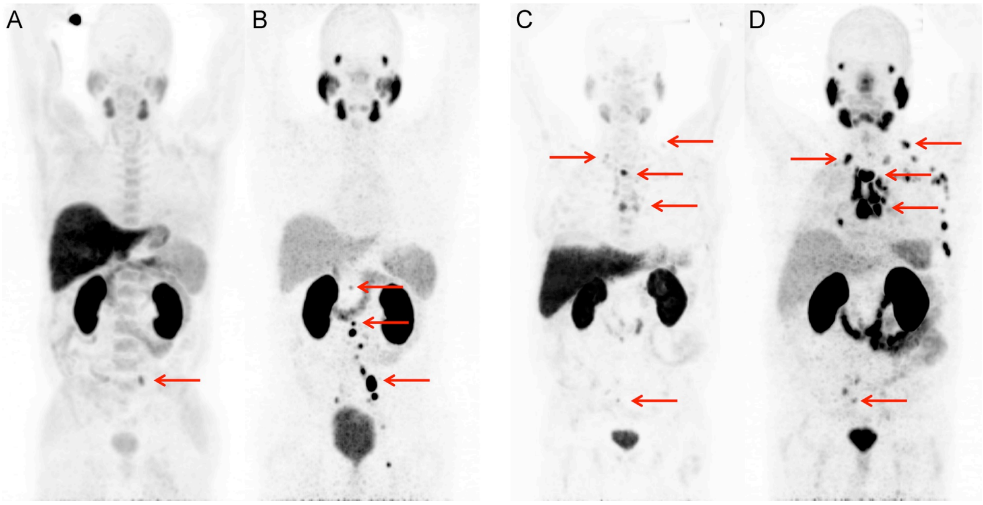
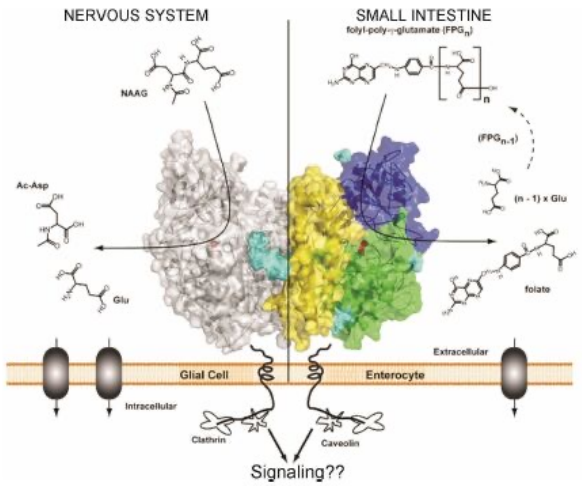
UKD Universitätsklinikum Düsseldorf

hhu Heinrich Heine Universität Düsseldorf

Sequenz:
Molekulare Diagnostik mittels PSMA-liganden beim Prostatakarzinom





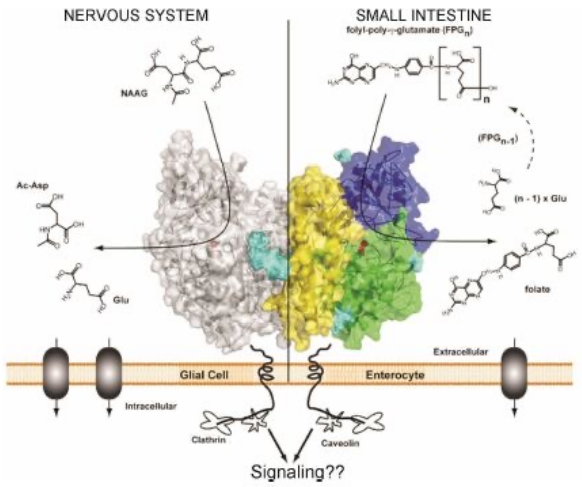
Univ.-Prof. Dr. Frederik L. Giesel

Director and Chairman
Department of Nuclear Medicine
University Hospital Düsseldorf
Düsseldorf, Germany

frederik@egiesel.com

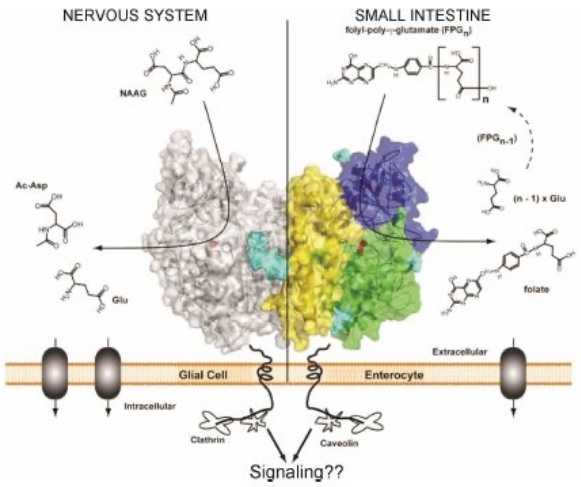
Dislcosure

- Advisor: ABX, SOFIE, Telix, Alpha-Fusion
- Co-Founder/ Patentapplications: PSMA-1007, PSMA-GSK-01, FAP-ligands



Overview

- Background + biology and different PSMA-ligands
- Recurrent prostate cancer
- Primary staging and detection
- PSMA-ligand therapy



Overview

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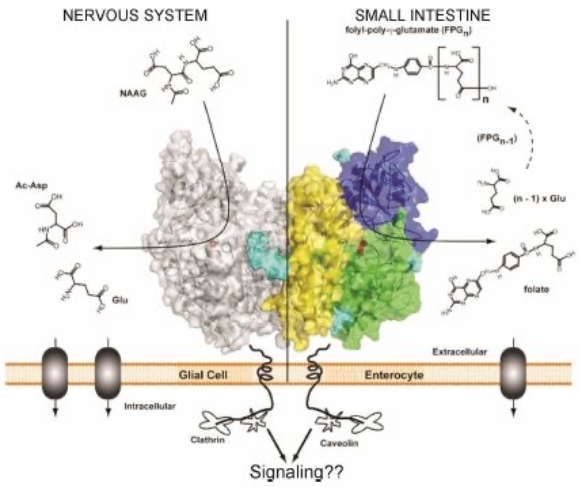
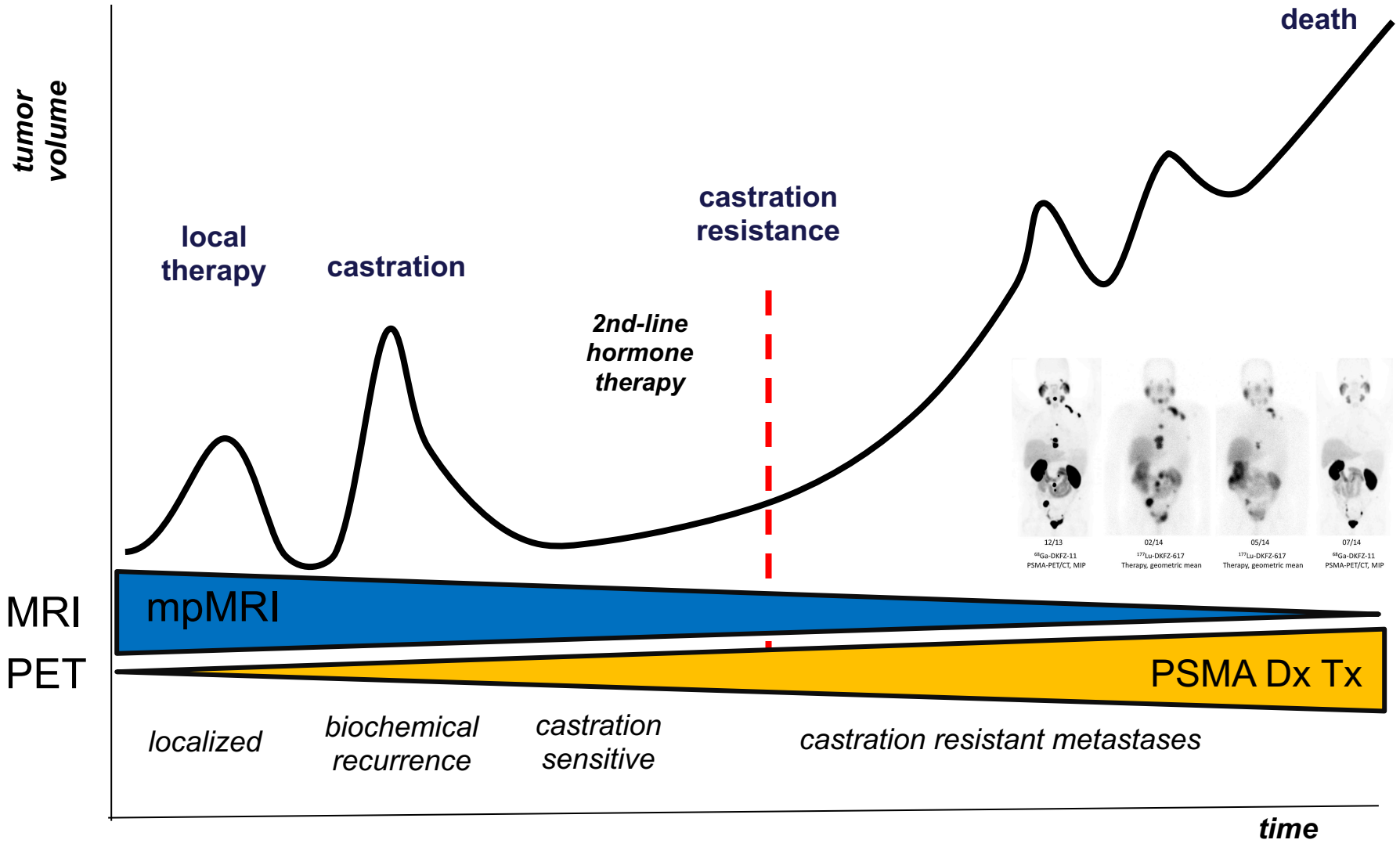
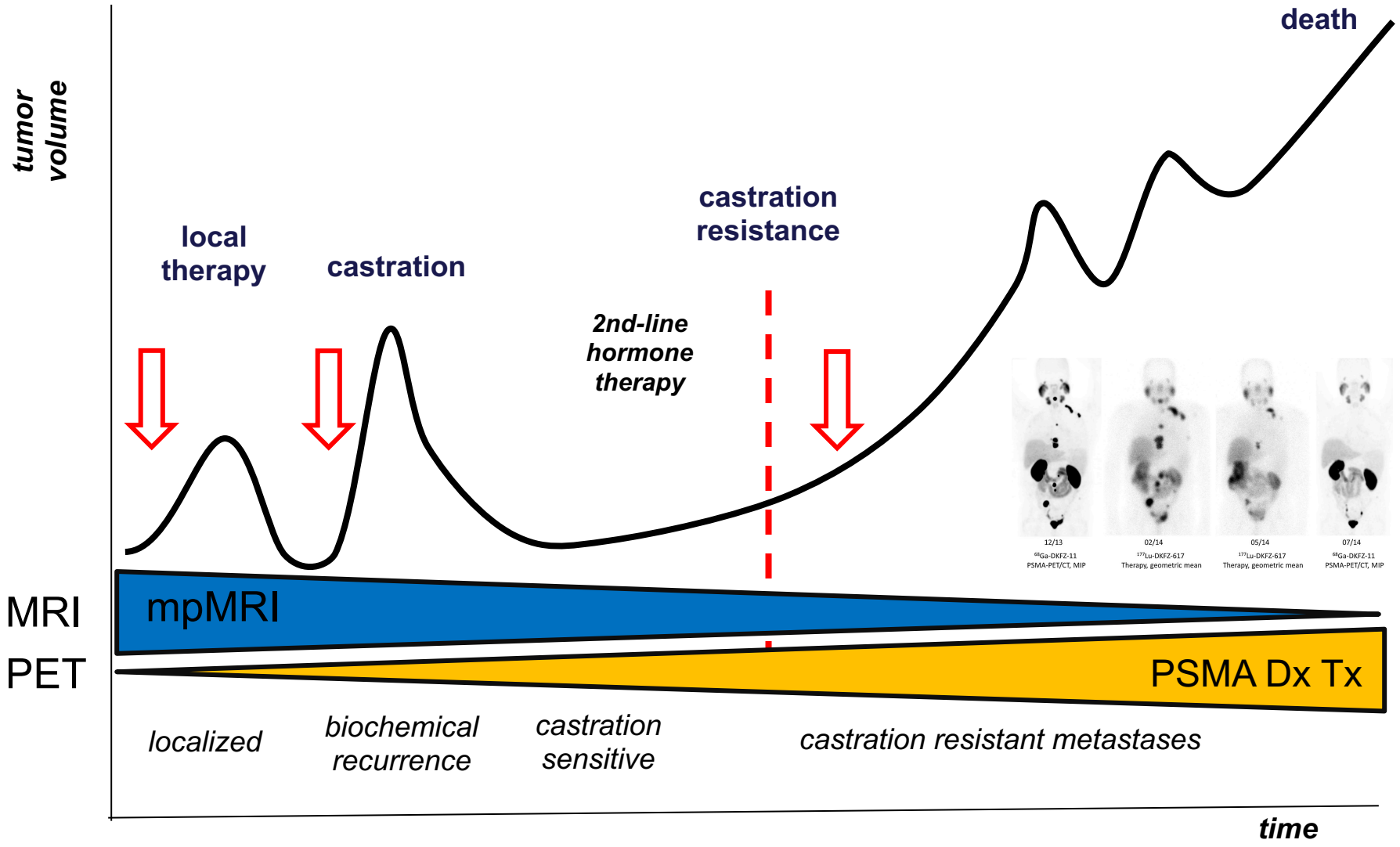


Background


tumor volume
death
local therapy
castration
castration resistance
2nd-line hormone therapy
12/13
68Ga-DKFZ-11
PSMA-PET/CT, MIP
02/14
177Lu-DKFZ-617
Therapy, geometric mean
05/14
177Lu-DKFZ-617
Therapy, geometric mean
07/14
68Ga-DKFZ-11
PSMA-PET/CT, MIP
MRI
mpMRI
PET
PSMA Dx Tx
localized
biochemical recurrence
castration sensitive
castration resistant metastases
time

Background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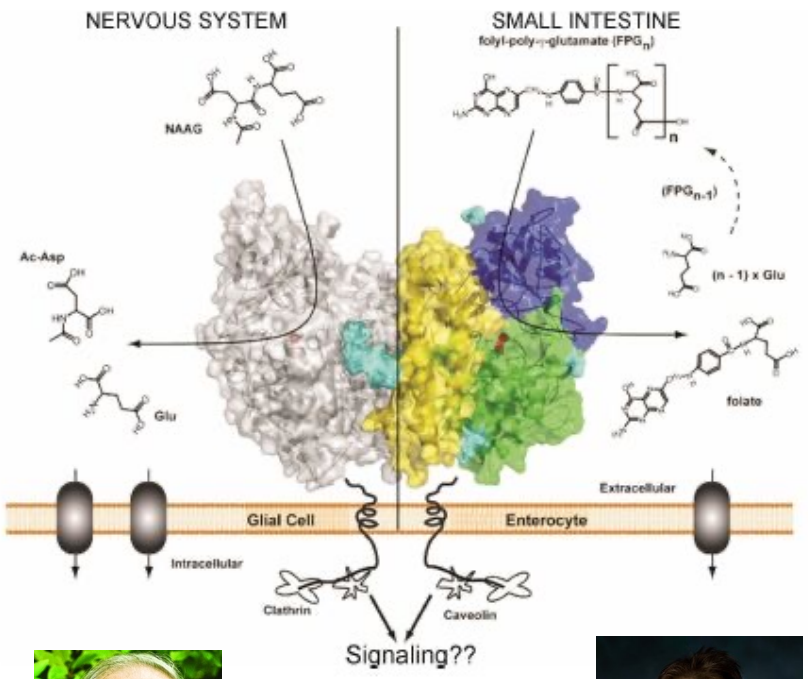
time

Background + Biology

- **Prostate-specific membran antigen**
- [syn. **Glutamate carboxyeptidase II (GCP-II)**]

- Cell surface protein with overexpression in prostate cancer (750 AS, 84 kDa)

- **PSMA expression increases progressively** in:
  - Higher graded tumors
  - Under androgen deprivation
  - Metastastic disease
  - Hormone-refractory prostate cancer
  - Also in tumor neovasculature



