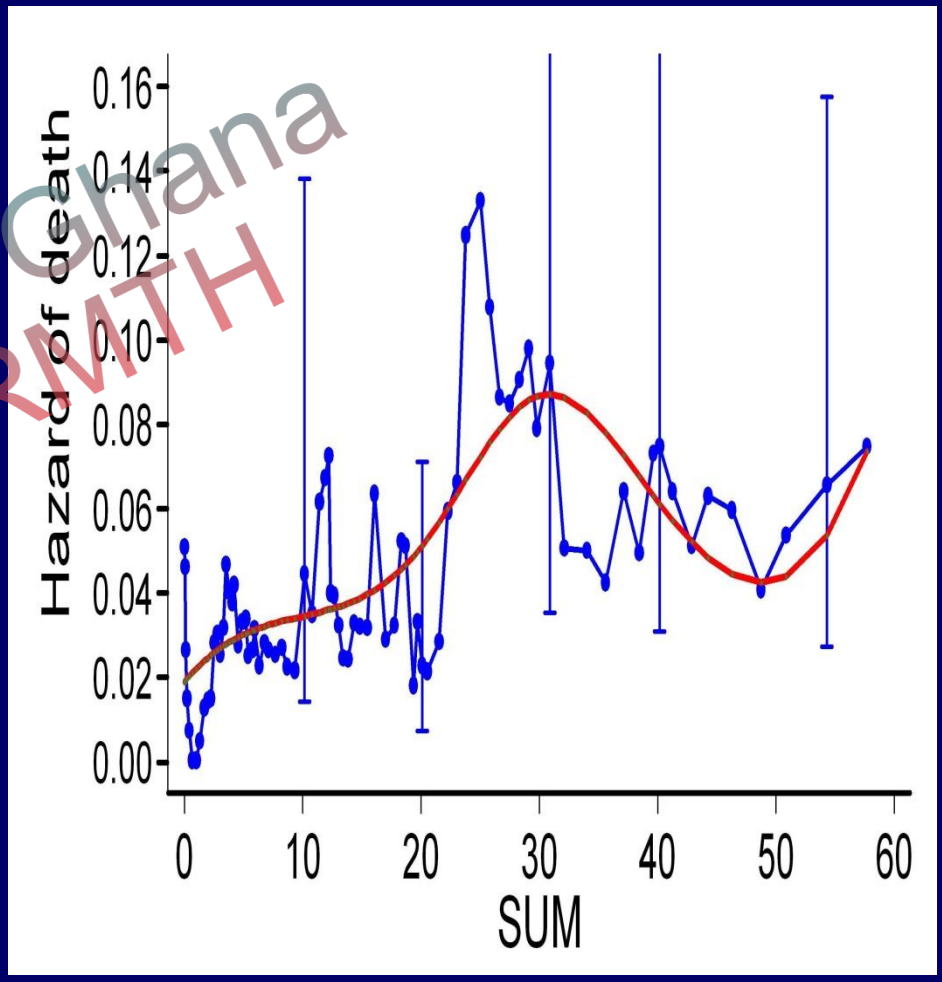
Metastatic Castrate-Resistant Prostate Cancer

Sum of SUVmax (SUM) as Predictor of OS

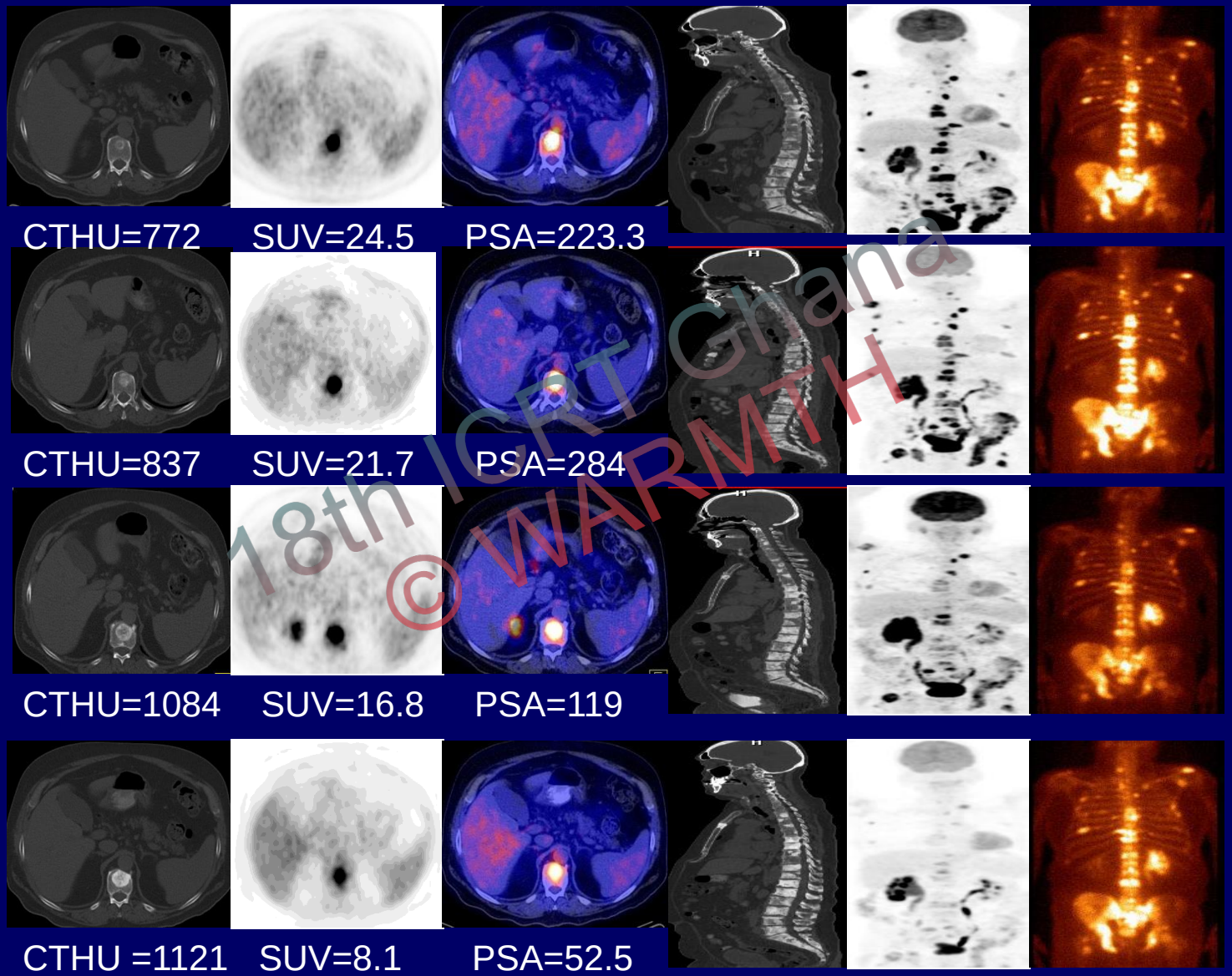
Jadvar, JNM 2013

NIH R01-CA111613





FDG PET/CT in mCRPC: Treatment Response Evaluation



NIH R01-CA111613

USC Norris Comprehensive Cancer Center

Jadvar, JNM 2013

IVYSPRING INTERNATIONAL PUBLISHER

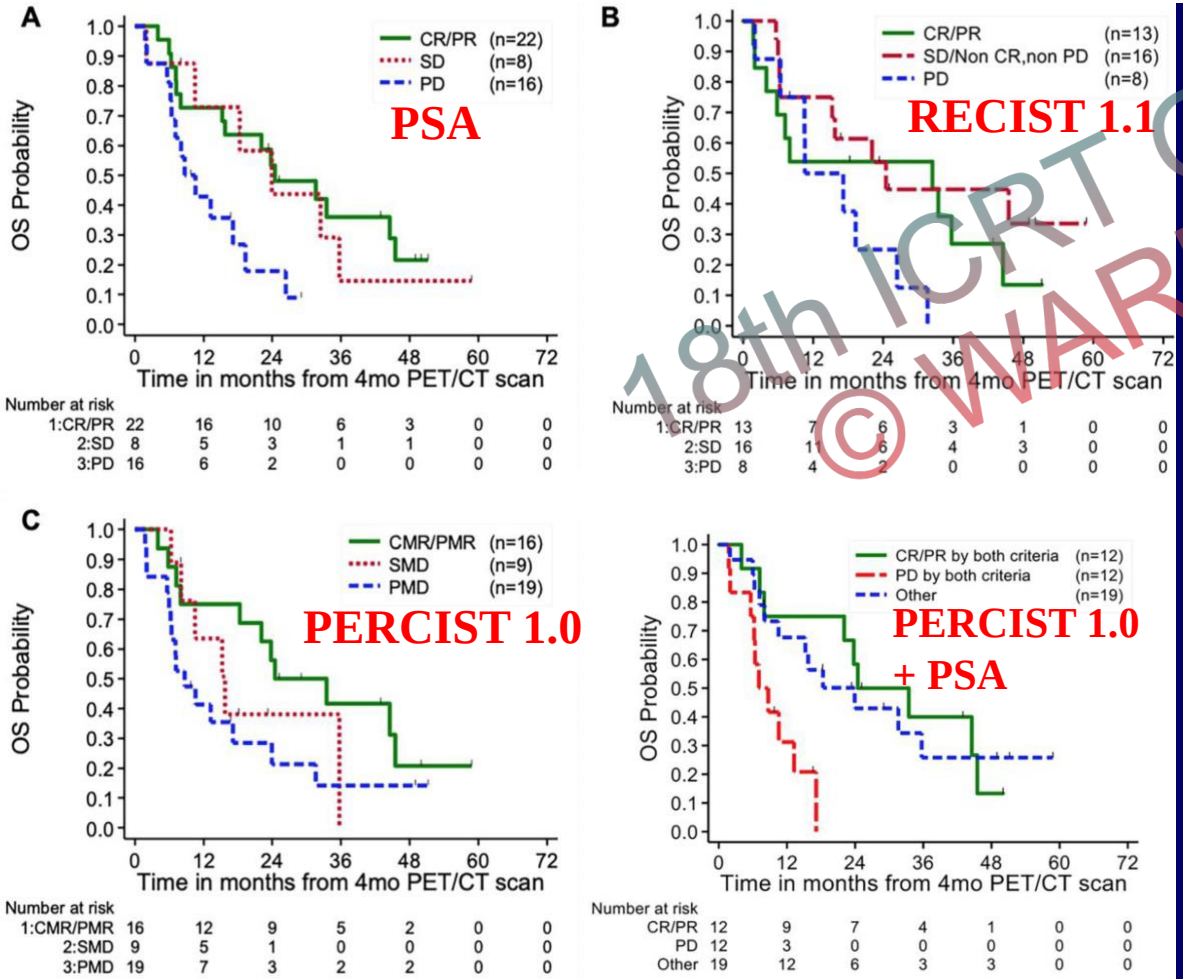
Theranostics

2020; 10(7): 3254-3262. doi: 10.7150/thno.39838

Research Paper

Comparative prognostic implication of treatment response assessments in mCRPC: PERCIST 1.0, RECIST 1.1, and PSA response criteria

Erik M. Velez[1], Bhushan Desai[1], Lingyun Ji[2], David I. Quinn[3], Patrick M. Colletti[1], Hossein Jadvar[1]✉



47 mCRPC pts; FDG PET/CT at baseline & 4-m post-chemoRx

Pts with progressive disease by both PERICST 1.0 and PSA response criteria had significantly worse OS (12-m OS: 31% ± 14%) compared to pts with progressive disease by either response criteria alone

Velez…Jadvar, *Theranostics* 2020

NIH R01-CA111613

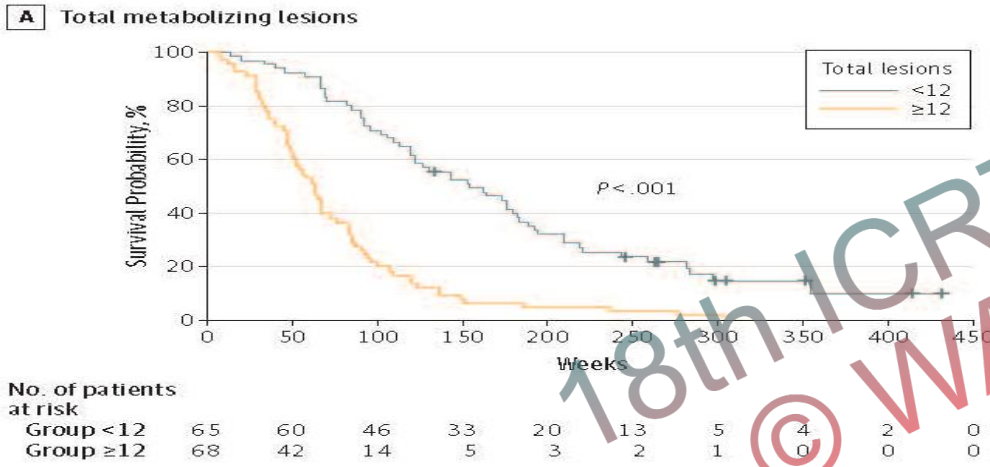
JAMA Oncology | Original Investigation

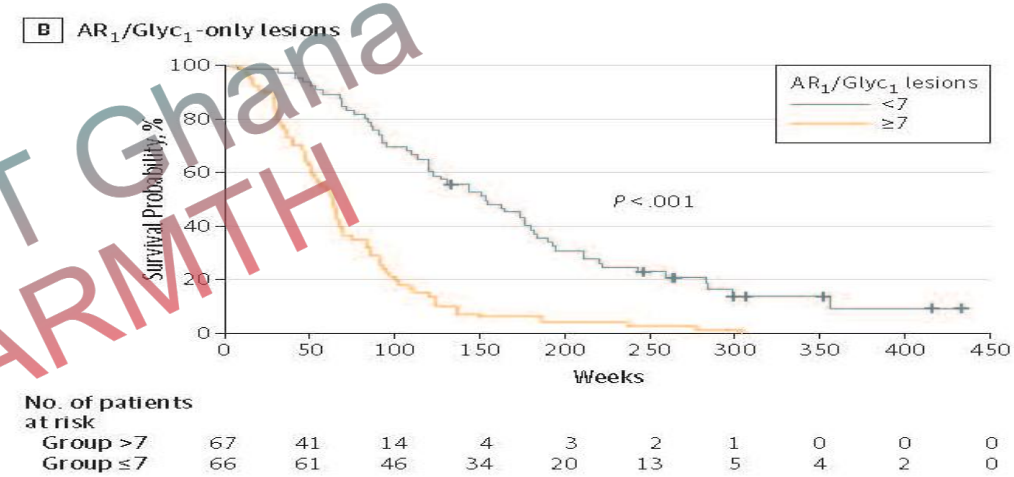
JAMA Oncol 2017

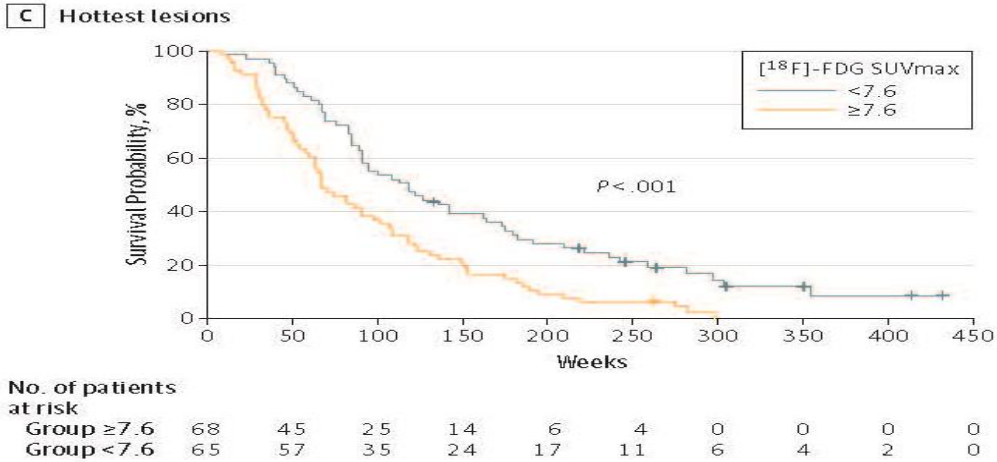
Positron Emission Tomography/Computed Tomography–Based Assessments of Androgen Receptor Expression and Glycolytic Activity as a Prognostic Biomarker for Metastatic Castration-Resistant Prostate Cancer

Josef J. Fox, MD; Somali C. Gavane, MD; Estelle Blanc-Autran, MD; Sadek Nehmeh, PhD; Mithat Gönen, PhD; Brad Beattie, MS; Hebert A. Vargas, MD; Heiko Schöder, MD; John L. Humm, PhD; Samson W. Fine, MD; Jason S. Lewis, PhD; Stephen B. Solomon, MD; Joseph R. Osborne, MD, PhD; Darren Veach, PhD; Charles L. Sawyers, MD; Wolfgang A. Weber, MD; Howard I. Scher, MD; Michael J. Morris, MD; Steven M. Larson, MD

Figure 3. Correlations With Overall Survival of 133 Patients







Concordant: AR1Glyc1 (26%)
AR-predominant: AR1Glyc1+AR1Glyc0 (25%)
Glyc-predominant: AR1Glyc1+AR0Glyc1 (30%)
Mixed: AR1Glyc1+AR1Glyc0+AR0Glyc1 (19%)

Additional risk of death w/ each additional lesion: AR0Glyc1 (11%), AR1Glyc1 (5%), AR1Glyc0 (3%),

FDG+FDHT

mCRPC Tumor Heterogeneity (PSMA-/FDG+)

- 22% concordance between ^{18}F-DCFPyL and FDG (Fourquet, JNM 2021)
- PSMA-/FDG+ associated with significantly shorter OS (Khreish, Cancers 2021, Michalski, EJNMMI 2021)
- LuPSMA trial ineligible patients with PSMA-/FDG+ mets had poor OS of 2.5 m despite additional systemic therapy (Thang, Eur Urol Oncol 2019)
- 13% patients with new PSMA-/FDG+ mets after 2 LuPSMA cycles (Hartrampf, Cancers 2021)

Prediction of Discordant (PSMA-/FDG+) mCRPC

- 23.2% total discordance between ^{68}Ga-PSMA-11 & FDG (Chen, JNM 2021)
  - GS<8 & PSA<7.9 ng/mL → No mismatch
  - GS<8 & PSA>7.9 ng/mL → 21.7% mismatch
  - GS>8 & PSA>7.9 ng/mL → 61.5% mismatch
- Liquid biopsy
  - Neuron-specific enolase (Rosar, EJNMMI Res 2020)
  - LDH, ALP (Ferdinadus, EJNMMI 2020)

[^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study

Michael S Hofman, John Violet*, Rodney J Hicks, Justin Ferdinandus, Sue Ping Thang, Tim Akhurst, Amir Iravani, Grace Kong, Aravind Ravi Kumar, Declan G Murphy, Peter Eu, Price Jackson, Mark Scalzo, Scott G Williams, Shahneen Sandhu*