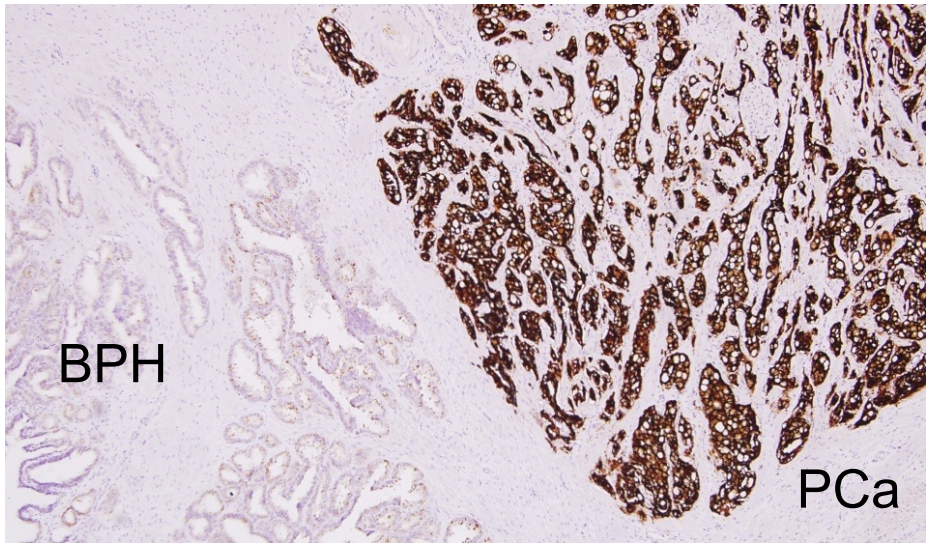
A. Kozikowski

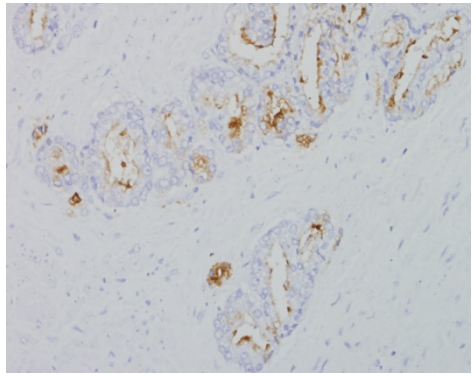
M. Pomper

Kozikowski AP et al., J Med Chem 2004

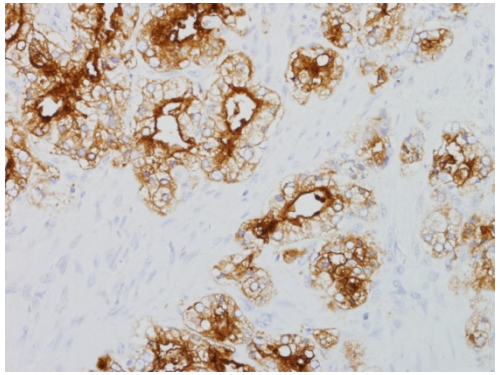
Biology + PSMA-Expression

# Cases Studied	% Cases Reported to be PSMA Positive	Reference
251	94%	Wright et al
184	100%	Bostwick et al
51	84%	Mannweiler, et al
42	88%	Kusumi, et al
21	100%	Ananias, et al
905	99.9%	Loda, et al

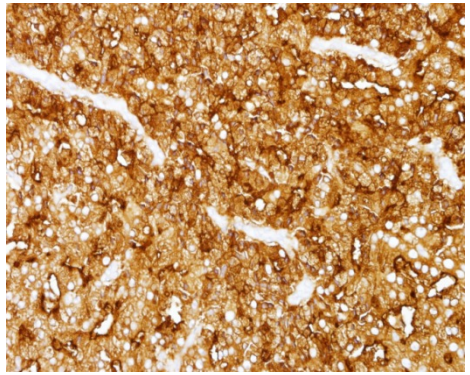




Gleason 3



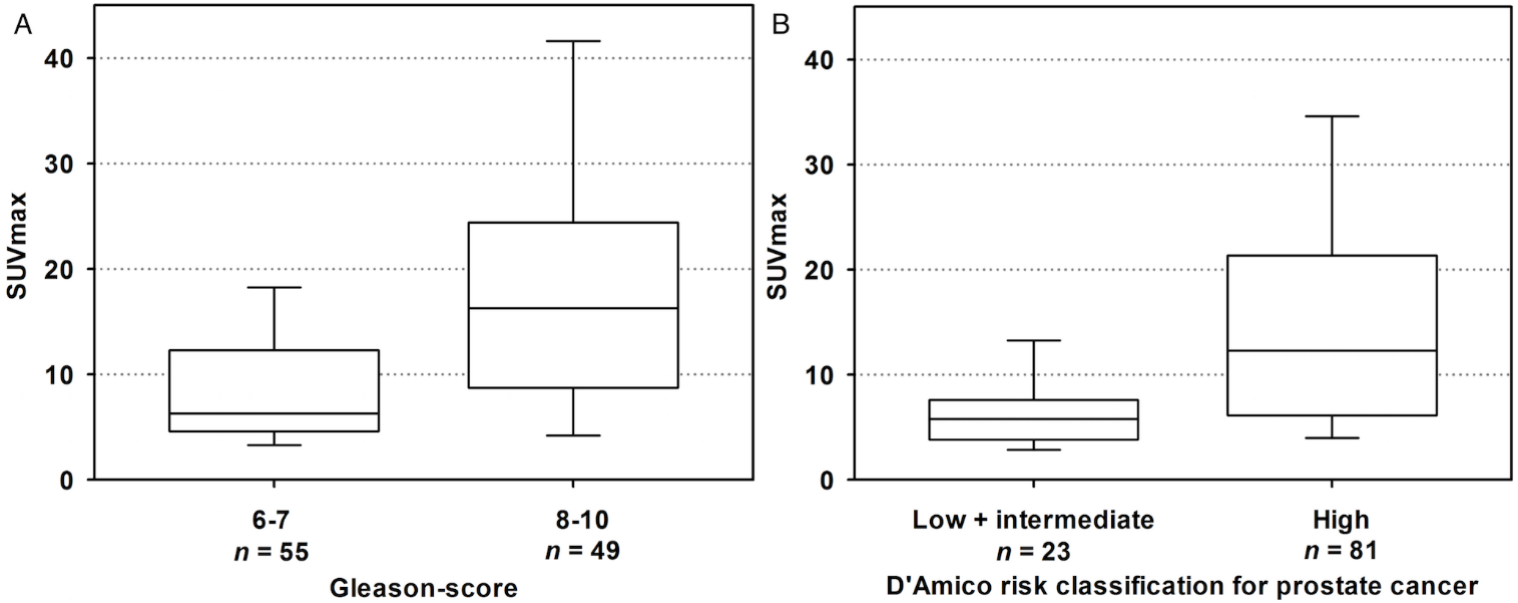
Gleason 4

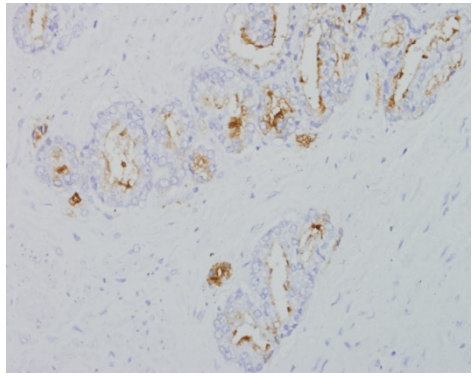


Gleason 5

Courtesy of Dr. Neil Bander New York-Presbyterian Hospital

Biology + PSMA-Expression





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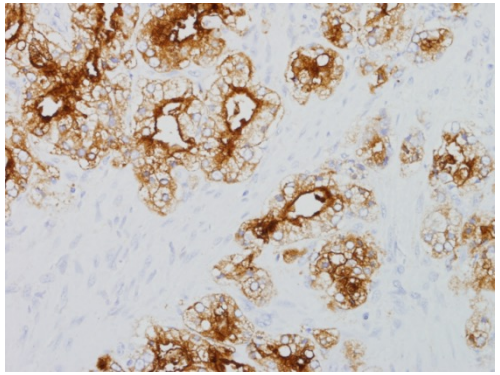

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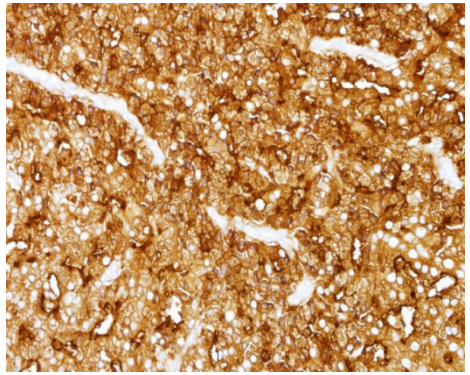
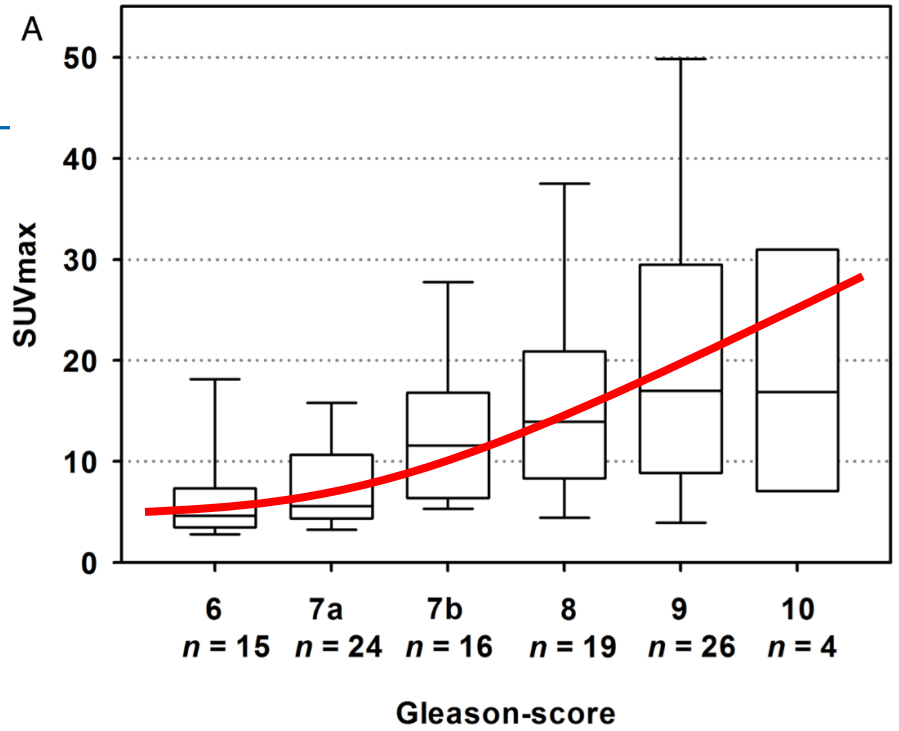
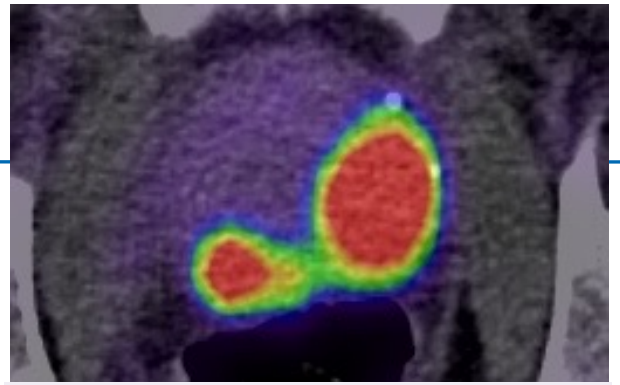
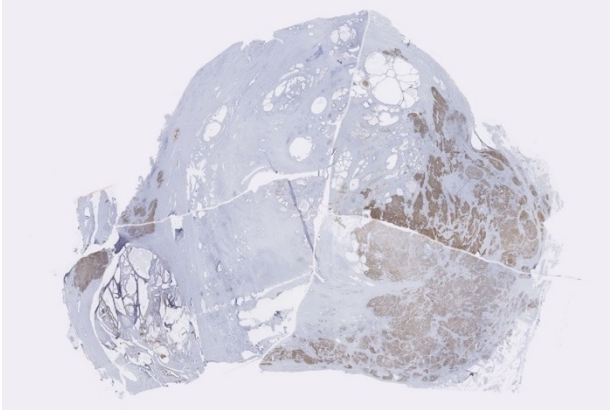


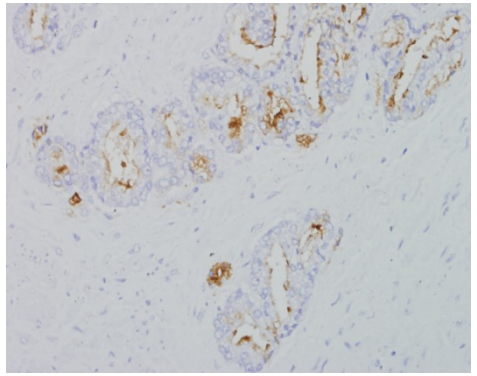
Gleason 5

Körber et al., JNM 2017, in print and Uprimy et al, EJNMMI 2017









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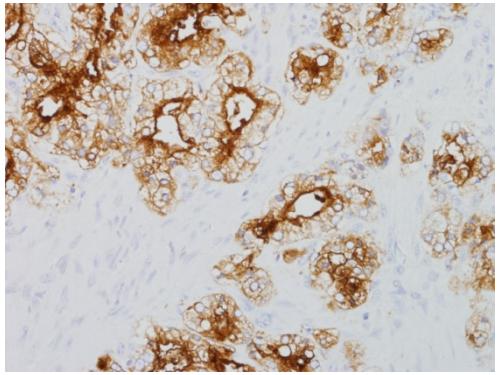

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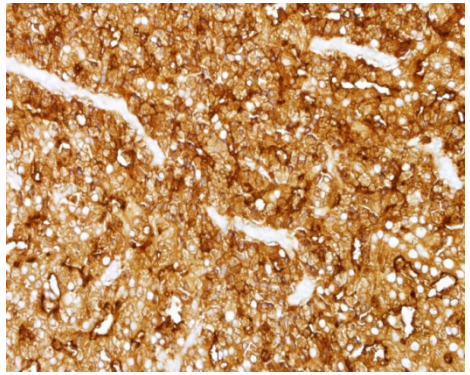

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Körber et al., JNM 2017, in print and Uprimy et al, EJNMMI 2017

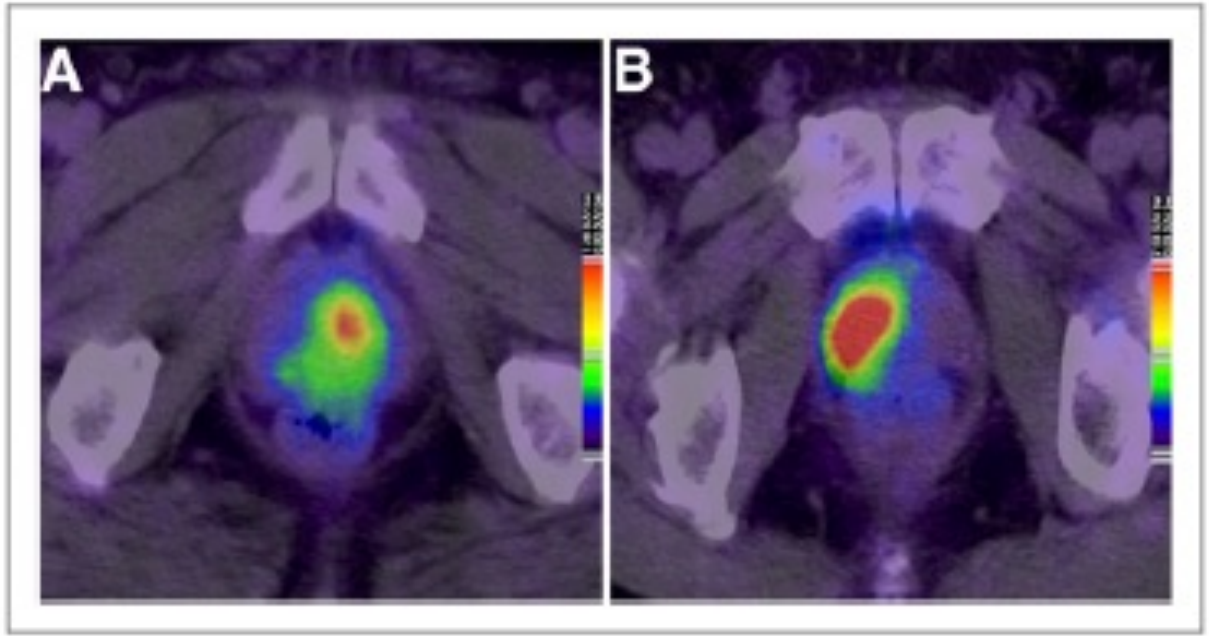
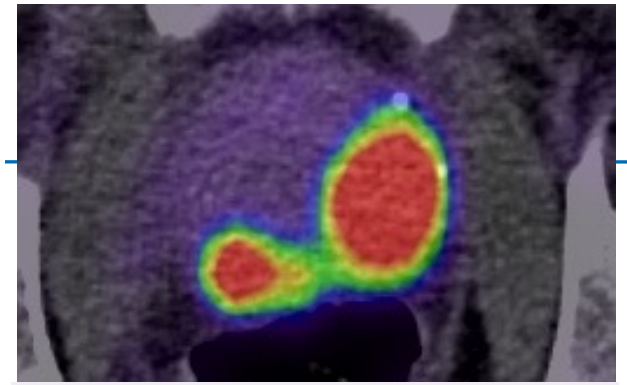
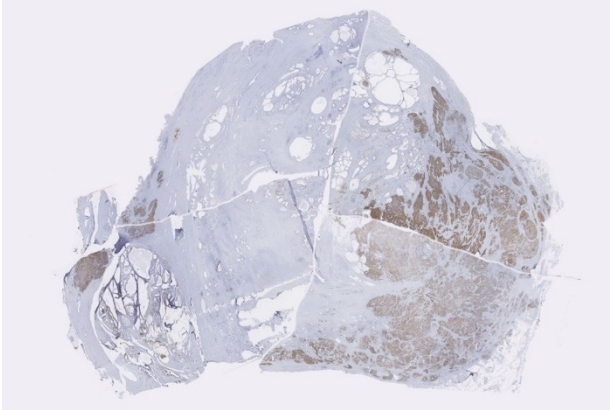
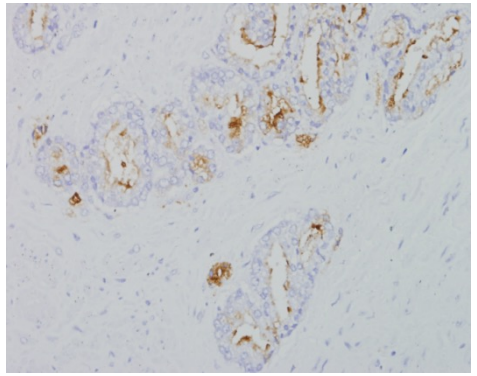


FIGURE 5. Different PSMA tracer uptake according to GS: 1 patient with GS 6 prostate cancer and SUV_{max} of 7.33 (A) compared with a GS 9 tumor and SUV_{max} of 16.64 (B).







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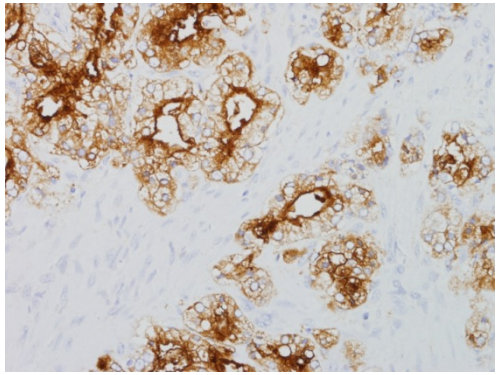

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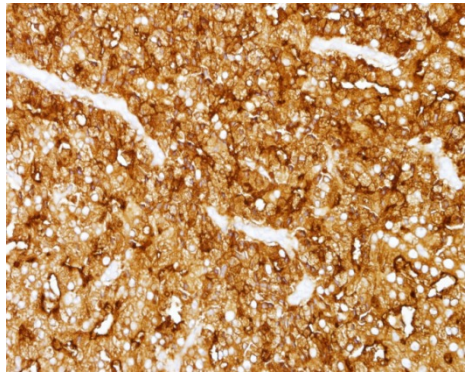


Gleason 5

Körber et al., JNM 2017, in print and Uprimy et al, EJNMMI 2017

PSMA-Expression + Histopathology

Diagnostic Accuracy of ^{18}F-PSMA-1007 PET/CT Imaging for Lymph Node Staging of Prostate Carcinoma in Primary and Biochemical Recurrence

Katharina Sprute[1], Vasko Kramer[2,3], Stefan A. Koerber[4–6], Manuel Meneses[7], Rene Fernandez[3], Cristian Soza-Ried[3], Mathias Eiber[8], Wolfgang A. Weber[8], Isabel Rauscher[8], Kambiz Rahbar[9], Michael Schaefers[9], Tadashi Watabe[10], Motohide Uemura[11], Sadahiro Naka[12], Norio Nonomura[11], Jun Hatazawa[13], Constantin Schwab[14], Viktoria Schütz[15], Markus Hohenfellner[15], Tim Holland-Letz[16], Juergen Debus[4–6,17–19], Clemens Kratochwil[1,20], Horacio Amaral[2,3], Pete L. Choyke[21], Uwe Haberkorn[1,20], Camilo Sandoval[7], and Frederik L. Giesel[1,10,17,20]

Results After Comparison Between PET/CT and Histopathology

Tracer	Study	Number of patients	Sensitivity	Specificity	PPV	NPV
^{68}Ga-PSMA-11	Hope, 2019 (*17*)	266 patients, 29 articles	74%	96%	93%	85%
	Perera, 2016 (*4*)	239 patients, 5 studies	80%	97%	—	—
	Afshar-Oromieh, 2015 (*3*)	42 patients	76.6%	100%	100%	91.4%
	Kuten, 2020 (*18*)	16 patients	85.7%	98.2%	96.8%	91.5%
^{18}F-PSMA-1007	Kuten, 2020 (*18*)	16 patients	100%	90.9%	87.5%	100%
	Giesel, 2017 (*8*)	8 patients	94.7%	—	—	—
	Kesch, 2017 (*9*)	10 patients	71%	81%	83%	68%
	Sprute et al. (this work)	96 patients, overall	71.2%	99.5%	91.3%	97.9%
		96 patients, lymph nodes >3mm	81.7%	99.6%	92.4%	98.9%

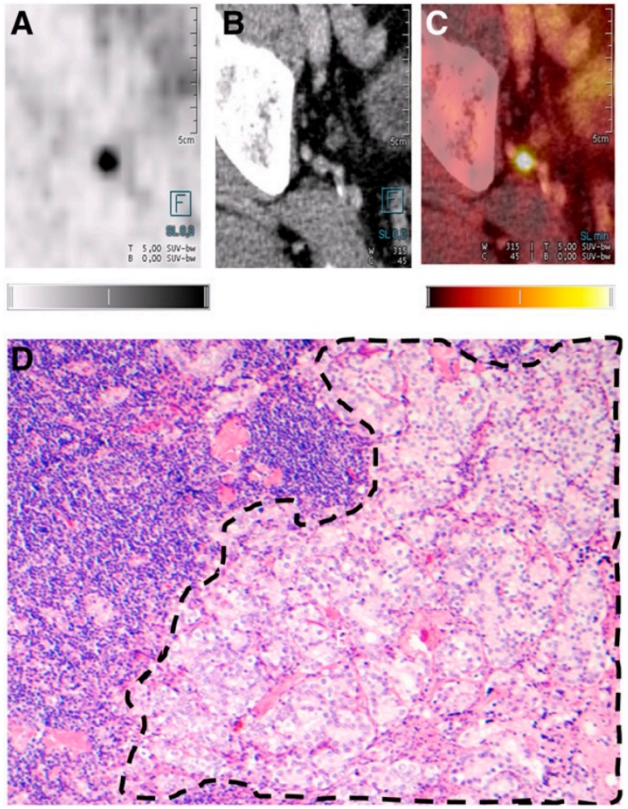
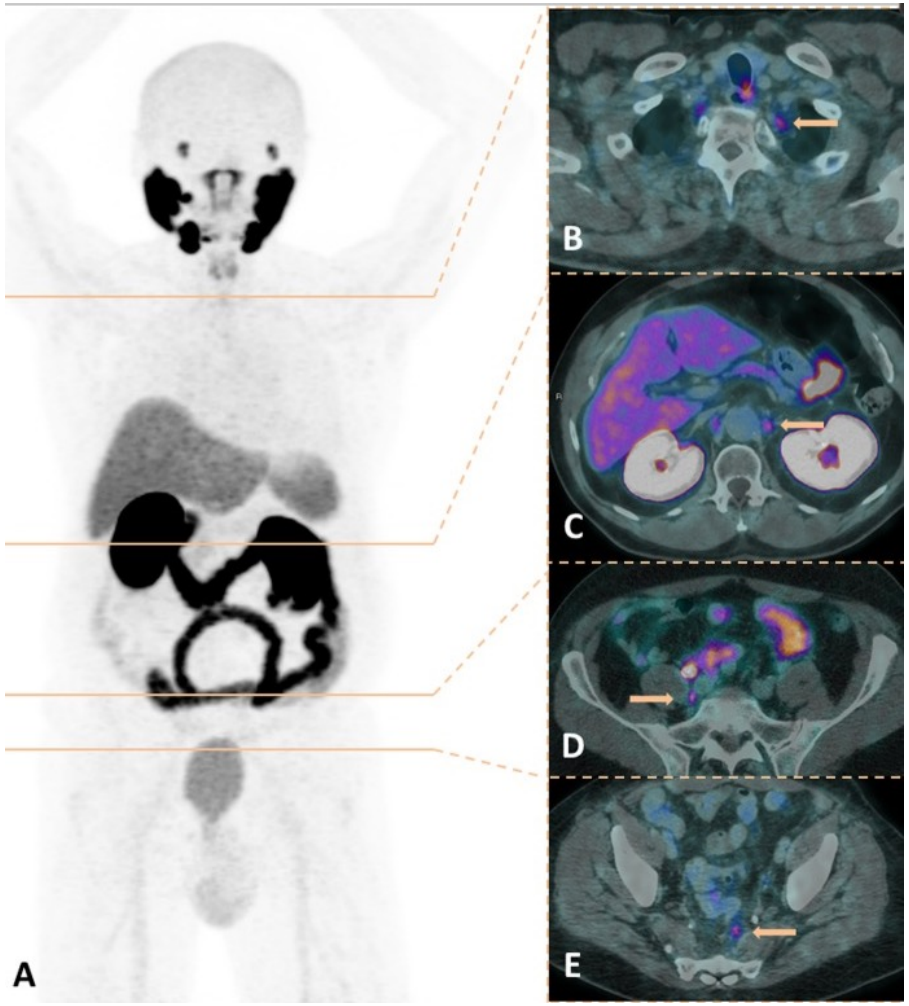


FIGURE 1. (A–C) Axial ^{18}F-PSMA-1007 PET (A), CT (B), and ^{18}F-PSMA-1007 PET/CT (C) images of 73-y-old patient with prostate adenocarcinoma (Gleason score, 4 + 3; T3bN1M0; correlation between PET/CT and histopathology for exemplary LN). (D) Confirmed histopathologic staining (hematoxylin and eosin, ×10) of acinar structures of prostate adenocarcinoma (dashed outline) adjacent to normal LN structures. Quantitative gray scale and color scale represent SUV from 0.00 to 5.00.

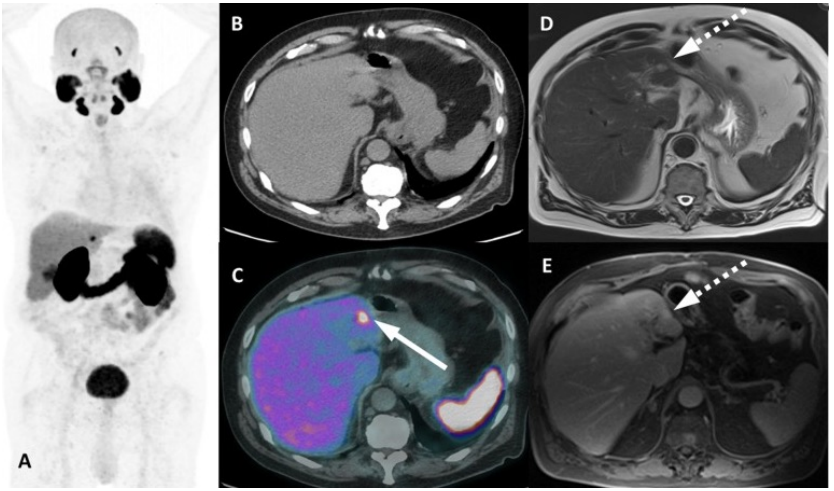
Sprute et al., JNM 2021

PSMA-Expression + non-prostate

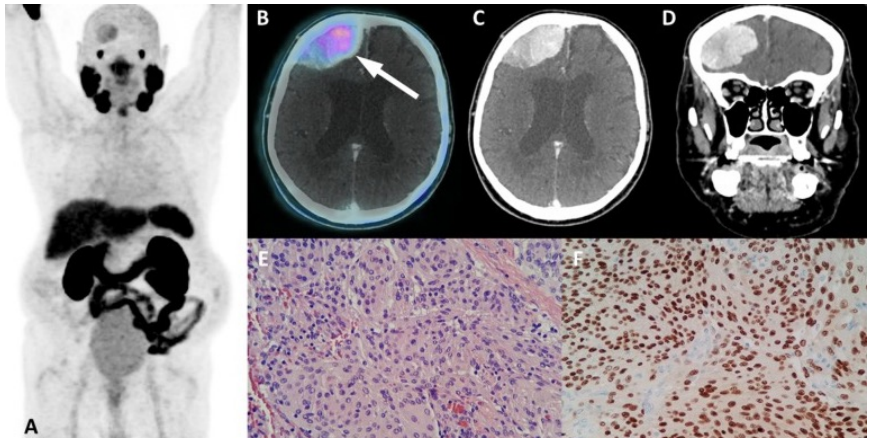
spinal ganglia



benign hemangioma

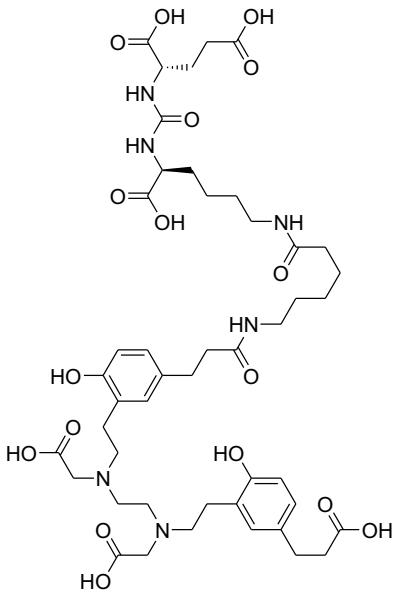


benign meningioma



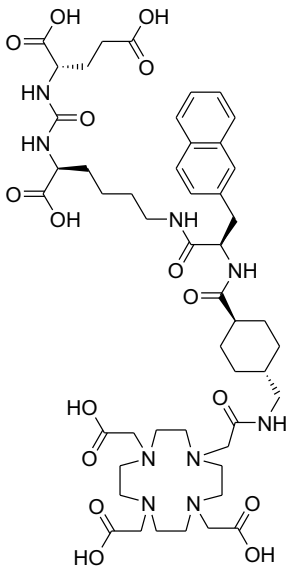
de Galiza Barbosa et al., Cancer Imaging 2020

PSMA-ligands in PET imaging



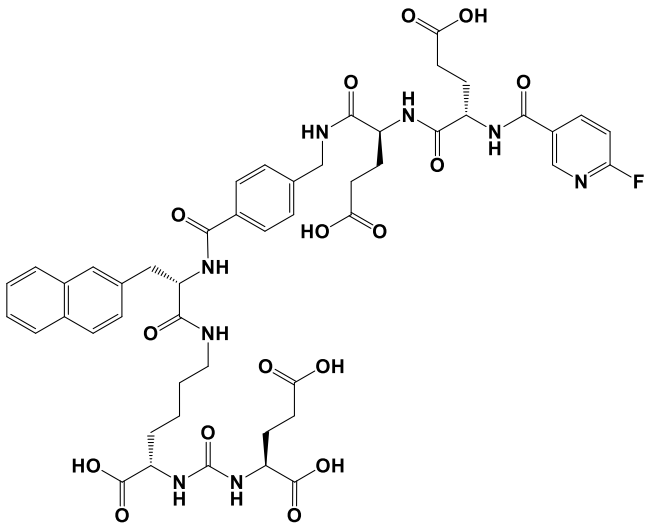
^{68}Ga-PSMA-11

Eder et al.
Bioconjugate Chem 2012



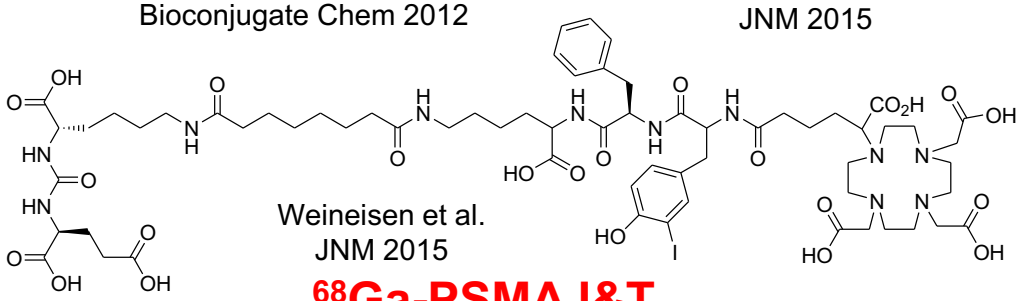
^{68}Ga-/^{177}Lu-PSMA-617 (Pluvicto®)

Benesova et al.,
JNM 2015



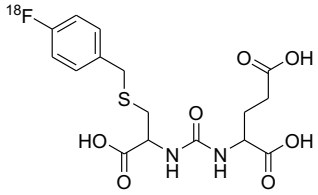
^{18}F-PSMA1007 (Radelumin®)

Giesel et al.
EJNMMI 2016



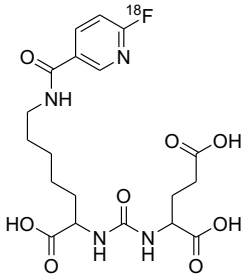
Weineisen et al.
JNM 2015

^{68}Ga-PSMA I&T



^{18}F-DCFBC

Cho et al.
JNM 2012



^{18}F-DCFPyL (Pylarify®)