LuPSMA

Lancet Oncol 2018

- 30 men mCRPC
- Prior Rx: 87% chemo, 83% ADT
- **PSMA+ / FDG-**
- RLT: 7.5 GBq/cycle x 4 cycles q6w
  - 1 (100%), 2 (93%), 3 (80%), 4 (47%)
- **PSA50 -- 57% of patients**
- 82% objective response
- 37% improvement in global health

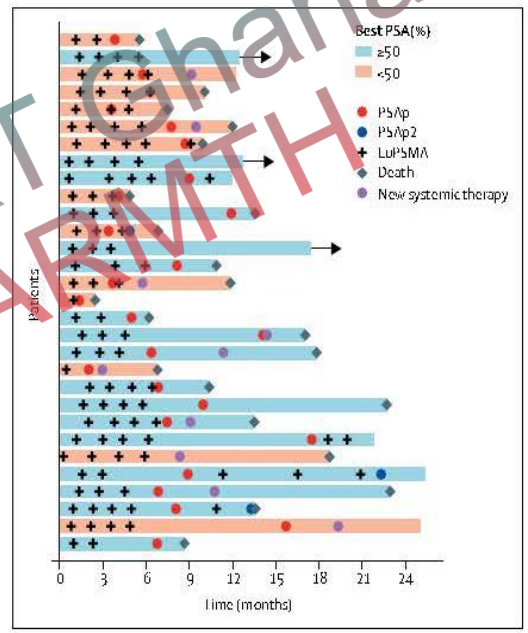


Figure 2: **Patient events**
Arrow indicates patients without PSA progression up to cut-off date. PSA=prostate-specific antigen. LuPSMA=lutetium-prostate-specific membrane antigen. PSAp2=second-PSA progression in patients with initial response who progressed after trial completion and responded to further LuPSMA.

study was sponsored by the Peter MacCallum Cancer Centre (Melbourne, Australia). All authors had full access to all of the data. The corresponding author takes final responsibility for the analysis and decision to submit for publication.

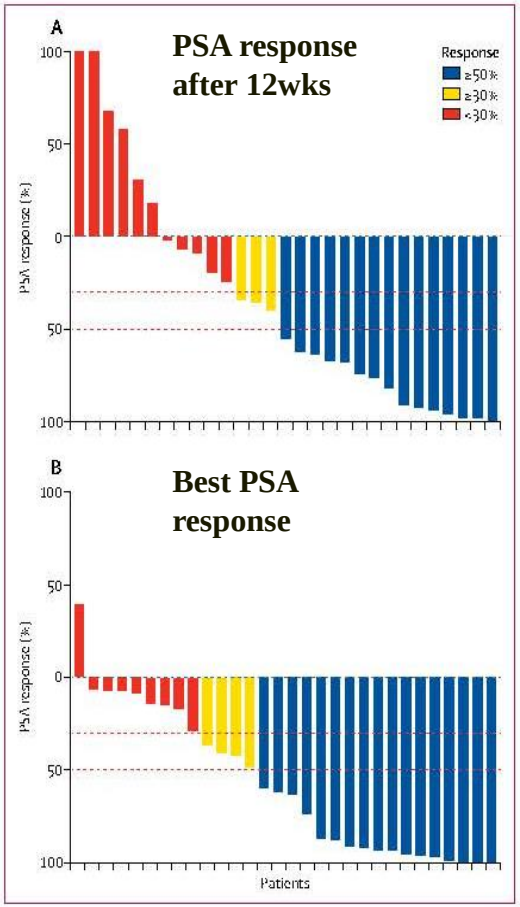


Figure 3: (A) PSA response after 12 weeks* and (B) best PSA response from

[^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

TheraP

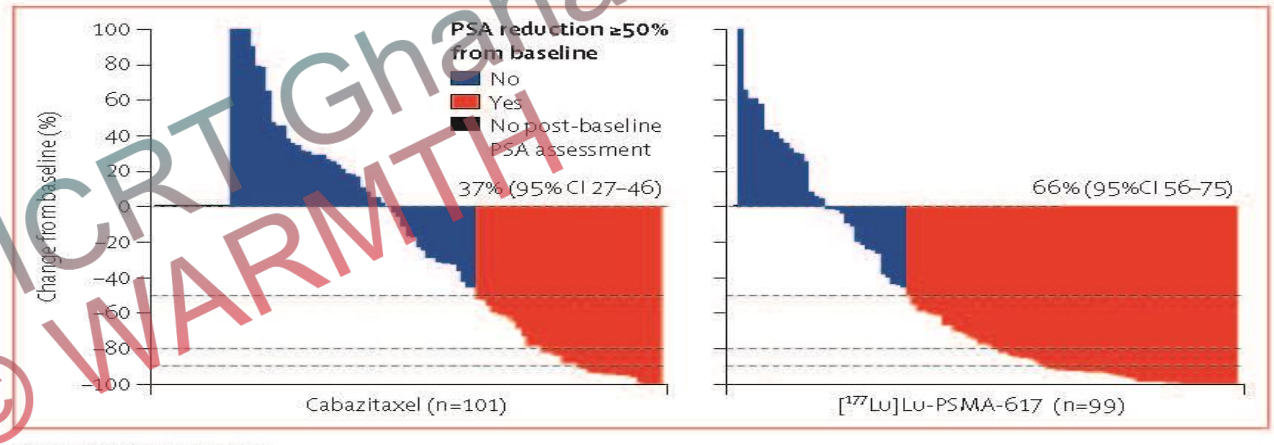
Lancet 2021

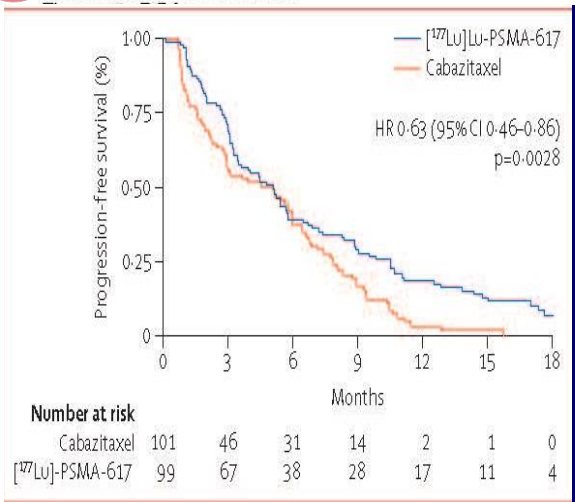
Michael S Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Roslyn J Francis, Craig Gedye, Natalie K Rutherford, Andrew Weickhardt, Andrew M Scott, Sze-Ting Lee, Edmond M Kwan, Arun A Azad, Shakher Ramdave, Andrew D Redfern, William Macdonald, Alex Guminski, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McJannett, Martin R Stockler, John A Violet, Scott G Williams, Andrew J Martin, Ian D Davis, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†*

	[^{177}Lu]Lu-PSMA-617 (n=98)		Cabazitaxel (n=85)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Fatigue	69 (70%)	5 (5%)	61 (72%)	3 (4%)
Pain*	60 (61%)	11 (11%)	52 (61%)	4 (5%)
Dry mouth	59 (60%)	0	18 (21%)	0
Diarrhoea	18 (18%)	1 (1%)	44 (52%)	4 (5%)
Nausea	39 (40%)	1 (1%)	29 (34%)	0
Thrombocytopenia	18 (18%)	11 (11%)	4 (5%)	0
Dry eyes	29 (30%)	0	3 (4%)	0
Anaemia	19 (19%)	8 (8%)	11 (13%)	7 (8%)
Neuropathy†	10 (10%)	0	22 (26%)	1 (1%)
Dysgeusia	12 (12%)	0	23 (27%)	0
Haematuria	3 (3%)	1 (1%)	12 (14%)	5 (6%)
Neutropenia‡	7 (7%)	4 (4%)	4 (5%)	11 (13%)
Insomnia	9 (9%)	0	12 (14%)	1 (1%)
Vomiting	12 (12%)	1 (1%)	10 (12%)	2 (2%)
Dizziness	4 (4%)	0	11 (13%)	0
Leukopenia	10 (10%)	1 (1%)	5 (6%)	1 (1%)
Any adverse event	53 (54%)	32 (33%)	34 (40%)	45 (53%)

Data are n (%). Events that occurred in at least 10% of participants are shown. ^{177}Lu=Lutetium-177. PSMA=prostate-specific membrane antigen. *Including bone, buttock, chest wall, flank, neck, extremity, tumour pain, or pelvic pain. †Motor or sensory. ‡Febrile neutropenia.

Table 2: Adverse events





-N: CBZ (85), Lu (98)

-No FDG+/PSMA - (28%)

-PSA50:

(CBZ 44% < Lu 66%)

-Gr. 3/4 AE (no xerostomia)

(CBZ 53% > Lu 33%)

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

TheraP

Lancet Oncol 2022

*James P Buteau, Andrew J Martin, Louise Emmett, Amir Iravani, Shahneen Sandhu, Anthony M Joshua, Roslyn J Francis, Alison Y Zhang, Andrew M Scott, Sze-Ting Lee, Arun A Azad, Margaret M McJannett, Martin R Stockler, Scott G Williams, Ian D Davis, Michael S Hofman, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group**

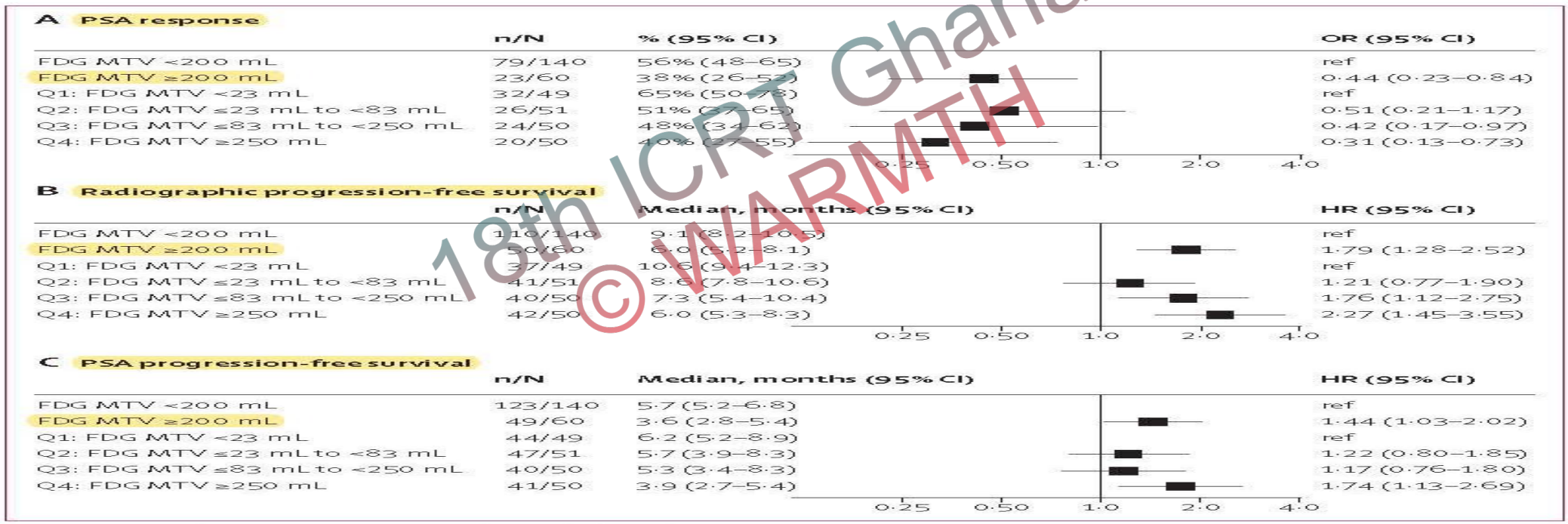


Figure 4: Post-hoc sensitivity analyses of clinical outcomes according to FDG-PET MTV

- WB PSMA PET SUVmean (< or ≥ 10): predictive of response to Lu-PSMA
- WB FDG PET MTV (< or ≥ 200 ml): prognostic of outcome regardless of Rx

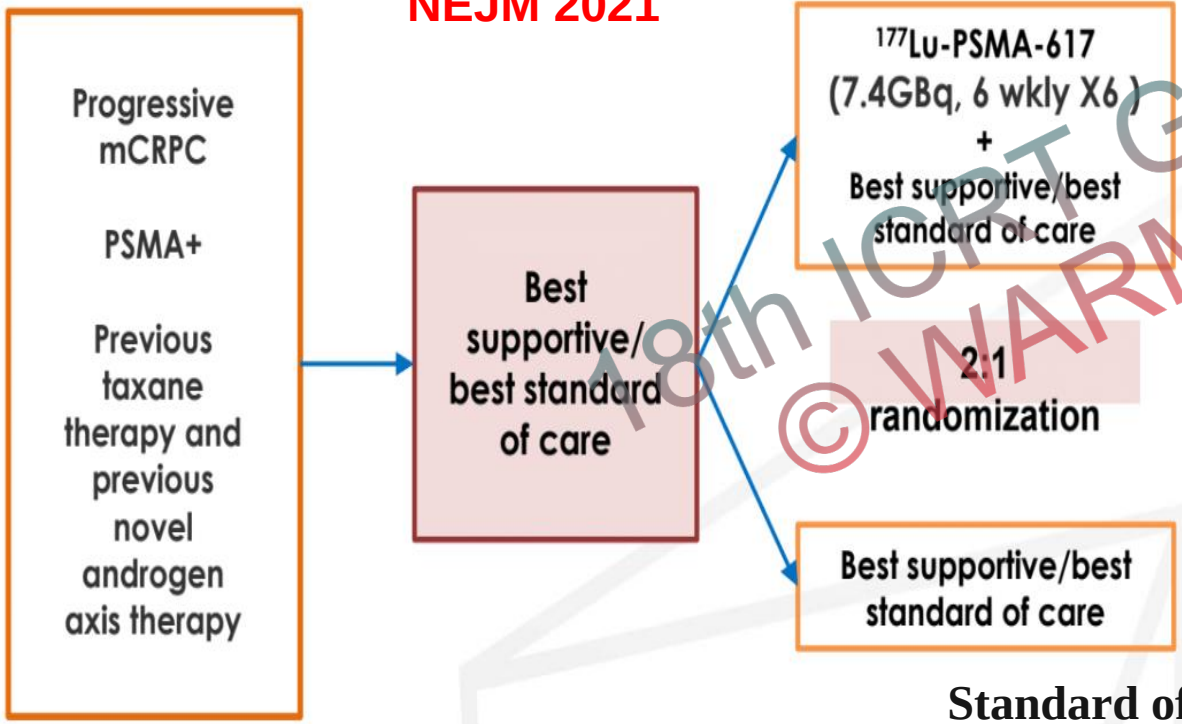
VISION Trial: ^{177}Lu-PSMA versus best supportive care

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

Oliver Sartor, M.D., Johann de Bono, M.B., Ch.B., Ph.D., Kim N. Chi, M.D., Karim Fizazi, M.D., Ph.D., Ken Herrmann, M.D., Kambiz Rahbar, M.D., Scott T. Tagawa, M.D., Luke T. Nordquist, M.D., Nitin Vaishampayan, M.D., Ghassan El-Haddad, M.D., Chandler H. Park, M.D., Tomasz M. Beer, M.D., Alison Armour, M.B., Ch.B., M.D., Wendy J. Pérez-Contreras, M.P.A., Michelle DeSilvio, Ph.D., Euloge Kpamegan, Ph.D., Germo Gericke, M.D., Ph.D., Richard A. Messmann, M.D., M.H.S., Michael J. Morris, M.D., and Bernd J. Krause, M.D. et al., for the VISION Investigators*

NEJM 2021

- **40% decline in risk of death**
- **60% decline in radiographic progression**
- **4-m OS benefit; 5.3-m rPFS benefit**
- **More side effects but low grade and manageable**



Primary Endpoint
- Overall survival

Key Secondary Endpoints
- Radiographic progression-free survival (rPFS)
- RECIST response
- Time to first symptomatic skeletal event (SSE)

- 9 Countries (NA and EU)
- >750 patients recruited
- 12-14 months FU min 15 month

Standard of Care:
NOT ALLOWED - chemo, Ra, immunoRx, investigational drugs
ALLOWED: ADT, bone-directed Rx, palliative XRT

Endocyte/Novartis
NCT03511664

Characterization of PSMA-/FDG+ mCRPC

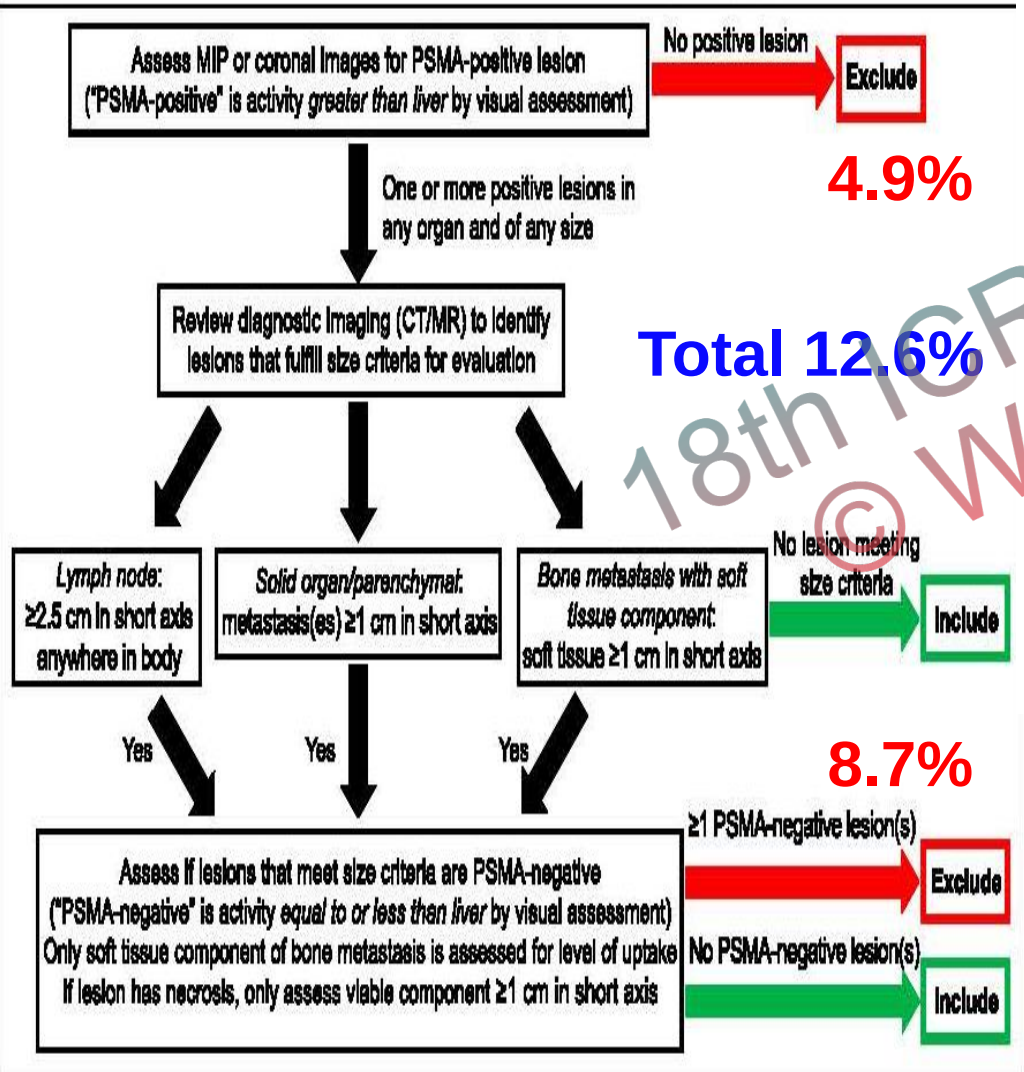
- **LuPSMA trial** (Hofman, Lancet Oncol 2018)
  - PSMA+: met SUVmax >1.5 x liver SUVmean
  - No PSMA-/FDG+ → **excluded 16%**
- **TheraP trial** (Hofman, Lancet 2021)
  - PSMA+: met SUVmax > 20 & >10 at all measurable met sites
  - No PSMA-/FDG+ → **excluded 28%**
  - WB PSMA PET SUVmean (< or ≥ 10): predictive of PSA response to Lu-PSMA
  - WB FDG PET MTV (< or ≥ 200 ml): prognostic of outcome (rPFS) irrespective of Rx
- **VISION trial** (Sartor, NEJM 2021)
  - PSMA+: at least 1 met uptake > liver for any size/organ
  - No PSMA-: uptake ≤ liver in measurable lesions on dCT
    - LN SA ≥ 2.5 cm, organ lesion ≥ 1.0 cm, bone with ST component ≥ 1.0 cm
  - No FDG PET/CT → **excluded 12.6%**