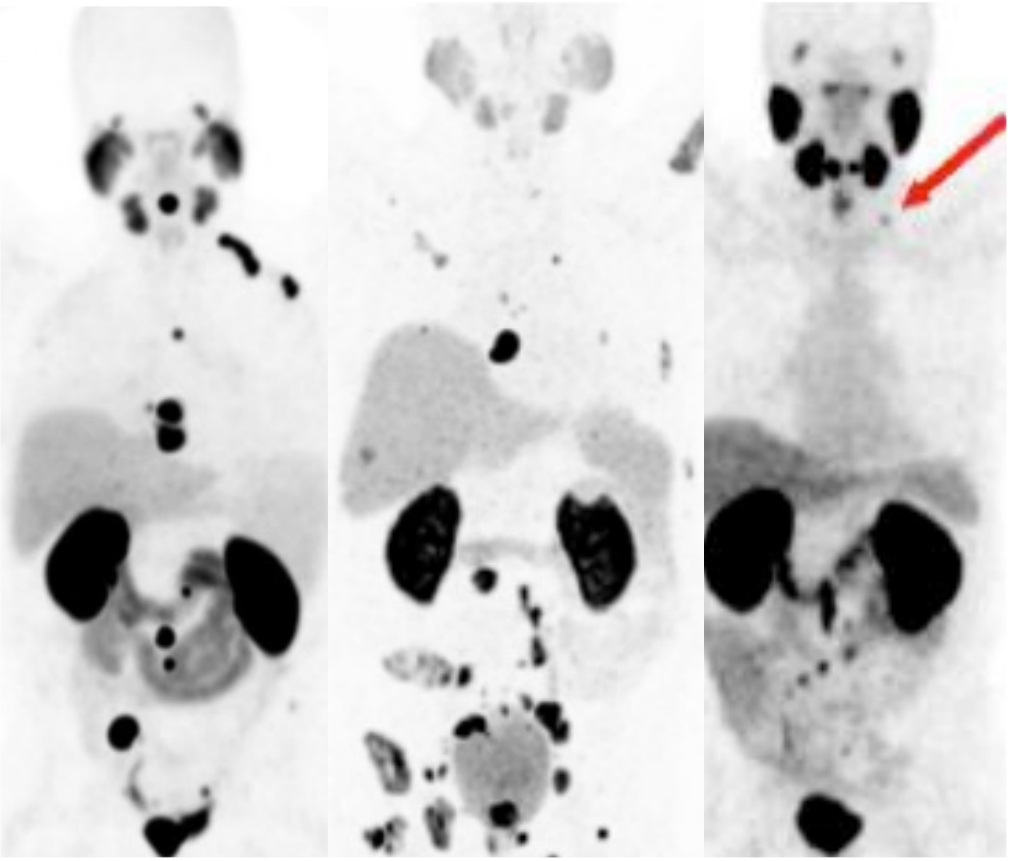
Szabo et al.
Mol Im Biol 2015

PSMA-ligands in PET imaging

^{68}Ga-PSMA-11 (PSMA HBED-CC)

^{68}Ga-PSMA-I&T

^{68}Ga-PSMA-617



Afshar-Oromieh A al. EJNMMI 2013

Weineisen M et al. JNM 2015

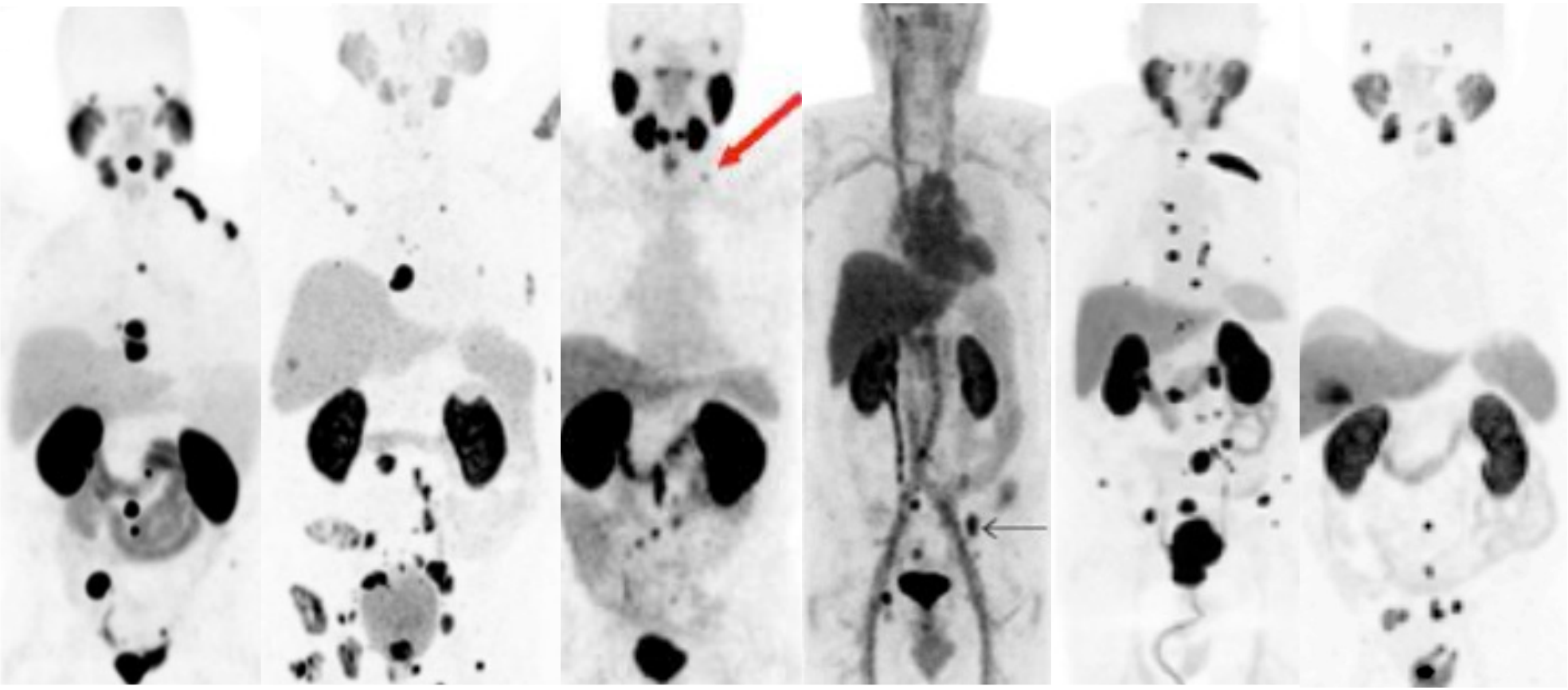
Afshar-Oromieh A al. EJNMMI 2015

^{68}Ga-PSMA ligands

^{18}F-PSMA ligands

PSMA-ligands in PET imaging

^{68}Ga-PSMA-11 (PSMA HBED-CC)	^{68}Ga-PSMA-I&T	^{68}Ga-PSMA-617	^{18}F-DCFBC	^{18}F-DCFPyL	^{18}F-PSMA1007



Afshar-Oromieh A al. EJNMMI 2013	Weineisen M et al. JNM 2015	Afshar-Oromieh A al. EJNMMI 2015	Cho S et al. JNM 2012	Szabo Z et al. Mol Im Biol 2015	Giesel et al. EJNMMI 2016

^{68}Ga-PSMA ligands

^{18}F-PSMA ligands

PSMA-Ligands + drug approval

PSMA Imaging

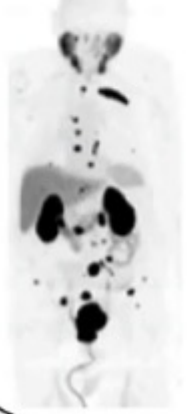
US/EU Market / FDA/EMA drug approval

Lantheus Medical Imaging

(Pylarify®)

PyL (^{18}F-PSMA)
BCR patients

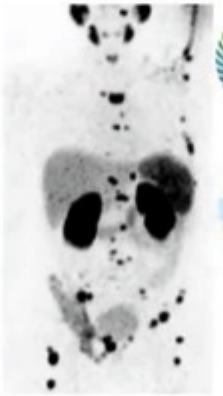
06/2021



TELIX PHARMACEUTICALS

TLX591 (^{68}Ga-PSMA)
BCR patients

12/2021



ABX

(Radelumin®)

^{18}F-PSMA-1007
BCR patients

PSMA-Ligands + drug approval

PSMA Imaging

US/EU Market / FDA/EMA drug approval

Lantheus Medical Imaging

(Pylarify®)

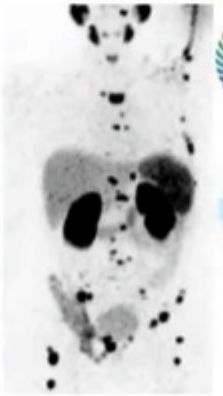
PyL (^{18}F-PSMA)
BCR patients

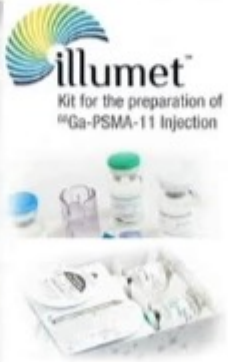
06/2021

TELIX PHARMACEUTICALS

TLX591 (^{68}Ga-PSMA)
BCR patients

12/2021





ABX

(Radelumin®)

^{18}F-PSMA-1007
BCR patients

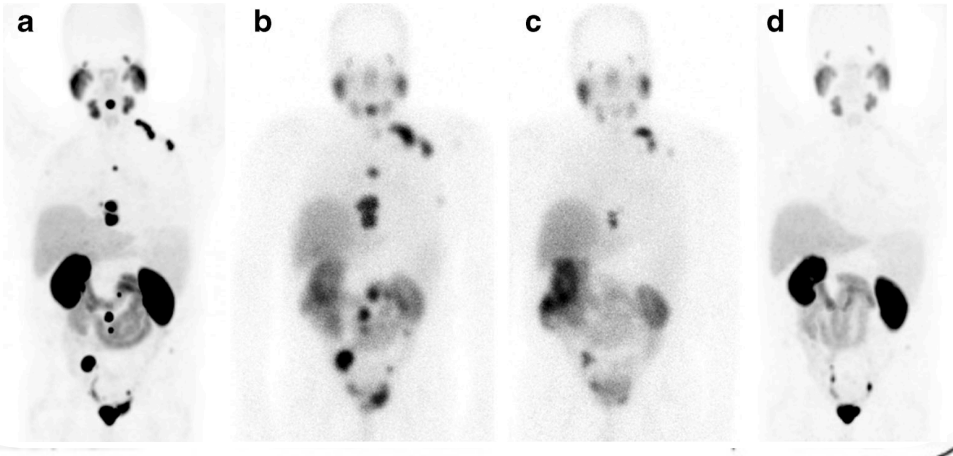
PSMA Therapy

US/EU Market / FDA/EMA drug approval

NOVARTIS

^{177}Lu-PSMA-617 /**Pluvicto®**

03/2022



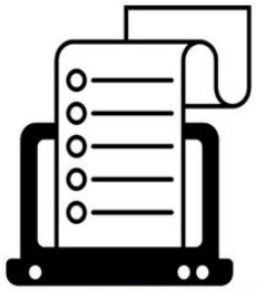
PSMA-Ligands + market visibility world wide

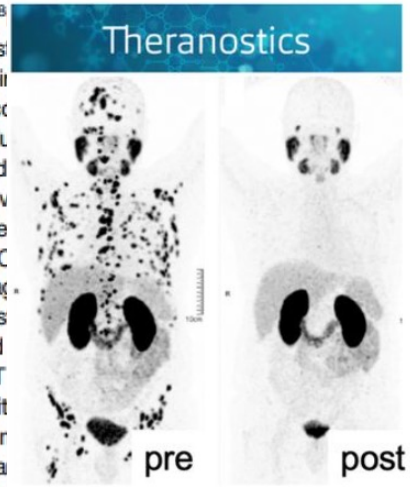
A 2022 International Survey on the Status of Prostate Cancer Theranostics

Thomas Beyer[1], Johannes Czernin[2], Lutz Freudenberg[3], Frederik Giesel[4], Marcus Hacker[5], Rodney J. Hicks[6], and Bernd J. Krause[7]

[1]QIMP Team, Centre Medical Physics and Biome
Molecular and Medical Pharmacology, UCLA, Lo
of Nuclear Medicine, Medical Faculty, Heinrich-H
Department of Nuclear Medicine, University Hosp
of Biomedical Imaging and Image-guided Therapy
St Vincent's Hospital, the University of Melbourne
of Nuclear Medicine, Rostock, Germany

Growing interest in PSMA imaging using [68Ga]- or [18
and PSMA-based radioligand therapy (RLT) of prost
prompted us to survey the global community on their
expectations. **Methods:** A web-based survey was co
rogate areas specific to PET imaging, the clinical valu
applications. International responses were collected
total, over 300 valid responses were received and ev
Most responses (83%) were given by nuclear me
with extensive experience in PET. At 22% of sites, PC
cancer-type–specific PET indications, with an averag
15% and 10% of all cases, respectively. The mos
PSMA PET tracers were [68Ga]PSMA (32%) and
(31%). Users reported a steady growth in PSMA PET
past 5 y, averaging 50% and 82%, respectively, wit
median growth projected over the next 5 y. Of note, r
indicated cognizance of personalized dosimetry tha
routinely. The most commonly identified barriers to future growth in
PCa theranostics were radiopharmaceutical supply, reimbursement,

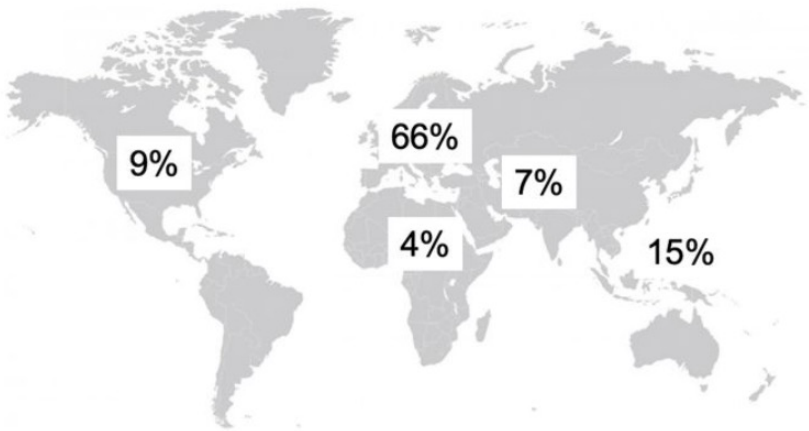




evaluation of high-risk PCa (11,12).
The high PSMA expression in most metastatic, castration-resis-

JNM
The Journal of Nuclear Medicine

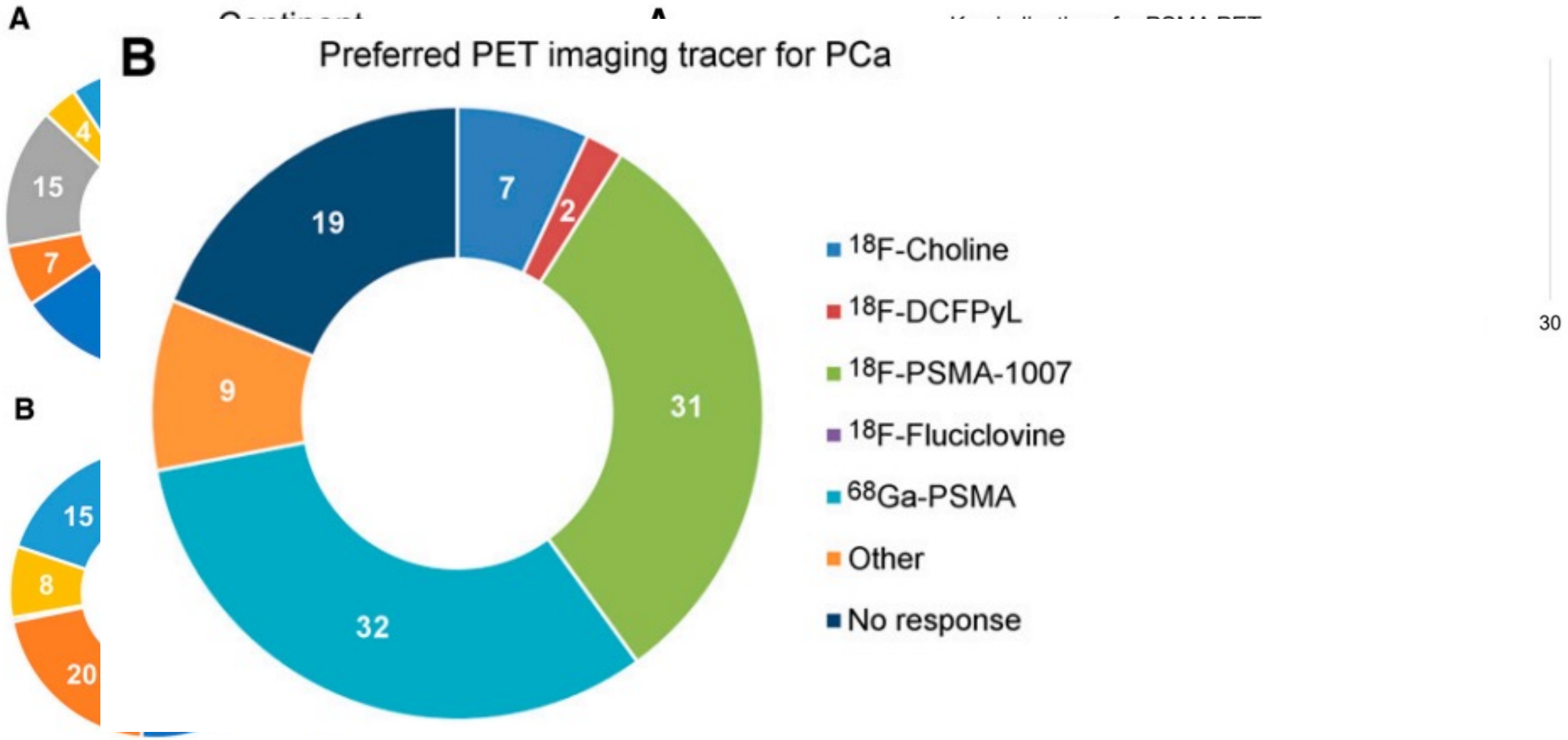
2022 Status | Prostate cancer theranostics