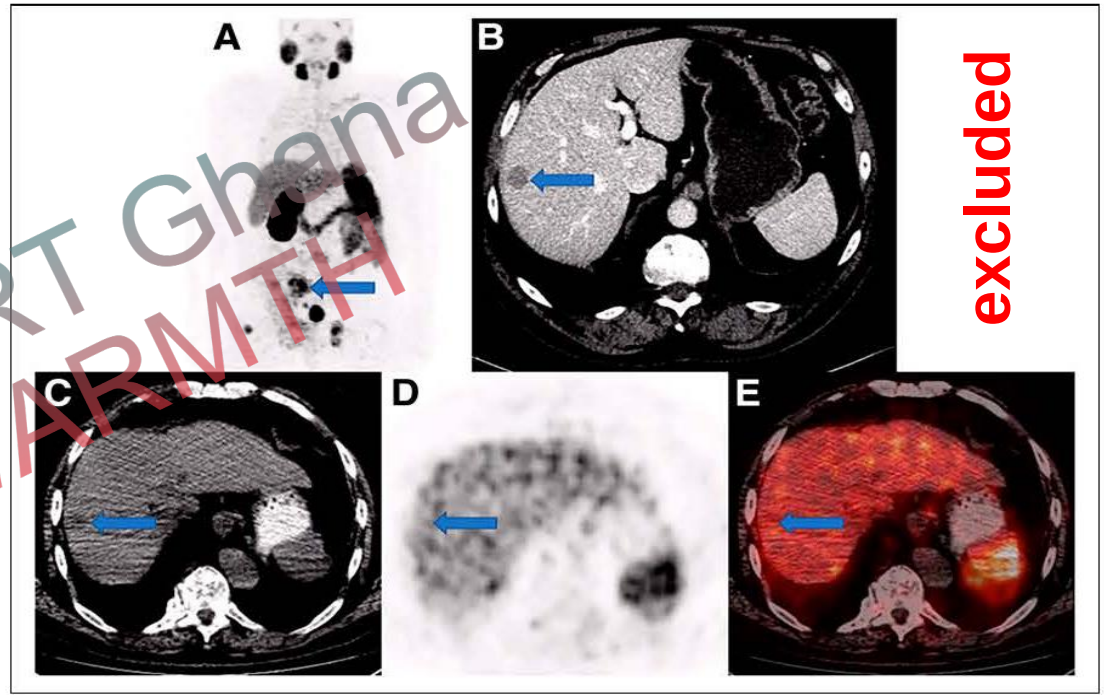
EDITORIAL

Why We Did What We Did: PSMA PET/CT Selection Criteria for the VISION Trial

Kuo, JNM 2022

Phillip H. Kuo[1], Taylor Benson[2], Richard Messmann[2], and Michael Groaning[3]



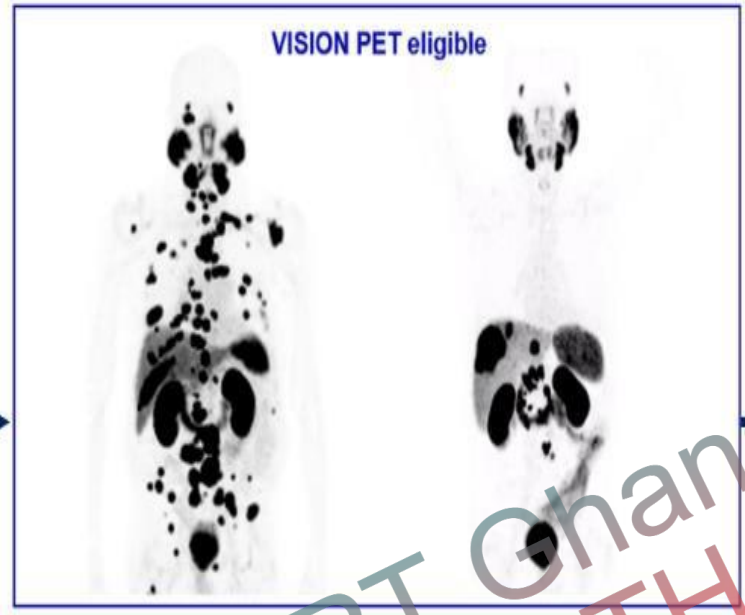


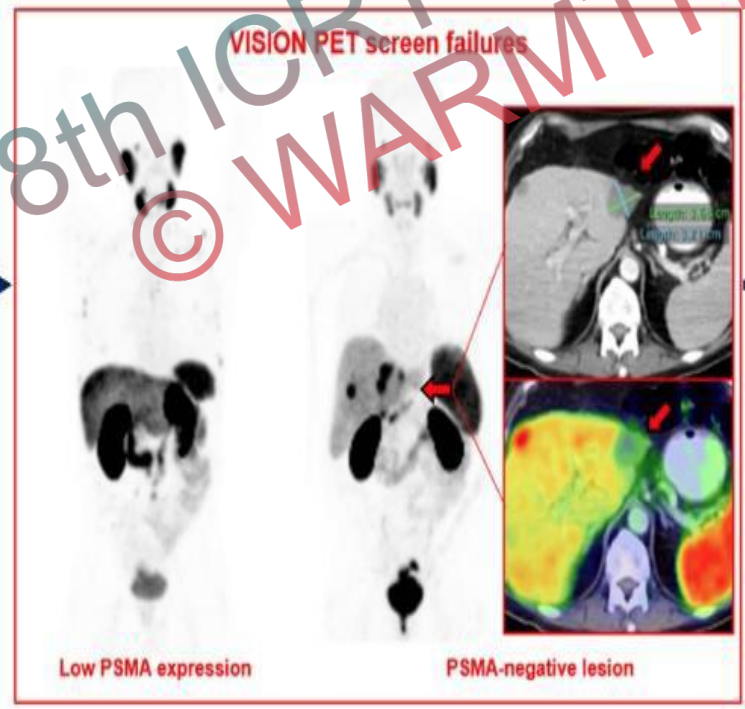
- compromise between too restrictive & nonrestrictive (10-20% excl. acceptable)
- operational complexity with FDG PET
- Visual (no SUV); liver background ref.
- RECIST 1.1 measurable disease

- Retrospective multicenter
- 301 mCRPC patients treated with PSMA RLT
- VISION-PET-E v. VISION-PET-SF

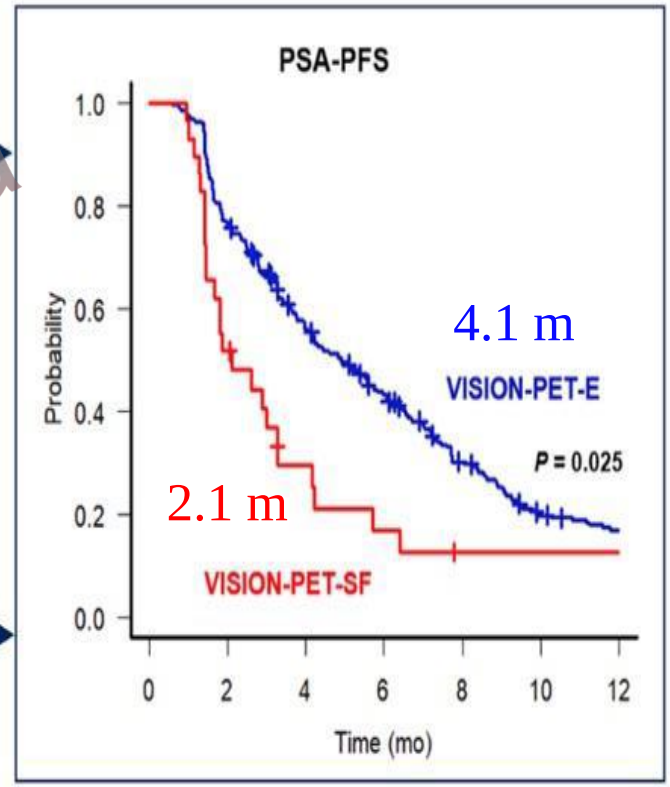
1. mCRPC patients treated with 177Lu-PSMA
2. Retrospective review of baseline PSMA PET
3. Application of VISION PET criteria
   - ≥ 1 PSMA-positive metastasis (> liver)
   - No PSMA-negative metastasis (≤ liver)