- PET for prostate cancer accounts for 15% indications
- 32% and 31% performed with ^{68}Ga- and ^{18}F-PSMSA, respectively
- Growth of 100% in next 5 y
- Challenges: assessment of heterogeneous response, interaction with urologists and oncologists, limited reimbursement, and capacity building

hhu Heinrich Heine Universität Düsseldorf

PSMA-Ligands + market visibility world wide



Overview

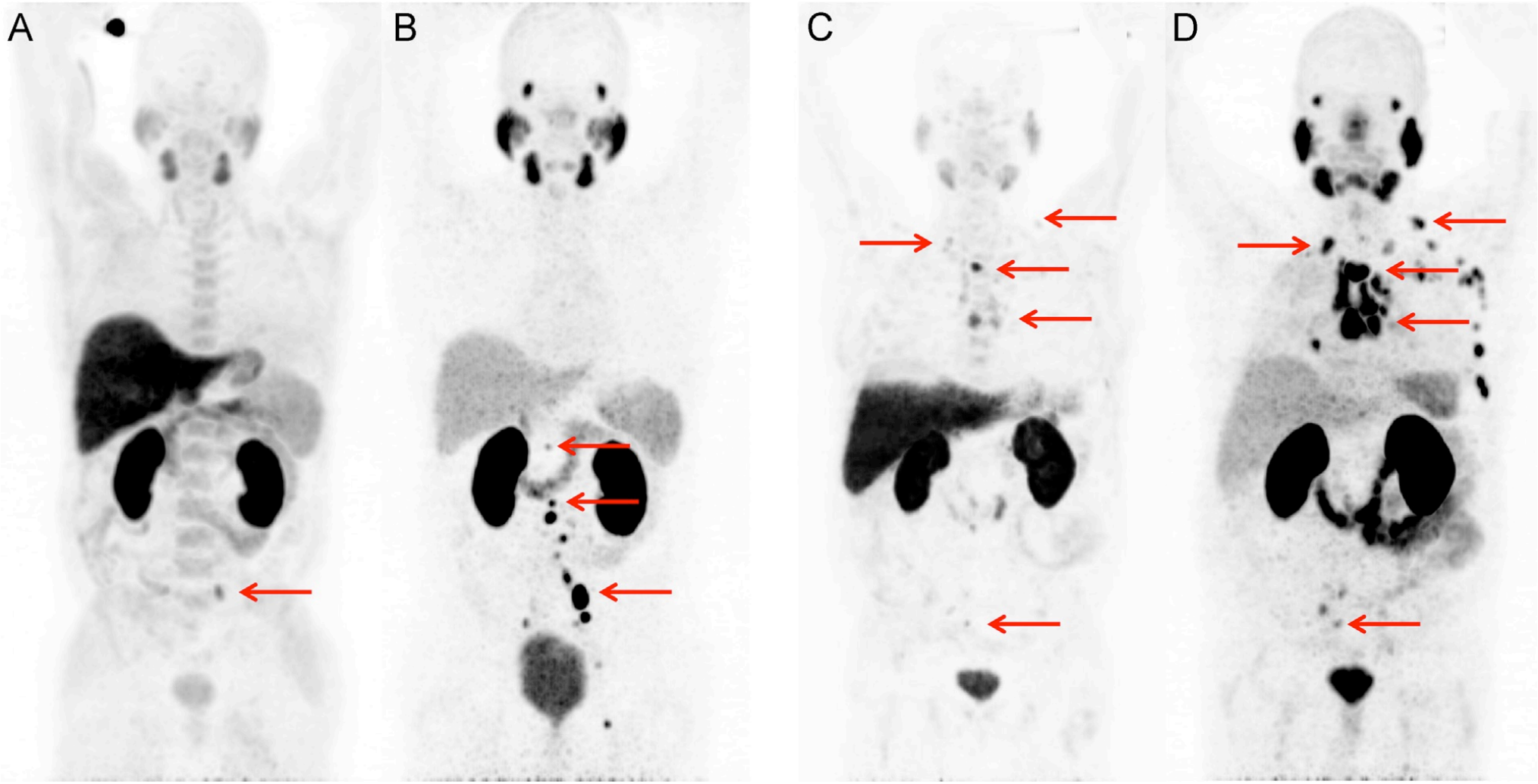
- Background + biology and different PSMA-ligands
- **Recurrent prostate cancer**
- Primary staging and detection
- PSMA-ligand therapy

Recurrent prostate cancer (Choline vs. PSMA)

^{18}FECh-PET/CT

^{18}FECh-PET/CT

Recurrent prostate cancer (Choline vs. PSMA)



^{18}FECh-PET/CT | ^{68}Ga-PSMA-PET/CT | ^{18}FECh-PET/CT | ^{68}Ga-PSMA-PET/CT

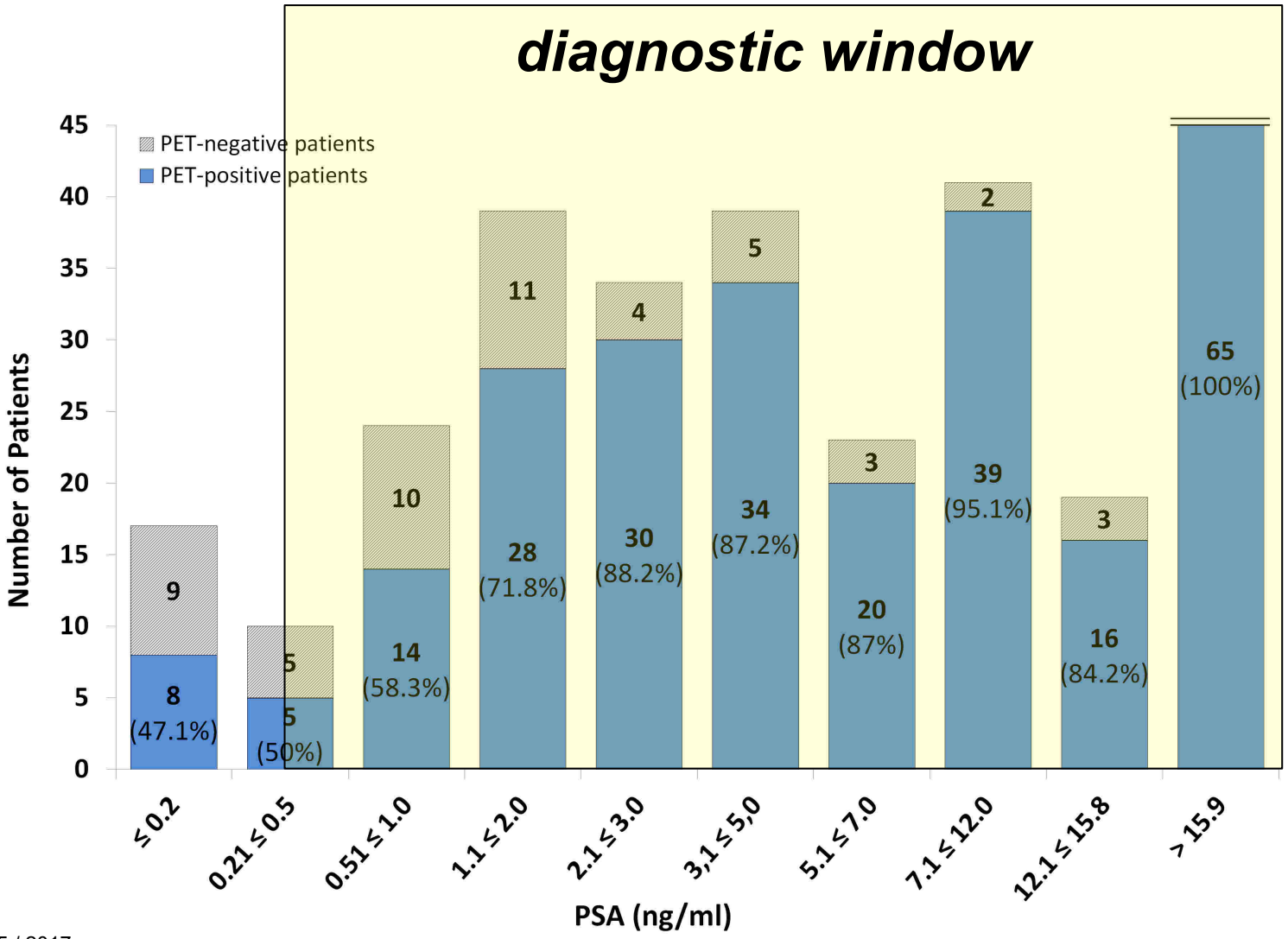
Prospective Multicenter Phase III Study (PSMA-1007 vs. Choline)

Phase III Study of ^{18}F-PSMA-1007 Versus ^{18}F-Fluorocholine PET/CT for Localization of Prostate Cancer Biochemical

Change in Diagnostic Thinking After Both PET/CT Scans (ITT Population) (n = 190)*

Change in diagnostic thinking	^{18}F-fluorocholine examination contributed more	^{18}F-PSMA-1007 examination contributed more	Both PET examinations contributed equally	Missing
Yes				
PET identified site of recurrence that was not known before	3 (1.6)	80 (42.1)	29 (15.3)	3 (1.6)
PET confirmed site of recurrence that was suspected before	1 (0.5)	6 (3.2)	3 (1.6)	
Other		4 (2.1)	15 (7.9)	
Missing		3 (1.6)	2 (1.1)	
No		38 (20)		
Missing				3 (1.6)

Recurrent prostate cancer (Detection efficacy)



Afshar-Oromieh et al. EJNMMI 2015 / 2017

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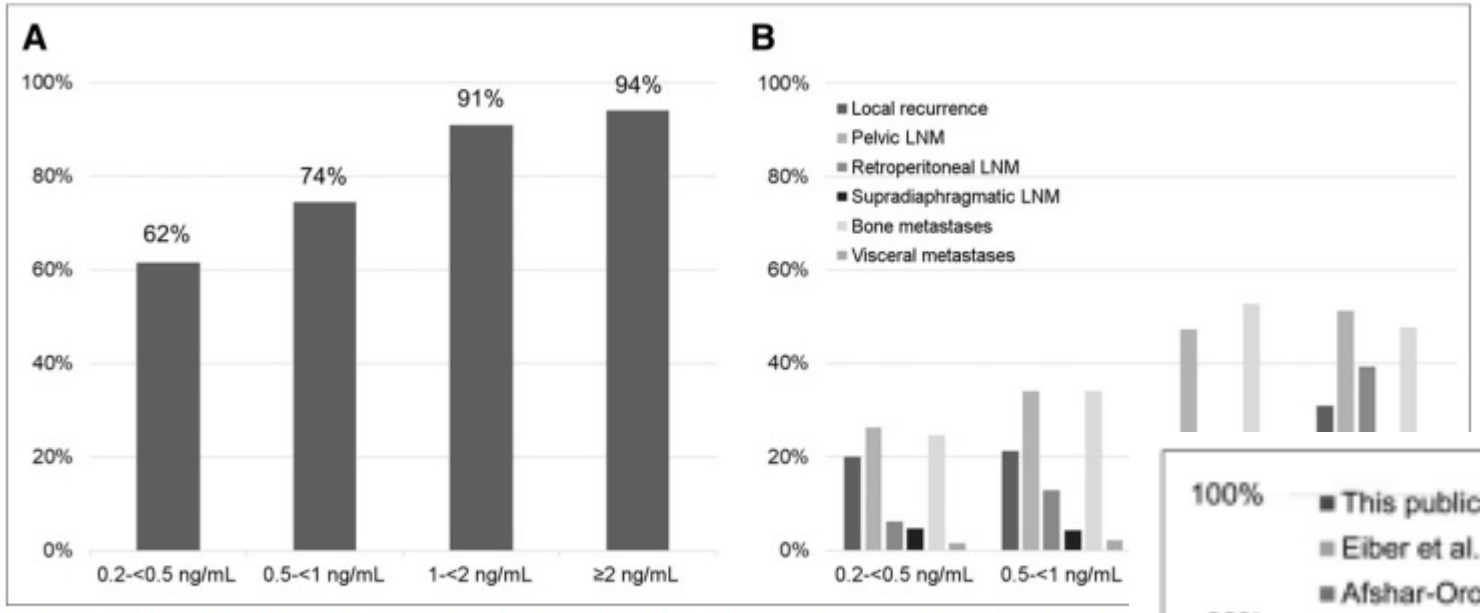


FIGURE 1. Overall rate of detection for ^{18}F-PSMA-1007 PET/CT (A) and relative number of lesions grouped by PSA levels. LNM = lymph node metastases.

Nuclear Medicine, Technical University Munich, Munich, Germany; [5]Department of Urology, Germany; [6]Division of Radiopharmaceutical Chemistry, German Cancer Research Center (D [7]Department of Radiation Oncology, Technical University Munich, Munich, Germany; [8]Cente FALP, Santiago, Chile; and [9]Molecular Imaging Program, National Cancer Institute, Bethesa

Prostate-specific membrane antigen (PSMA)–targeted PET imaging recently emerged as a new method for the staging and restaging of prostate cancer. Most published studies investigated the diagnostic potential of ^{68}Ga-labeled PSMA agents that are excreted renally. ^{18}F-PSMA-1007 is a novel PSMA ligand that has excellent preclinical characteristics and that is only minimally excreted by the urinary tract, a potential advantage for pelvic imaging. The aim of this study was to investigate the diagnostic efficacy of ^{18}F-PSMA-1007 for biochemical recurrence (BCR) after radical prostatectomy. **Methods:** From 3 academic centers, 251 patients with BCR after radical prostatectomy were evaluated in a retrospective analysis. Patients who had received second-line androgen deprivation therapy (ADT) or chemotherapy were excluded, but prior first-line ADT exposure was allowed. The median prostate-specific antigen (PSA) level was 1.2 ng/mL (range, 0.2–228 ng/mL). All patients underwent PSMA

detection efficacy trende
statistically significant (*P*
higher in patients who ha
6 mo before imaging (*P*
PET/CT offers high detect
tomy that are comparabl
^{68}Ga-labeled PSMA ligan

Key Words: ^{18}F-PSMA-1
cancer; biochemical recur

J Nucl Med 2019; 60:362
DOI: 10.2967/jnumed.118

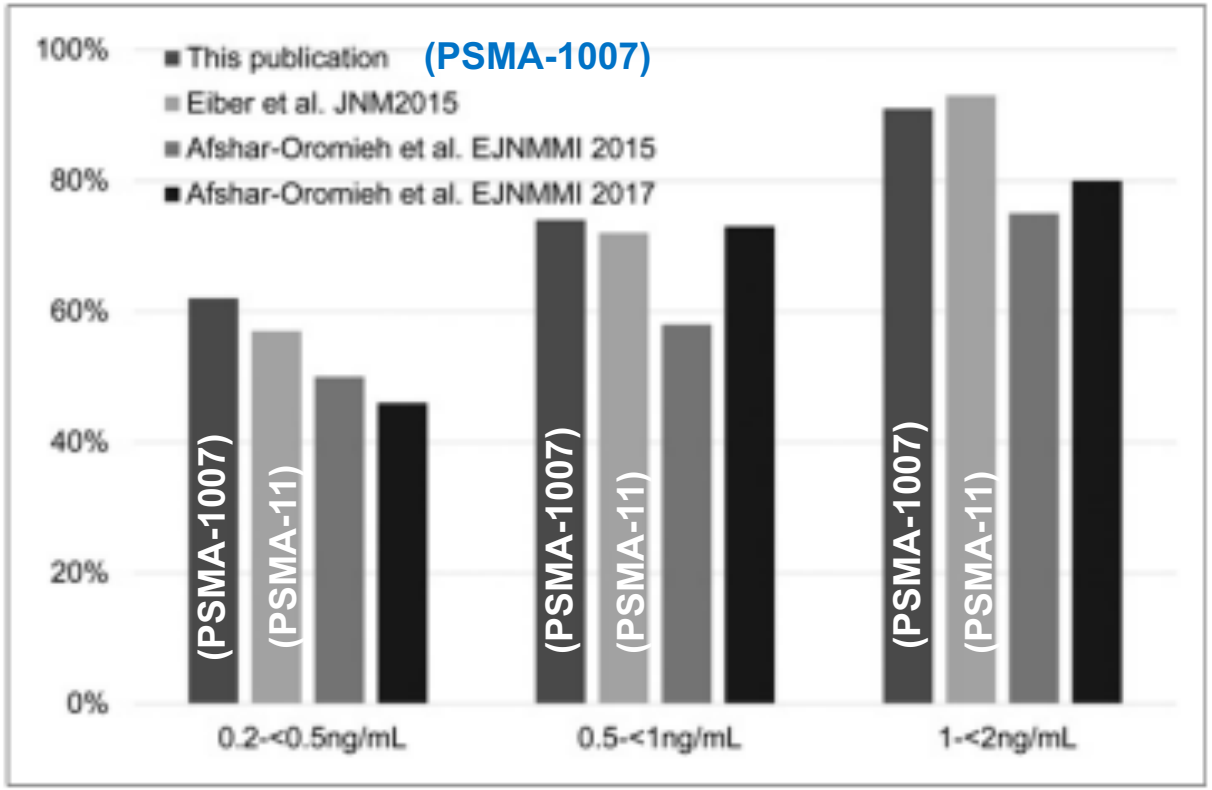
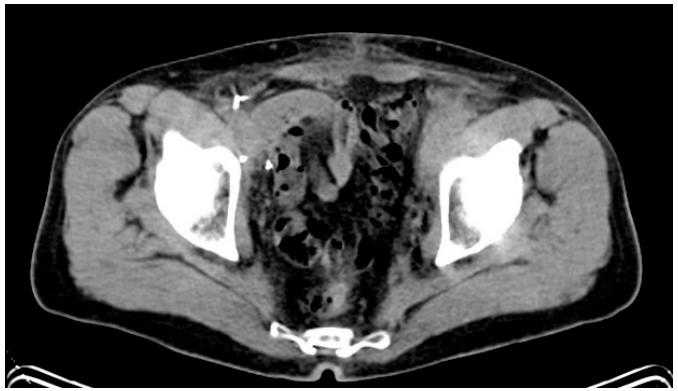


FIGURE 5. Comparison of rates of detection for ^{18}F-PSMA-1007 and ^{68}Ga-PSMA-11 derived from different studies.

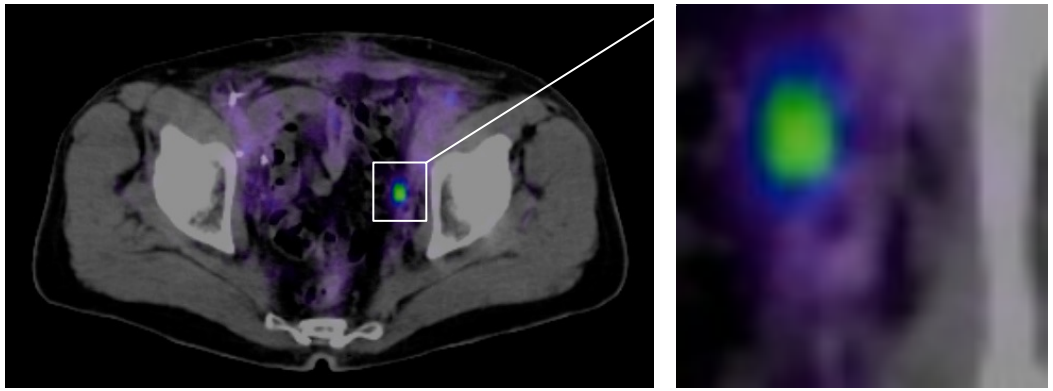
Recurrent prostate cancer

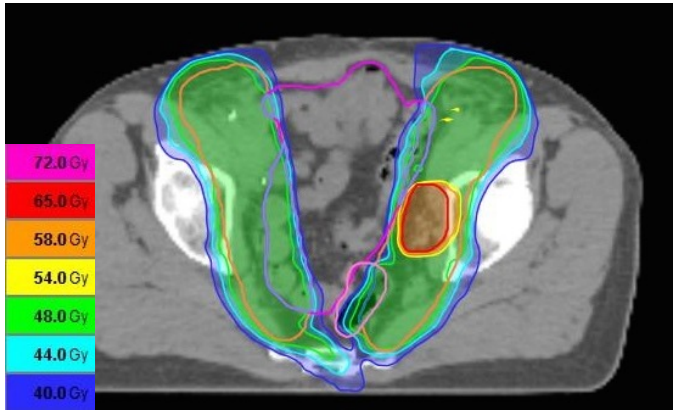
Impact Patient Management

$T_3N_0M_0$



$T_3N_1M_0$



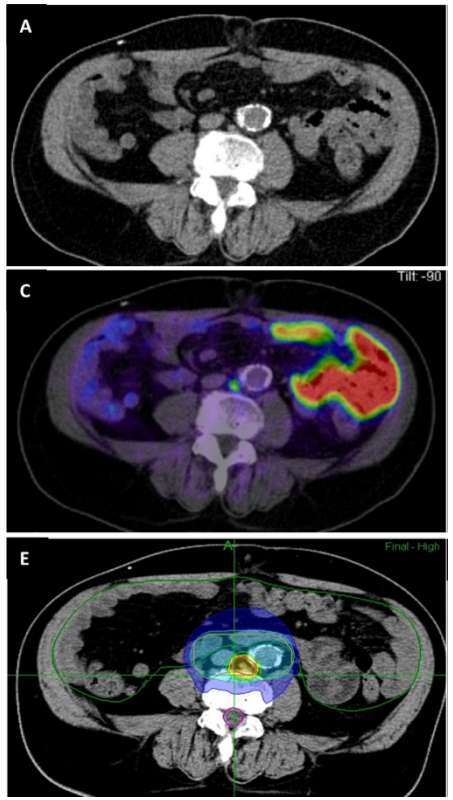


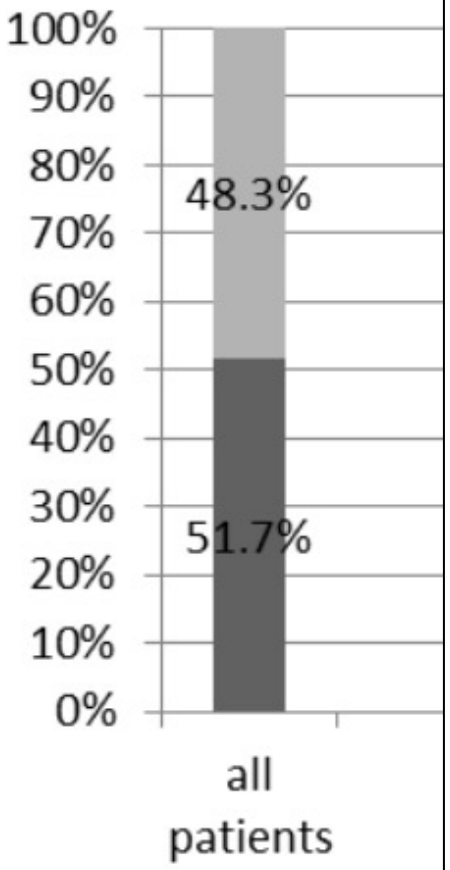
- conventional staging was $T_3N_0M_0$, ^{68}Ga-PSMA PET revealed inguinal and iliac metastases
- IMRT Plan was modified according to these findings with groins and simultaneous integrated boost (SIB)

Sterzing et al. EJNMMI 2015 / 2017

Recurrent prostate cancer

Impact Patient Management in RadioOncology





Sterzing et al, EJNMMI 2016

Dewes *et al. Radiation Oncology* (2016) 11:73
DOI 10.1186/s13014-016-0646-2
Radiation Oncology

RESEA

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Abstract

Backgrou
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Shakespeare *Radiation Oncology* (2015) 10:233
DOI 10.1186/s13014-015-0548-8
Radiation Oncology

SHORT REPORT Open Access

CrossMark

Effect of prostate-specific membrane antigen positron emission tomography on the decision-making of radiation oncologists

Thomas P. Shakespeare[1,2]

Abstract

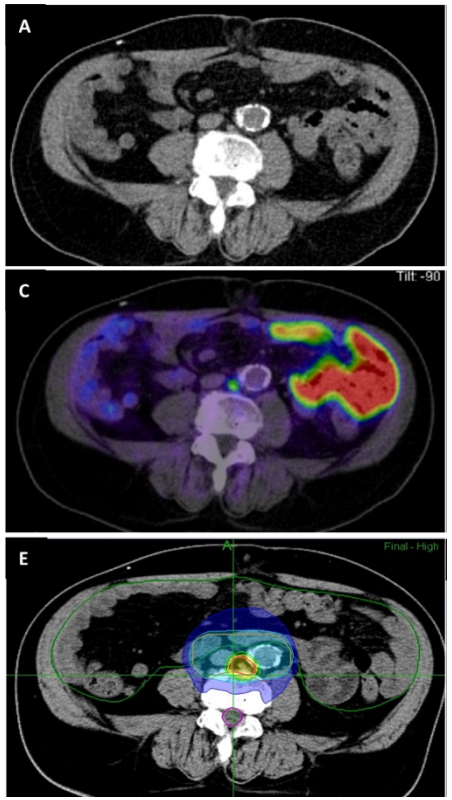
Background: Positron emission tomography (PET) imaging is routinely used in many cancer types, although is not yet a standard modality for prostate carcinoma. Prostate-specific membrane antigen (PSMA) PET is a promising new modality for staging prostate cancer, with recent studies showing potential advantages over traditional computed tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine bone scan imaging. However, the impact of PSMA PET on the decision-making of radiation oncologists and outcomes after radiotherapy is yet to be determined. Our aim was to determine the impact of PSMA PET on a radiation oncologist's clinical practice.

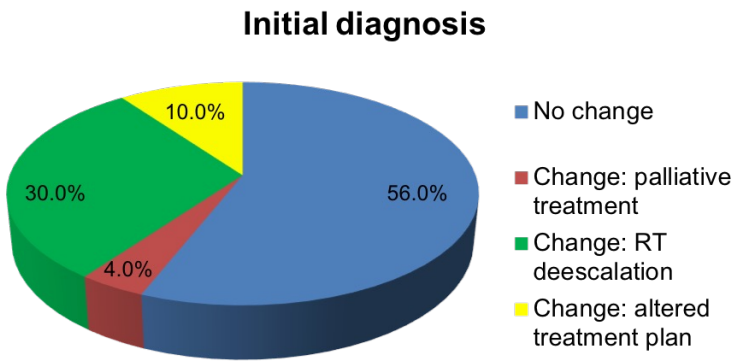
Findings: Patients in a radiation oncology clinic who underwent PSMA PET were prospectively recorded in an electronic oncology record. Patient demographics, outcomes of imaging, and impact on decision-making were evaluated.

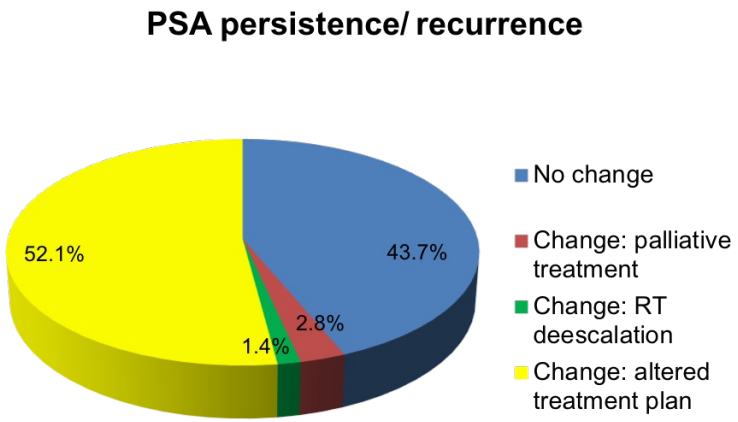
Fifty-four patients underwent PSMA PET between January and May 2015. The major reasons for undergoing PET included staging before definitive (14.8 %) or post-prostatectomy (33.3 %) radiotherapy, and investigation of PSA failures following definitive (16.7 %) or post-prostatectomy (33.3 %) radiotherapy. In 46.3 % of patients PSMA was

Recurrent prostate cancer

Impact Patient Management in RadioOncology







Körber et al., JNM 2018; n=212

Recurrent prostate cancer (Leitlinien): BCR

S3-Leitlinie Prostatakarzinom

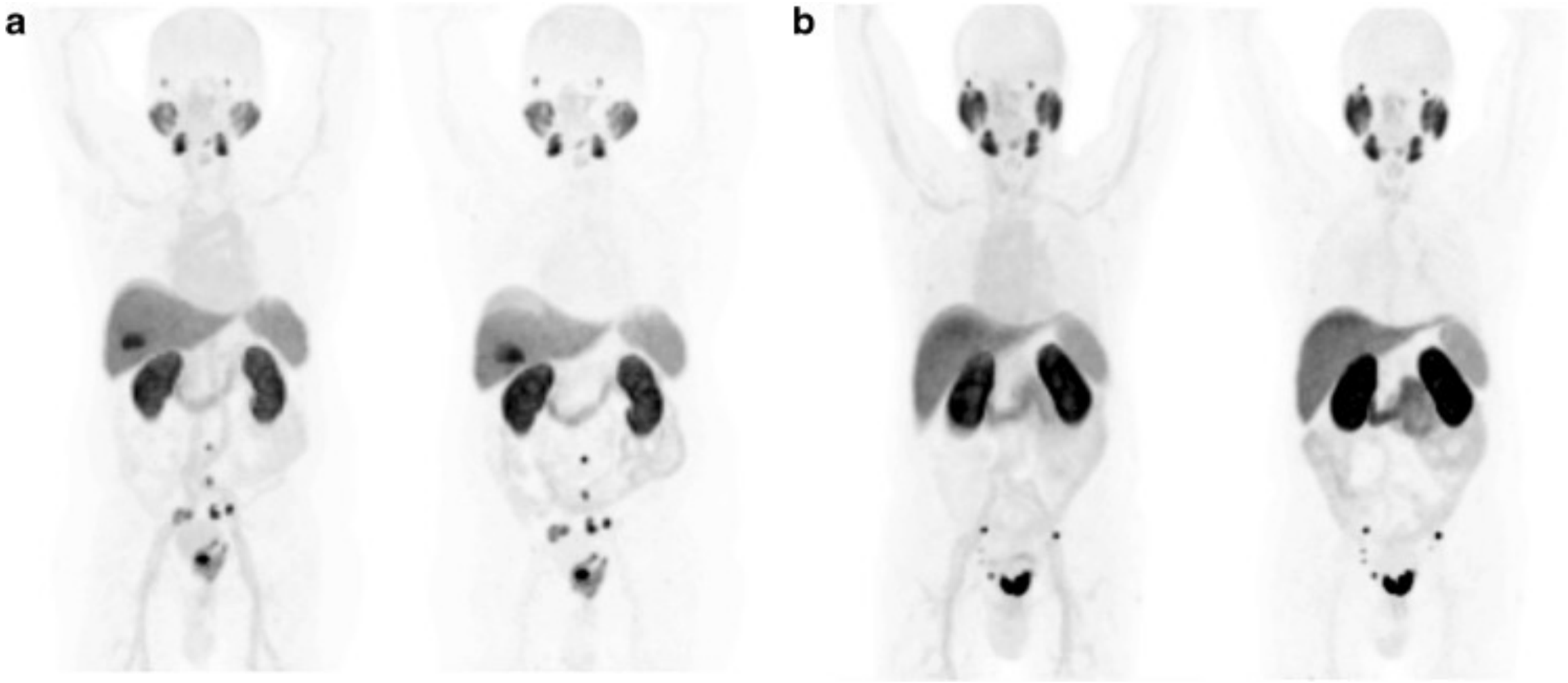
Version 6.2 – Oktober 2021
AWMF-Registernummer: 043/022OL

5.29	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad **0**	a. Im Rahmen einer Rezidivdiagnostik (nach primär kurativer Therapie, s. Empfehlung 7.2 und 7.3) kann primär eine PET Hybrid-Bildgebung mit radioaktiv markierten PSMA-Liganden zur Beurteilung der Tumorausdehnung erfolgen, falls sich aus dem Befund eine therapeutische Konsequenz ergibt.	
Empfehlungsgrad **A**	b. Ein negatives PSMA-PET soll eine frühe Salvage-Therapie nicht verzögern.	

Overview

- Background + biology and different PSMA-ligands
- Recurrent prostate cancer
- **Primary staging and detection**
- PSMA-ligand therapy

Primary staging and detection



Primary staging and detection

Shift from *retro*-spective to *pro*-spective evidence based studies

Multicenter Study > J Nucl Med. 2021 Feb;62(2):208-213. doi: 10.2967/jnumed.120.246363.
Epub 2020 Aug 17.

Diagnostic Accuracy of ^{18}F-PSMA-1007 PET/CT Imaging for Lymph Node Staging of Prostate Carcinoma in Primary and Biochemical Recurrence

Katharina Sprute [1], Vasko Kramer [2 3], Stefan A Koerber [4 5 6], Manuel Meneses [7],
Rene Fernandez [3], Cristian Soza-Ri
Isabel Rauscher [8], Kambiz Rahbar [1]
Motohide Uemura [11], Sadahiro Naka
Constantin Schwab [14], Viktoria Schi
Juergen Debus [4 5 6 6 17 18], Cler
Uwe Haberkorn [1 19], Camilo Sandor

Comparative Study > BMC Cancer. 2020 Aug 5;20(1):723. doi: 10.1186/s12885-020-07192-7.