- estimated 20-25% SFs in unselected pts
- Need demonstration of PSMA expression prior to PSMA RLT
- Refinement in PSMA PET selection criteria





Outcome of patients with PSMA-PET/CT screen failure by VISION criteria and treated with 177Lu-PSMA therapy: a multicenter retrospective analysis



Hotta, JNM 2022

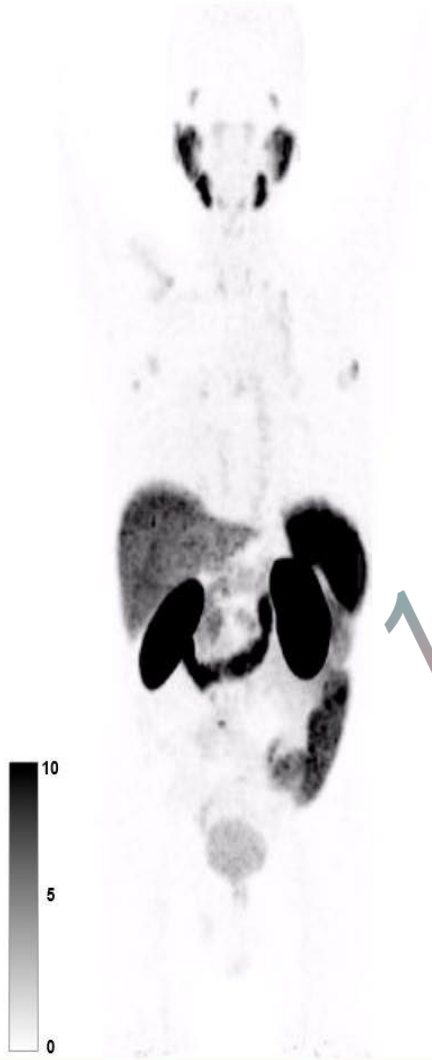
EAU-EANM Consensus Statement
PSMA PET/CT in LuPSMA RLT
Fanti, Eur Urol Oncol 2022

Statement	Consensus?	MS*
PSMA PET demonstration of PSMA expression mandatory before LuPSMA RLT	Yes	9
PSMA PET for evaluation of response to LuPSMA RLT	Yes	7
PSMA PET should be performed at end of LuPSMA RLT	Yes	6
PSMA PET in majority of mCRPC pts to evaluate progression	Yes	3
PSMA PET should be performed after each cycle of LuPSMA RLT	Yes	1.5
FDG PET should be performed before LuPSMA RLT	Yes	4
FDG PET should be performed at end of LuPSMA RLT	Yes	2
FDG PET should be performed after each LuPSMA RLT cycle	Yes	1

- Delphi process (2 rounds)
- 9-point Likert scale (1=strongly disagree, 9=strongly agree)