Clinical impact of PSMA PET/CT in primary prostate cancer compared to conventional nodal and distant staging: a retrospective single center study

Maarten L Donswijk [1], Pim J van Leeuwen [2], Erik Vegt [3 4], Zing Cheung [3],

Retrospektive Einzelstudien →

> World J Urol. 2020 Dec;38(12):3085-3090. doi: 10.1007/s00345-020-03131-0.
Epub 2020 Feb 26.

^{68}Ga-PSMA PET/CT based primary staging and histological correlation after extended pelvic lymph node dissection at radical prostatectomy

J Kopp [1 2], D Kopp [3 4], E Bernhardt [1], L Manka [1], A Beck [1], H Gerullis [5], P Karakiewicz [6 7],
W Schoerner [3], P Hammerer [1], Jonas Schiffmann [8]

Affiliations + expand
PMID: 32103332 DOI: 10.1007/s00345-020-03131-0

Affiliations + expand
PMID: 32103332 DOI: 10.1007/s00345-020-03131-0

2011

Randomized Controlled Trial > Lancet. 2020 Apr 11;395(10231):1208-1216.
doi: 10.1016/S0140-6736(20)30314-7. Epub 2020 Mar 22.

Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective,

Michael S Hofman [1], N
Paul Thomas [6], Natalie
Ramdave Shakher [10], L
Paul Roach [14], Michelle
Petra Marusic [19], Anett
Scott Williams [22], Decl

Affiliations + expand
PMID: 32209449 DOI

Clinical Trial > J Nucl Med. 2020 Aug;61(8):1153-1160. doi: 10.2967/jnumed.119.237602.
Epub 2020 Jan 10.

Impact of ^{68}Ga-PSMA-11 PET/CT on Staging and Management of Prostate Cancer Patients in Various Clinical Settings: A Prospective Single-Center Study

Ida Sonni [1], Matthias Eiber [2 3], Wolfgang P Fendler [2 4], Reiah M Alano [2], Sitaram S Vangala [5],
Amar U Kishan [7 8 9],
Johannes Czern

Prospektive Evidenzstudien

Clinical Trial > J Nucl Med. 2020 Apr;61(4):533-539. doi: 10.2967/jnumed.119.232504.
Epub 2019 Sep 27.

Comparison of 3 Interpretation Criteria for ^{68}Ga-PSMA11 PET Based on Inter- and Intrareader Agreement

Akira Toriihara [1], Tomomi Nobashi [1], Lucia Baratto [1], Heying Duan [1], Farshad Moradi [1],
Sonya Park [1], Negin Hatami [1], Carina Mari Aparici [1], Guido Davidzon [1], Andrei Iagaru [2]

Affiliations + expand
PMID: 31562226 DOI: 10.2967/jnumed.119.232504

2022

Primary staging and detection

Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multi-centre study

*Michael S Hofman, Nathan Lawrentschuk, Roslyn J Francis, Colin Tang, Ian Vela, Paul Thomas, Natalie Rutherford, Jarad M Martin, Mark Frydenberg, Ramdave Shakher, Lih-Ming Wong, Kim Taubman, Sze Ting Lee, Edward Hsiao, Paul Roach, Michelle Nottage, Ian Kirkwood, Dickon Hayne, Emma Link, Petra Marusic, Anetta Matera, Alan Herschtal, Amir Iravani, Rodney J Hicks, Scott Williams, Declan G Murphy, for the proPSMA Study Group Collaborators**

Summary

Background Conventional imaging using CT and bone scan has insufficient sensitivity when staging men with high-risk localised prostate cancer. We aimed to investigate whether novel imaging using prostate-specific membrane antigen (PSMA) PET-CT might improve accuracy and affect management.

Methods In this multicentre, two-arm, randomised study, we recruited men with biopsy-proven prostate cancer and high-risk features at ten hospitals in Australia. Patients were randomly assigned to conventional imaging with CT and bone scanning or gallium-68 PSMA-11 PET-CT. First-line imaging was done within 21 days following randomisation. Patients crossed over unless three or more distant metastases were identified. The primary outcome was accuracy of first-line imaging for identifying either pelvic nodal or distant-metastatic disease defined by the receiver-operating curve using a predefined reference-standard including histopathology, imaging, and biochemistry at 6-month follow-up. This trial is registered with the Australian New Zealand Clinical Trials Registry, ANZCTR12617000005358.

Findings From March 22, 2017 to Nov 02, 2018, 339 men were assessed for eligibility and 302 men were randomly assigned. 152 (50%) men were randomly assigned to conventional imaging and 150 (50%) to PSMA PET-CT. Of 295 (98%) men with follow-up, 87 (30%) had pelvic nodal or distant metastatic disease. PSMA PET-CT had a 27% (95% CI 23–31) greater accuracy than that of conventional imaging (92% [88–95] *vs* 65% [60–69]; p<0·0001). We found a lower sensitivity (38% [24–52] *vs* 85% [74–96]) and specificity (91% [85–97] vs 98% [95–100]) for conventional imaging compared with PSMA PET-CT. Subgroup analyses also showed the superiority of PSMA PET-CT (area under the curve of the receiver operating characteristic curve 91% vs 59% [32% absolute difference; 28–35] for patients with pelvic nodal metastases, and 95% vs 74% [22% absolute difference; 18–26] for patients with distant metastases). First-line conventional imaging conferred management change less frequently (23 [15%] men [10–22] *vs* 41 [28%] men [21–36]; p=0·008) and had more equivocal findings (23% [17–31] *vs* 7% [4–13]) than PSMA PET-CT did.

Published Online
March 22, 2020
https://doi.org/10.1016/S0140-6736(20)30314-7

See Online/Comment
https://doi.org/10.1016/S0140-6736(20)30527-4

*A complete list of members is provided in the appendix

Molecular Imaging and Therapeutic Nuclear Medicine (Prof M S Hofman MBBS, P Marusic BSc, A Iravani MD, Prof R J Hicks MBBS), **Centre for Biostatistics and Clinical Trials** (E Link DPhil, A Matera MSc, A Herschtal PhD), **Division of Radiation Oncology** (Prof S Williams MBBS), **Division of Cancer Surgery** (Prof D G Murphy MBBCh), **Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Sir Peter MacCallum Department of Oncology** (Prof M S Hofman, N Lawrentschuk MBBS, E Link,

Primary staging and detection

Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multi-centre study

*Michael S Hofman, Nathan Lawrentschuk, Roslyn J Francis, Colin Tang, Ian Vela, Paul Thomas, Natalie Rutherford, Jarad M Martin, Mark Frydenberg, Ramdave Shakher, Lih-Ming Wong, Kim Taubman, Sze Ting Lee, Edward Hsiao, Paul Roach, Michelle Nottage, Ian Kirkwood, Dickon Hayne, Emma Link, Petra Marusic, Anetta Matera, Alan Herschtal, Amir Iravani, Rodney J Hicks, Scott Williams, Declan G Murphy, for the proPSMA Study Group Collaborators**

INTERPRETATION

PSMA PET/CT is a suitable replacement for CT and bone scanning, providing :

- superior accuracy
- management change
- lower radiation

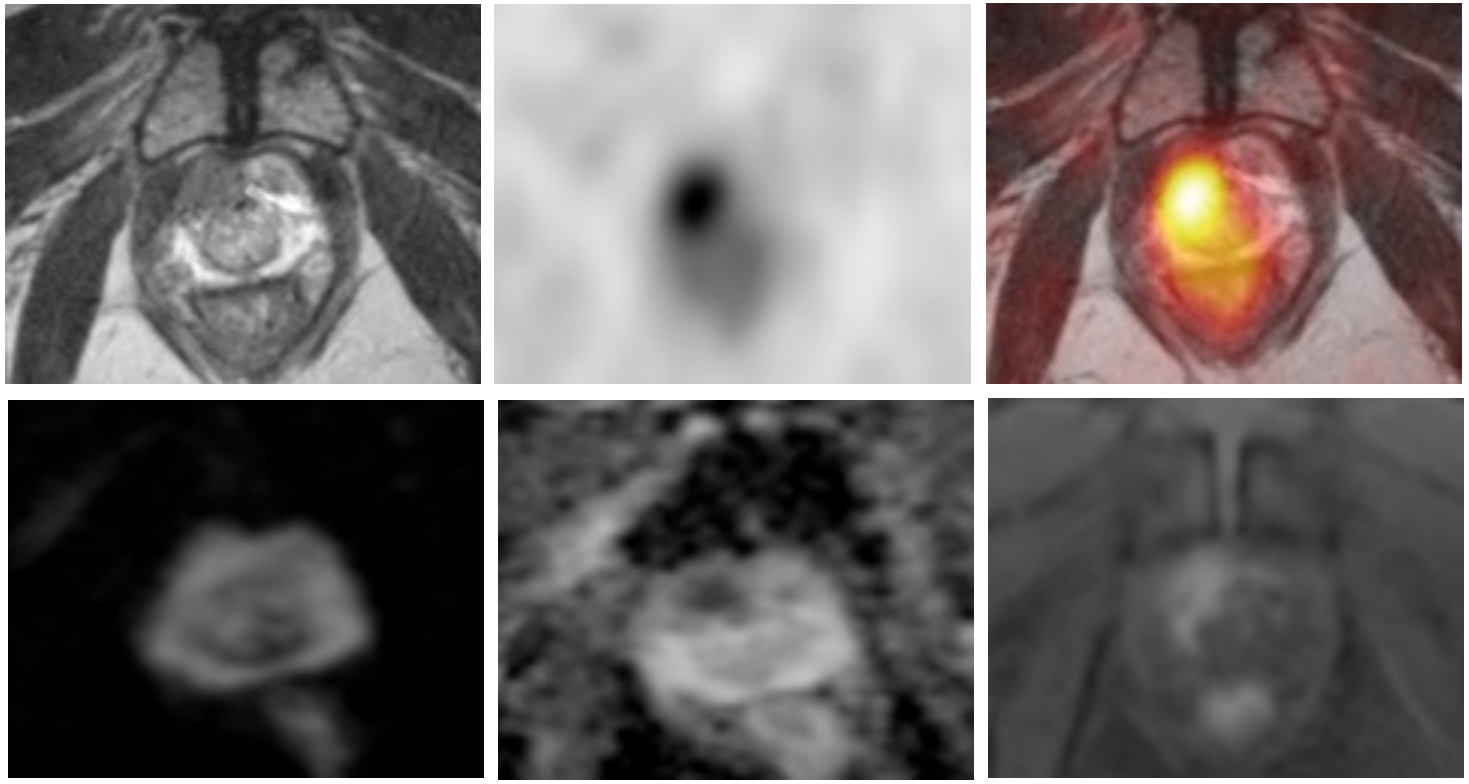
RESULTS

	CT + bone scan	PSMA PET/CT
medium / high management impact (% pt)	15%	28%
equivocal results (% pt)	23%	7%
radiation exposure (mSv)	19	8

Primary staging and detection

T-Staging using mpMRI and PSMA-PET

68y/o pat, prior neg Bx, continious PSA-increase 10.1 ng/ml

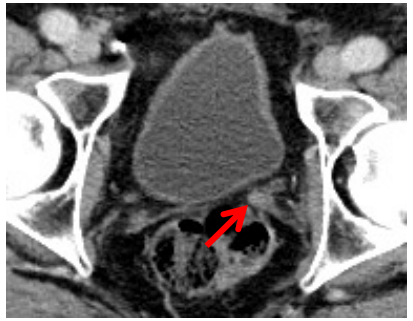


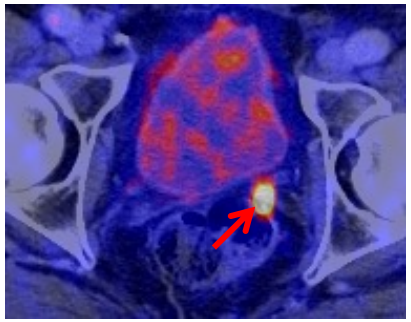
PIRDAS 5
⇒ Gleason 7b (4+3) at targeted biopsy

Local recurrence

Local recurrence

74y/o patient, s/p. RPE 2004 pT2a pN0 Gleason 7, s/p salvage RTx 2010, *PSA-value 05/15: 1.76 ng/ml*

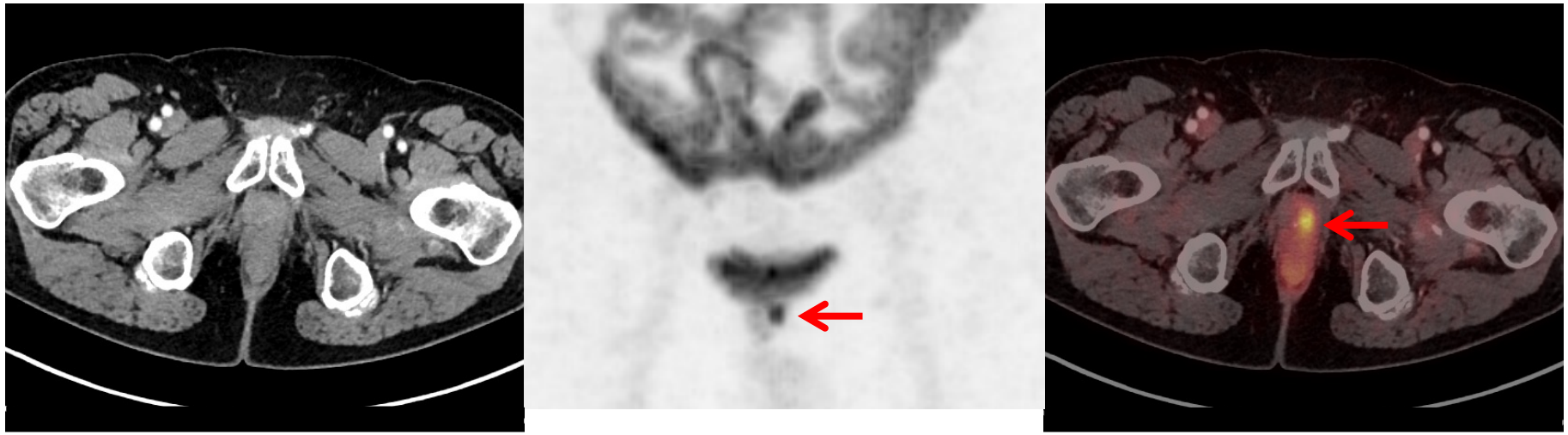




salvage operation:
soft-tissue including seminal vesicle with a cribriforme, poorly differentiated adenocarcinoma of the prostate (Gleason 7)