* MS=median scale score

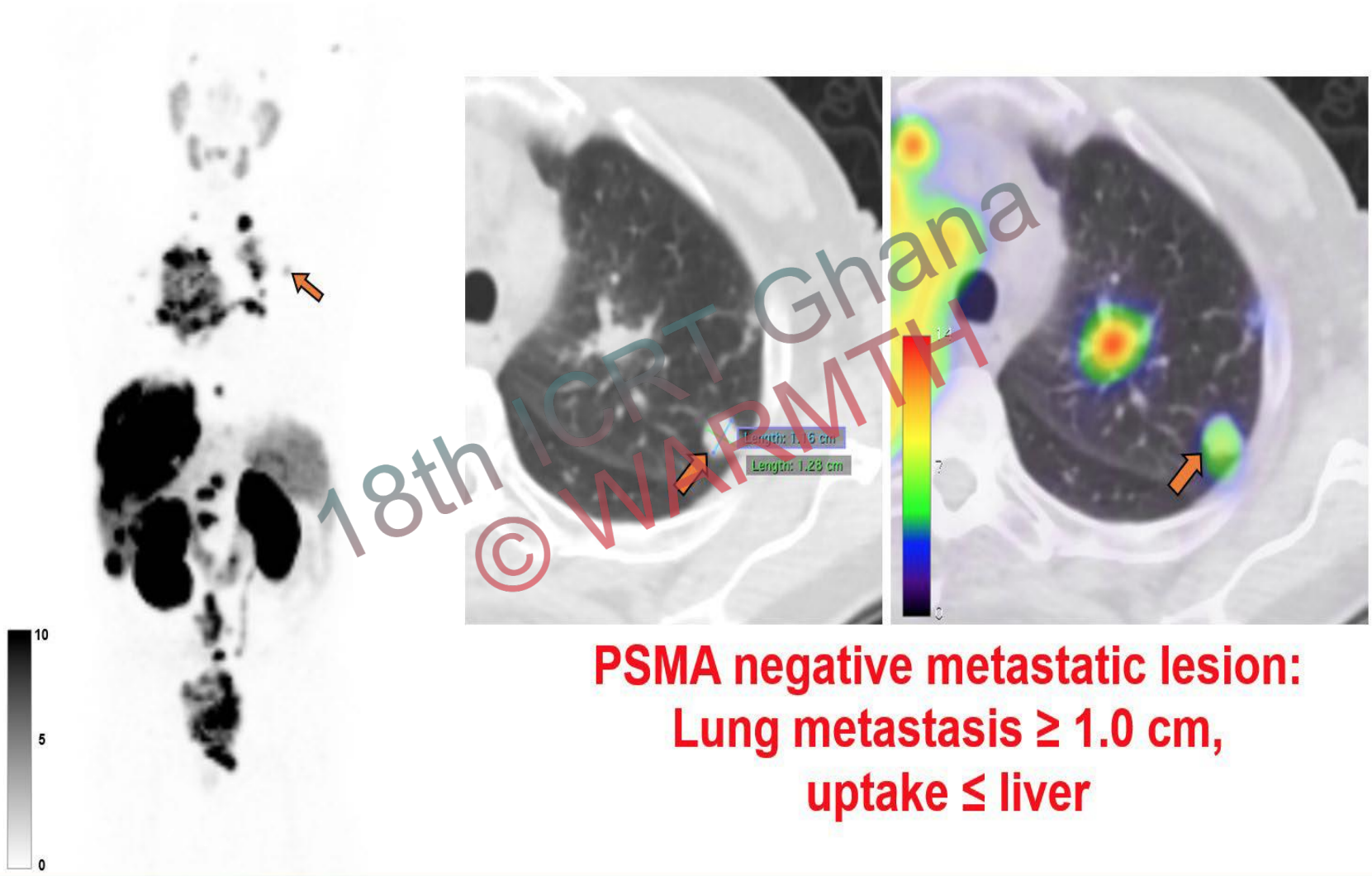
Patient: #2



No PSMA-positive (> liver) metastatic lesion

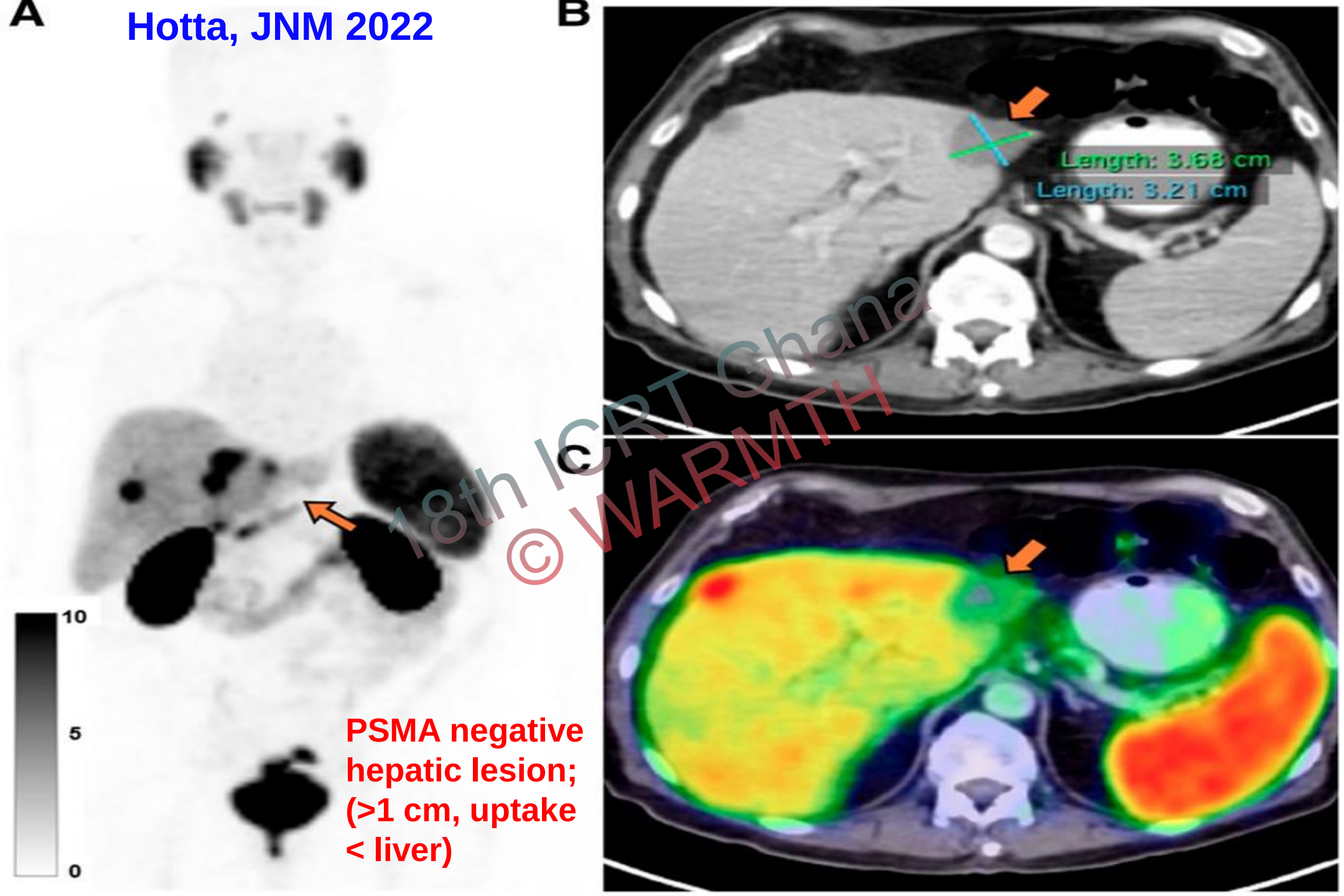
Hotta, JNM 2022

Patient: #12

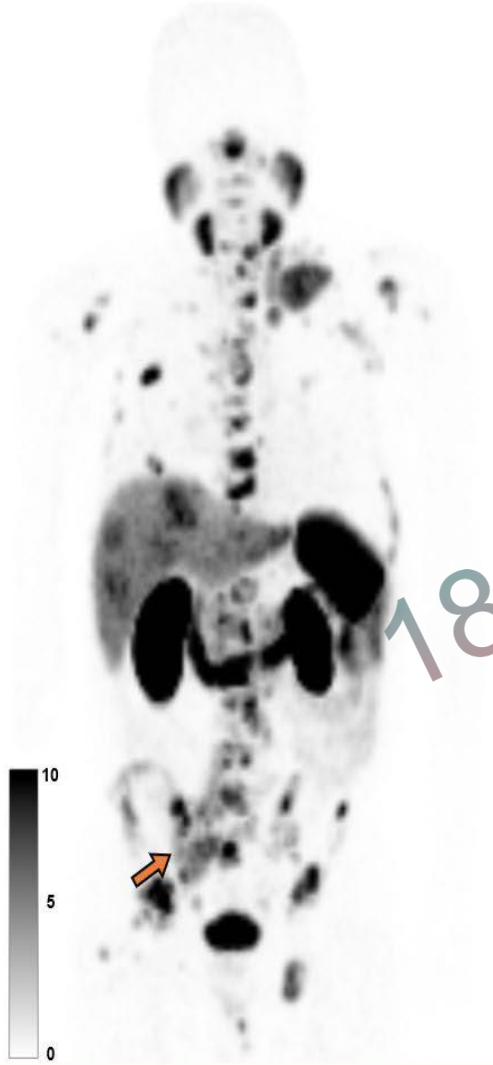


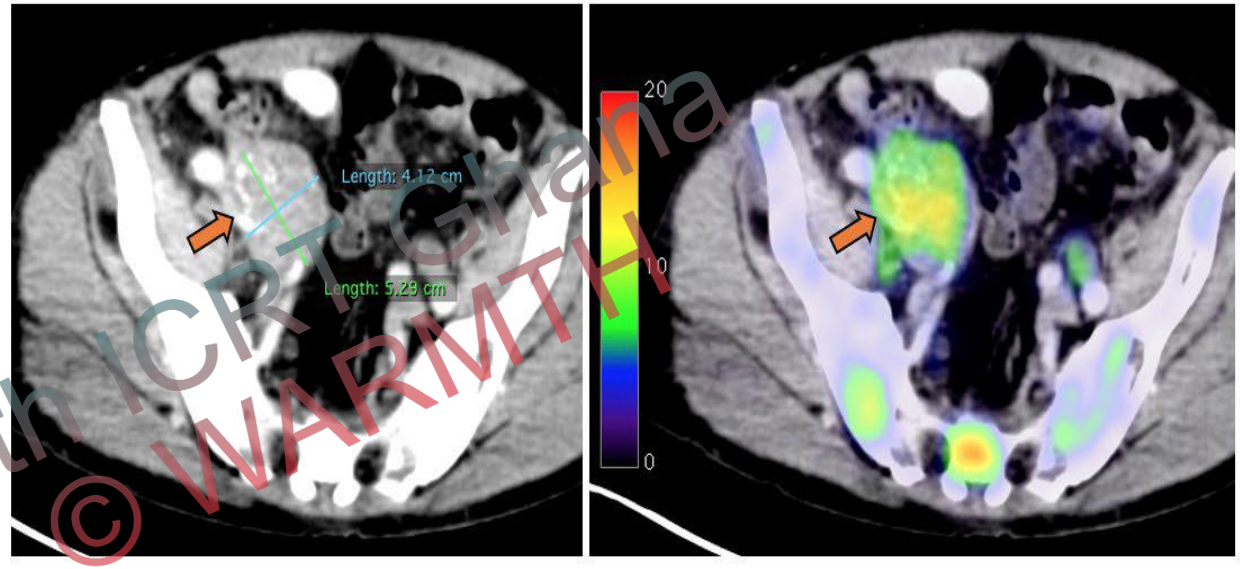
PSMA negative metastatic lesion:
Lung metastasis ≥ 1.0 cm,
uptake ≤ liver

Hotta, JNM 2022



Patient: #9

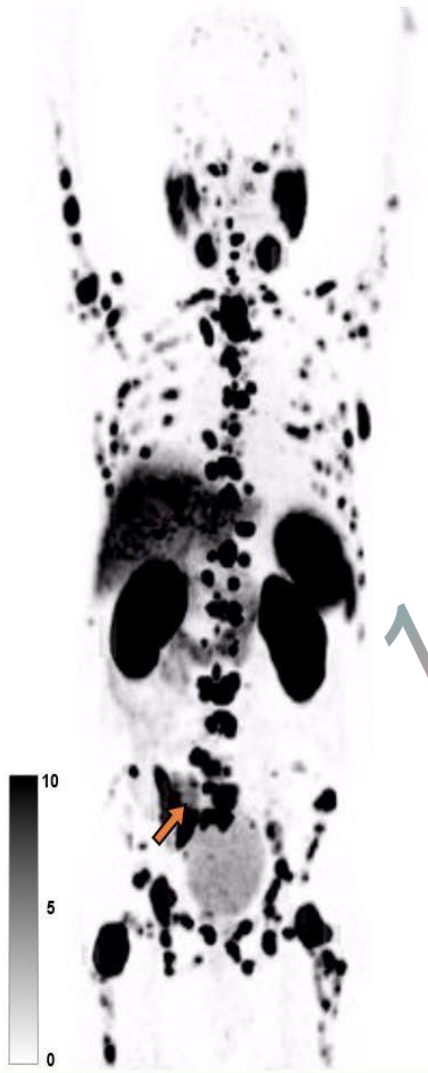


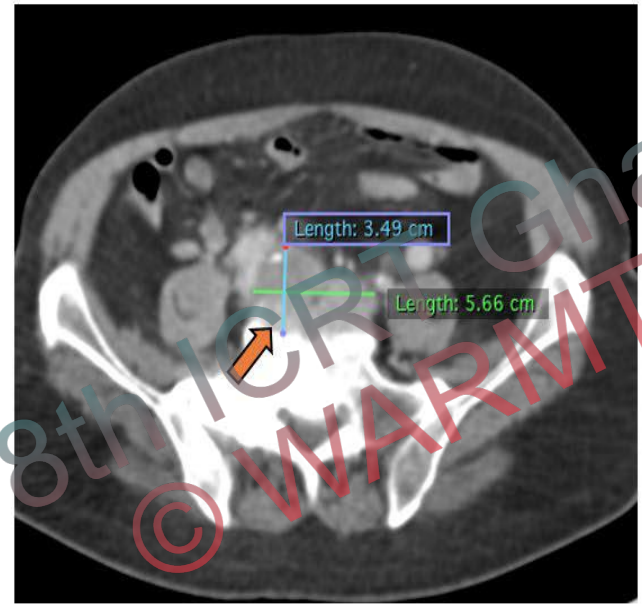


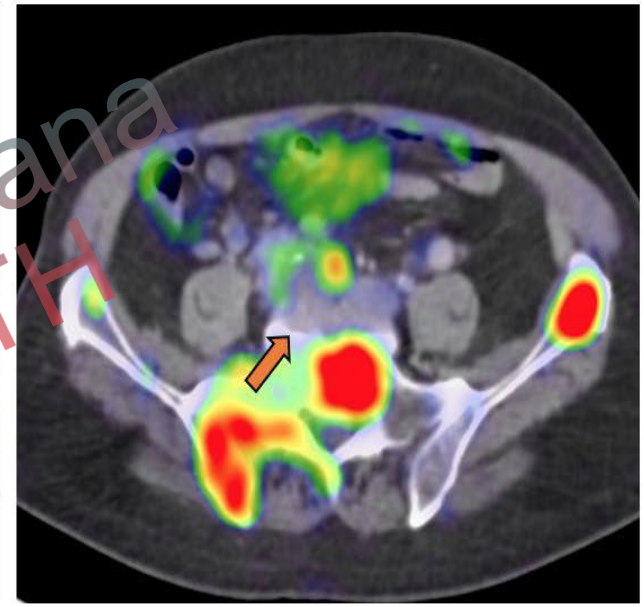
PSMA negative metastatic lesion:
Lymph node metastasis ≥ 2.5 cm,
uptake ≤ liver

Hotta, JNM 2022

Patient: #1



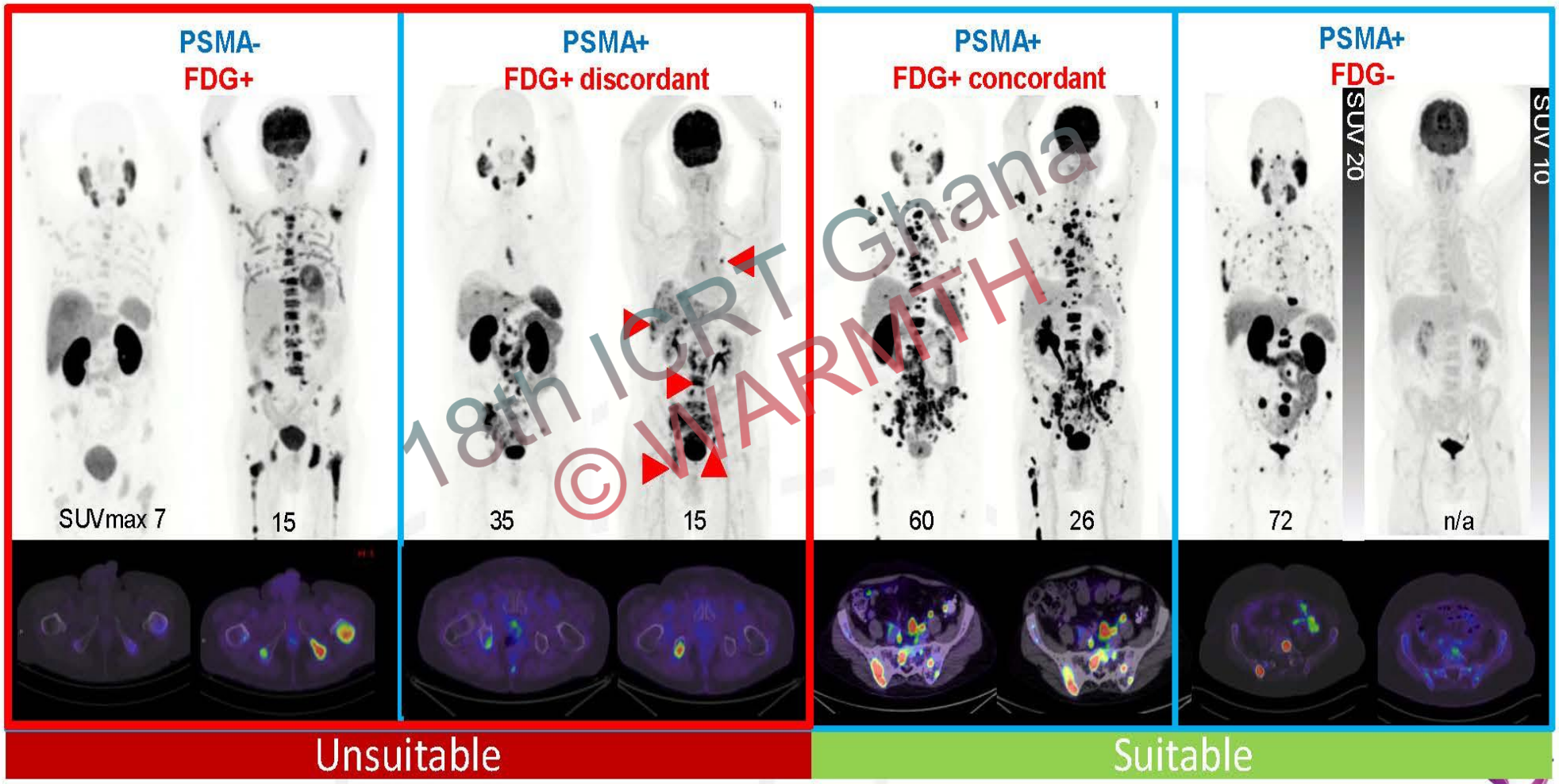




PSMA negative metastatic lesion:
Lymph node metastasis ≥ 2.5cm,
uptake ≤ liver

Hotta, JNM 2022

PSMA/FDG phenotypes



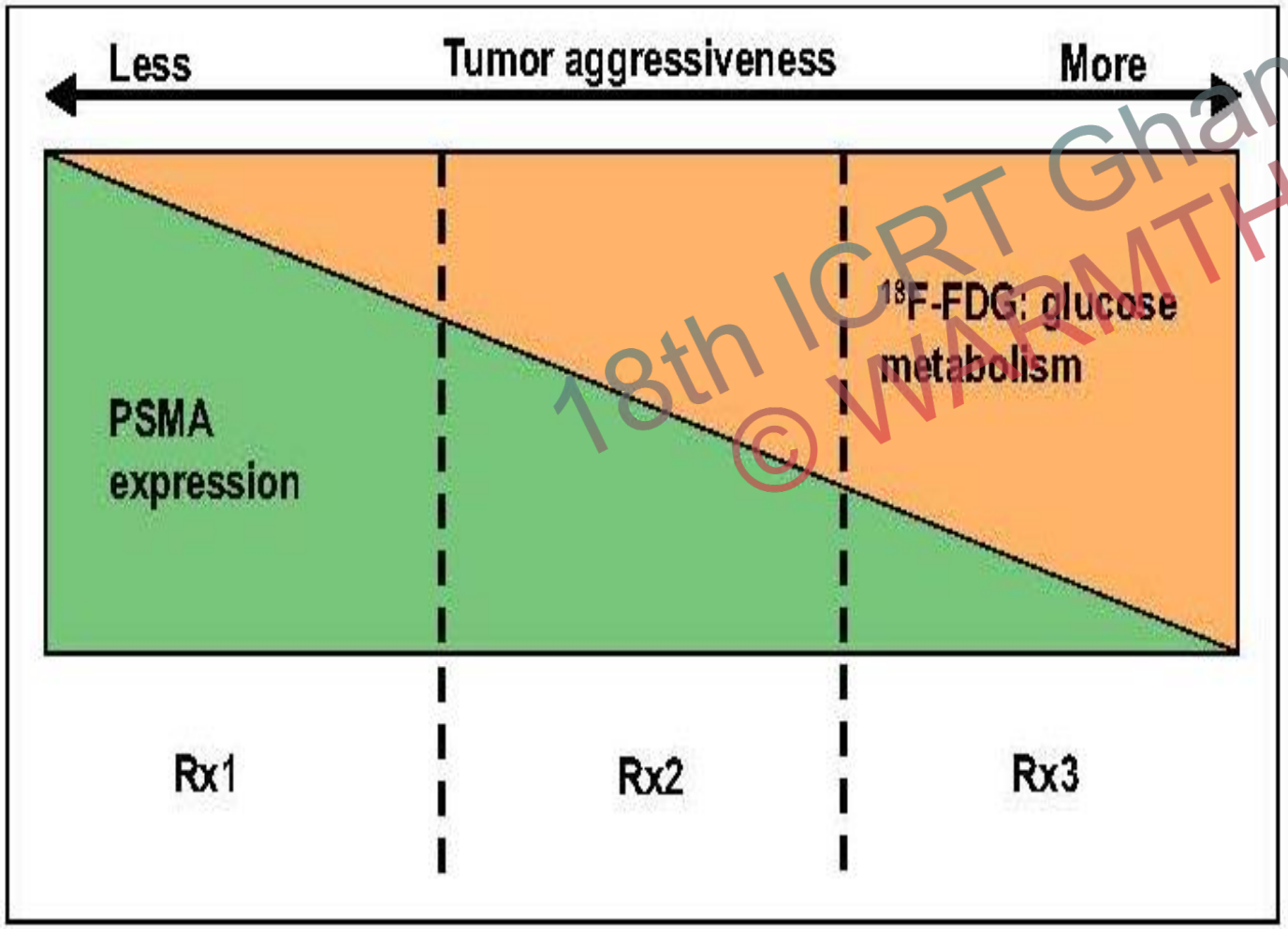
Up to 30% PSMA-/FDG+ lesions #APCCC2019

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

The VISION Forward: Recognition and Implication of PSMA−/^{18}F-FDG+ mCRPC

Hossein Jadvar

Jadvar, JNM 2022



RX1: PSMA RPT

RX2: PSMA RPT (? intensification), chemoRx, immunoRx, ADT

RX3: non-RPT
(? priming tumor phenotype to enable PSMA RPT)

Jadvar

Pros & Cons of FDG PET/CT in PSMA RPT

- Pros
  - Assessment of tumor burden and heterogeneity
  - May select patients who benefit most from PSMA RPT
  - May identify pts for combined Rx (PSMA RPT+ Chemo / Irx / PARPi / ADT if PolyM; PSMA RPT+MDT if OligoM)
  - Interim FDG PET/CT during PSMA RPT may inform regarding subsequent RPT cycles timing and dosage

Jadvar, JNM 2022

Pros & Cons of FDG PET/CT in PSMA RPT

- Cons
  - Standardization for reproducible total tumor burden quantification & comparison of PSMA & FDG PET
  - Need for simple combined PSMA+FDG PET reporting
  - Inconvenience to patient & motivation to receive PSMA RLT regardless of FDG PET findings
  - low PSMA/FDG+ pts may still benefit from PSMA RPT
  - Payment for 2 PET scans
  - Need for cost-utility analysis and impact on outcome

Jadvar, JNM 2022

Take-Home Message

- FDG PET in mCRPC
  - treatment response assessment in metastatic disease
  - prognostication
  - potential outcome-optimized PSMA RPT patient selection
  - *PSMA PET mandatory prior to PSMA RPT*
    - *Pluvicto Package Insert*
    - *NCCN Guidelines* *(Version 4.2022, May 10, 2022)*
    - *Appropriate Use Criteria* *(Jadvar H et al, JNM 2022)*

Optimal v. Required v. Practical *(Sartor, JNM 2022)*

Acknowledgement

NIH / NCI / NIBIB

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R21-EB017568

P30-CA014089

SC CTSI Southern California Clinical and Translational Science Institute

The Ming Hsieh Institute

for Research on Engineering-Medicine for Cancer

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