Maurer T et al, Nat Rev Uro 2016

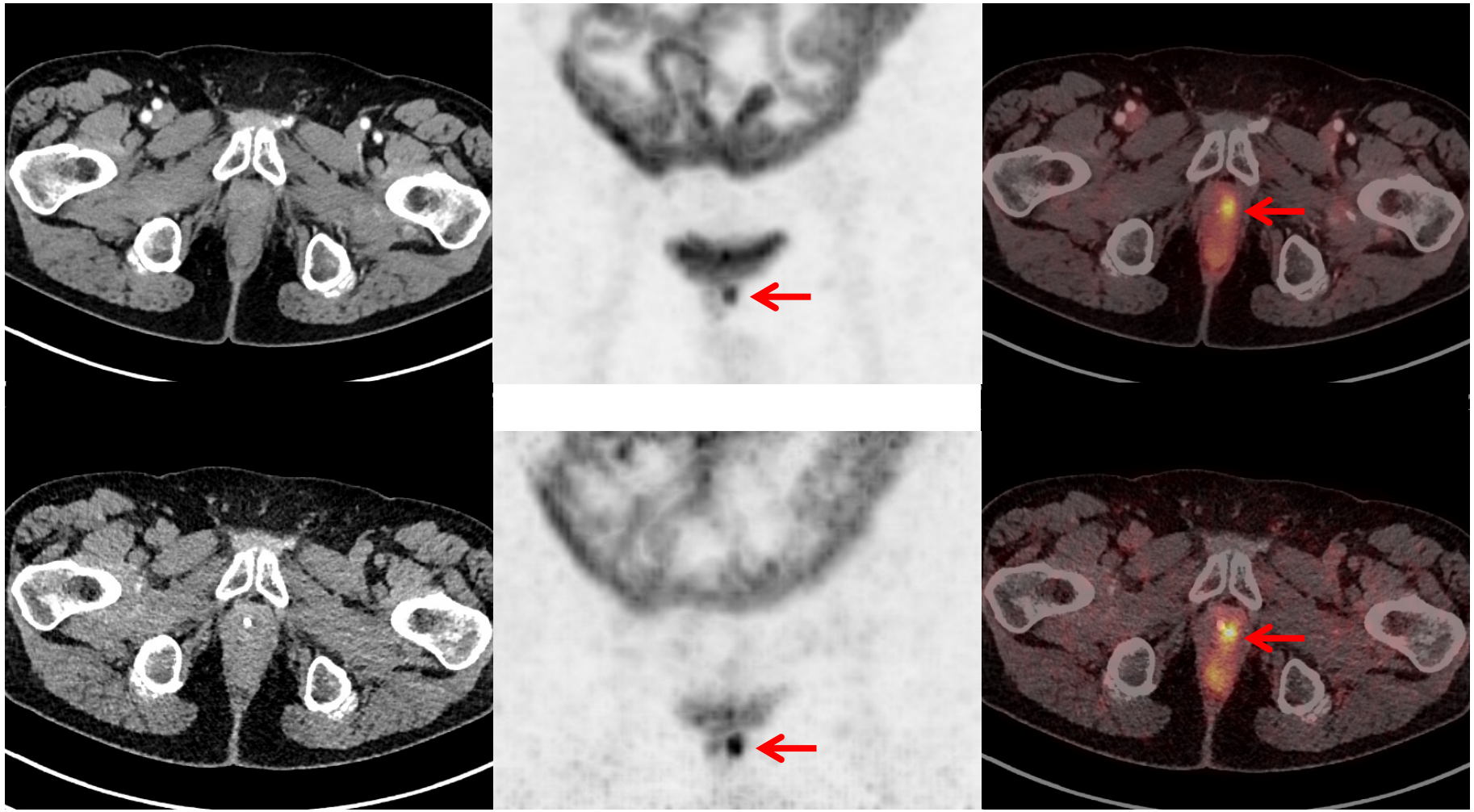
Local Recurrence



71 y.o.
PSAnadir: 0,04
GSC 7 b, RPE 09/2013
Monate nach RPE: 111
Z.n. Radiatio

Mamlins E., Giesel F.L., Schimmöller L. / MS in preparation

Local Recurrence



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GSC 7 b, RPE 09/2013
Monate nach RPE: 111
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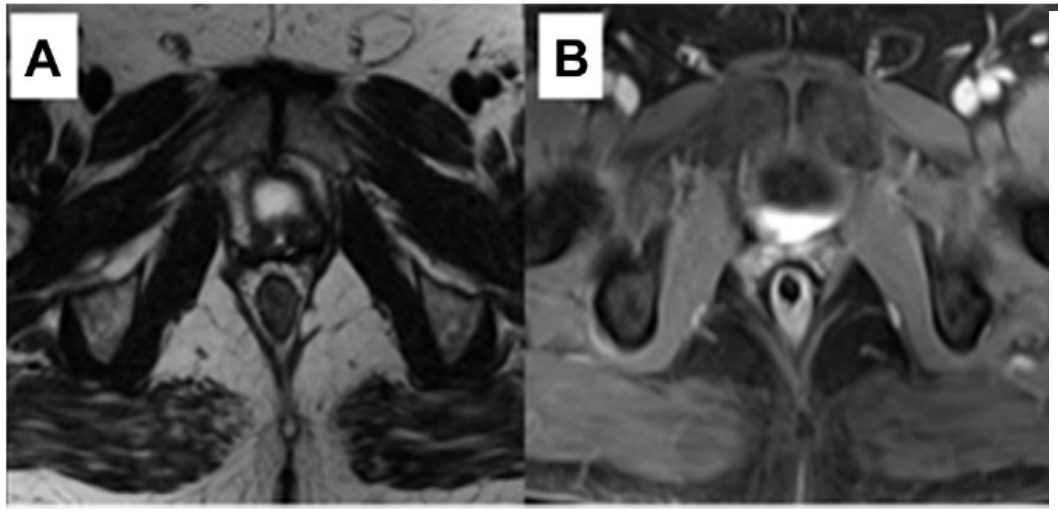
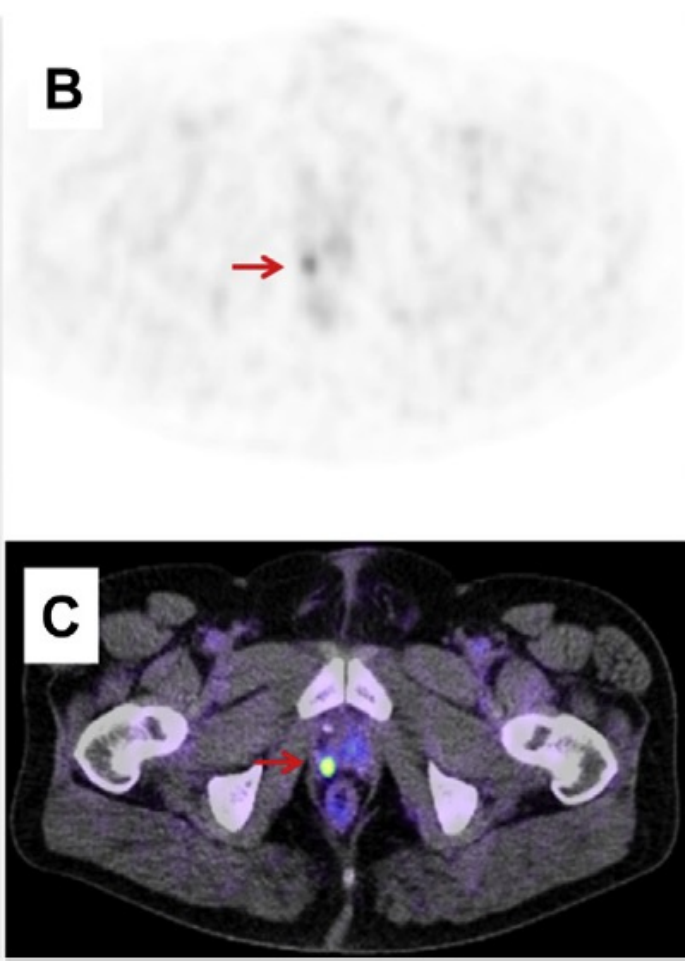
E. Mamlins, F. Giesel, G. Antoch, L. Schimmöller / MS in preparation

Local recurrent





Multiparametric Magnetic Resonance Imaging Examination of a 48-Year-old Patient 6 Months After Radical Prostatectomy

Gleason Score 7, Stage pT2cN0M0

PSA elevated: 0.3 ng/mL.

Primary Staging

S3-Leitlinie Prostatakarzinom

Version 6.2 – Oktober 2021
AWMF-Registernummer: 043/022OL

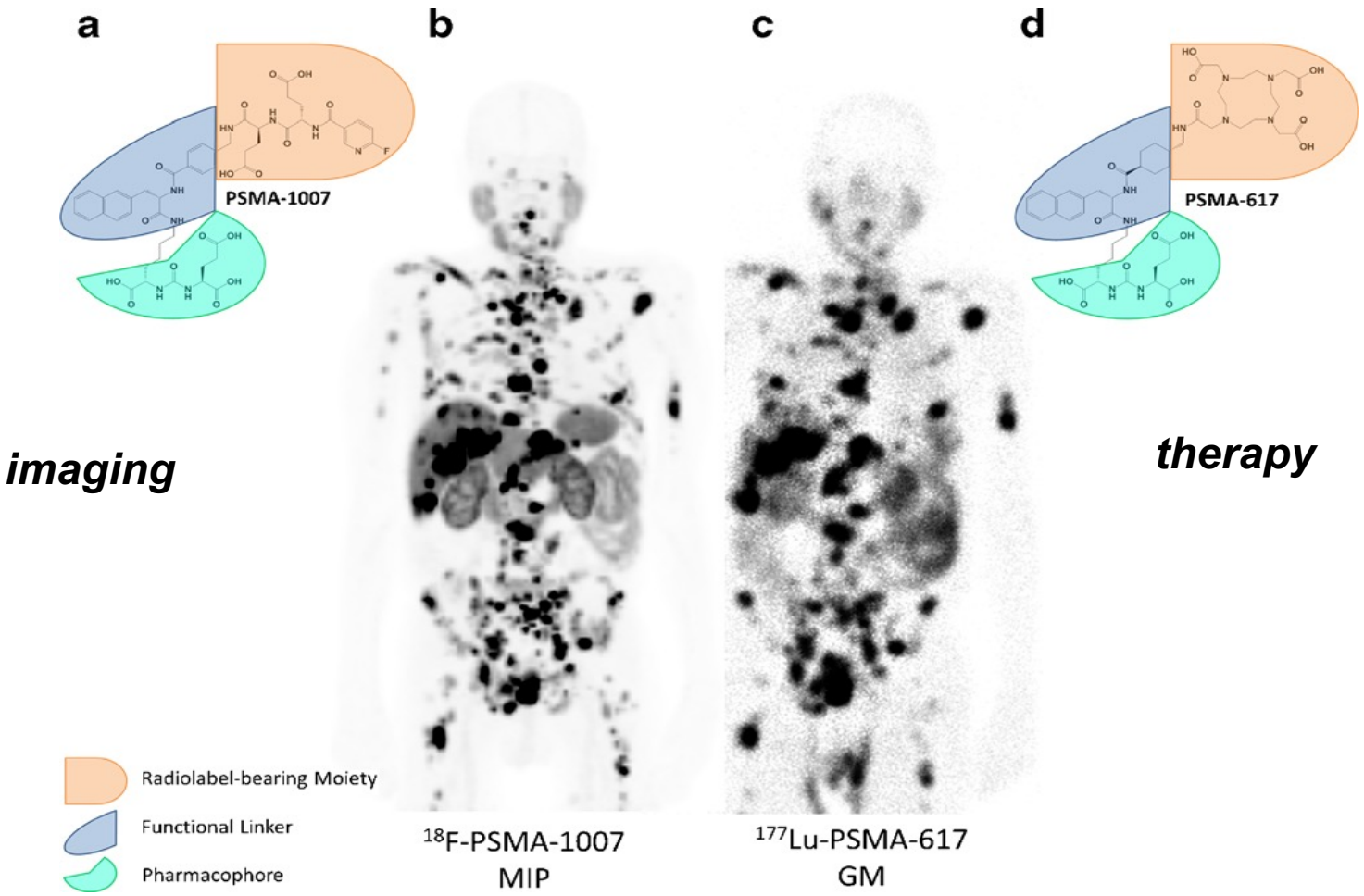
5.25	Evidenzbasierte Empfehlung / Statement	neu 2021
	a. Das PSMA-PET hat eine höhere Genauigkeit (accuracy) für den Nachweis von Prostatakarzinom-Metastasen als die Kombination aus Computertomographie und Knochenszintigraphie.	
Empfehlungsgrad **0**	b. Das PSMA-PET/CT kann beim High-Risk Prostatakarzinom (Gleason-Score 8-10 oder T-Kategorie cT3/cT4 oder PSA≥20ng/ml) zur Ausbreitungsdiagnostik eingesetzt werden.	

Overview

- Background + bioloy and different PSMA-ligands
- Recurrent prostate cancer
- Primary staging and detection
- **PSMA-ligand therapy**

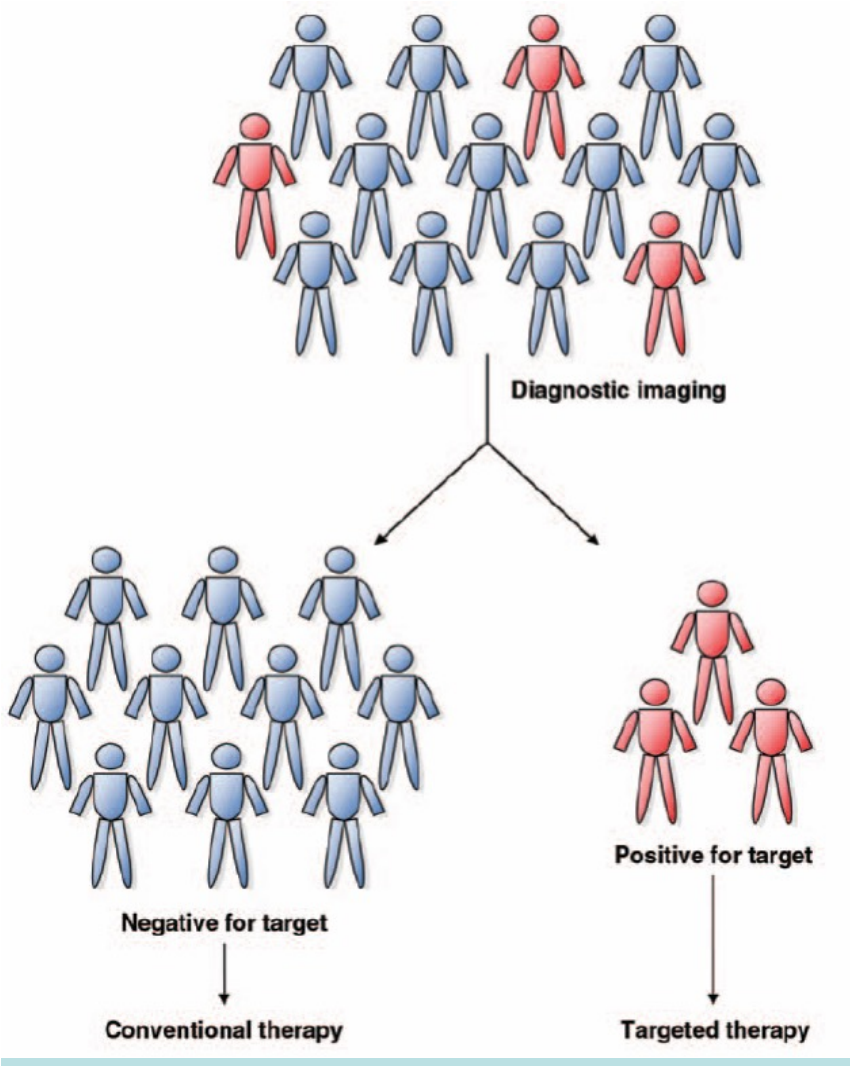
PSMA-ligand therapy

PSMA-1007 twin-brother of PSMA-617 / Pluvicto®



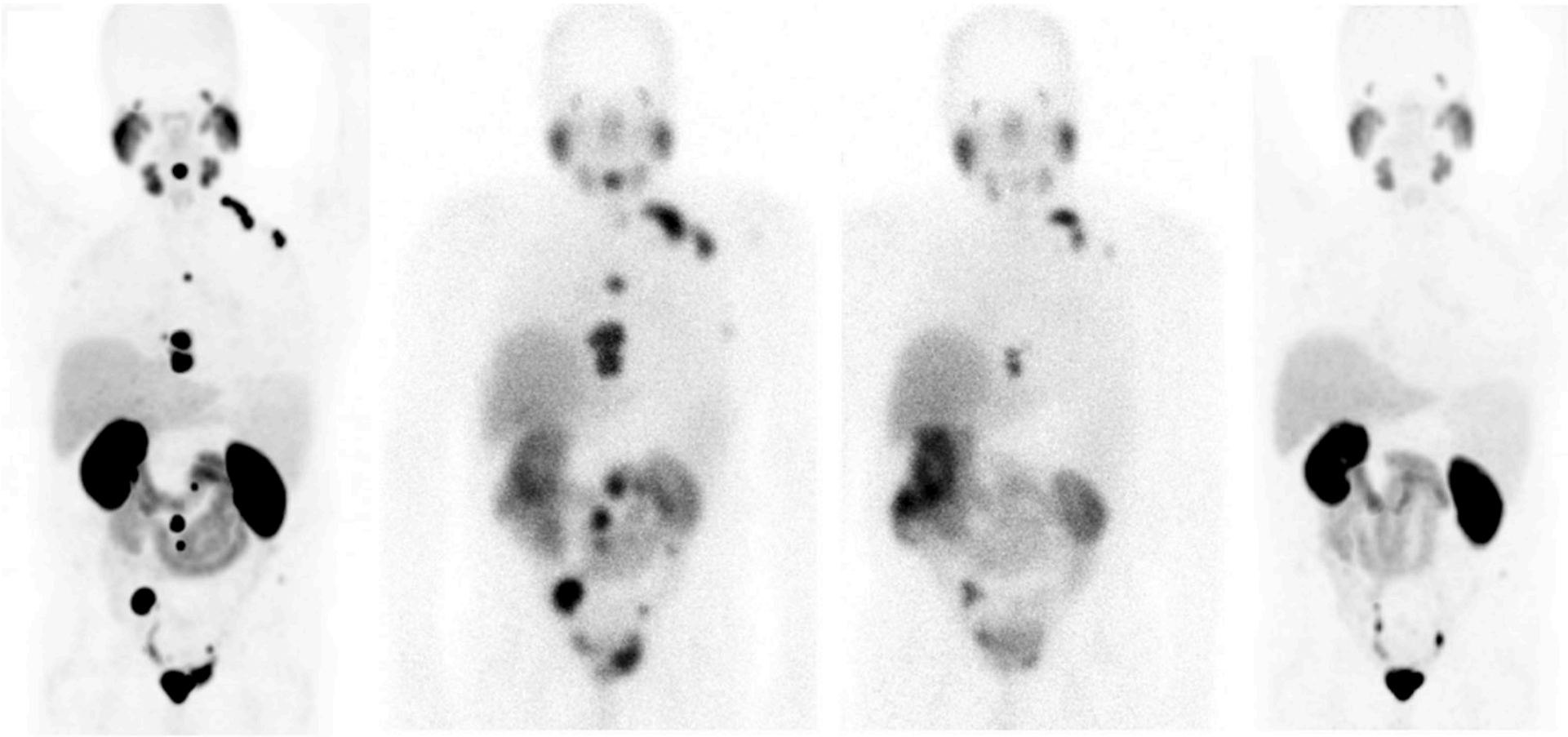
Giesel et al., EJNMMI 2016

PSMA-ligand therapy



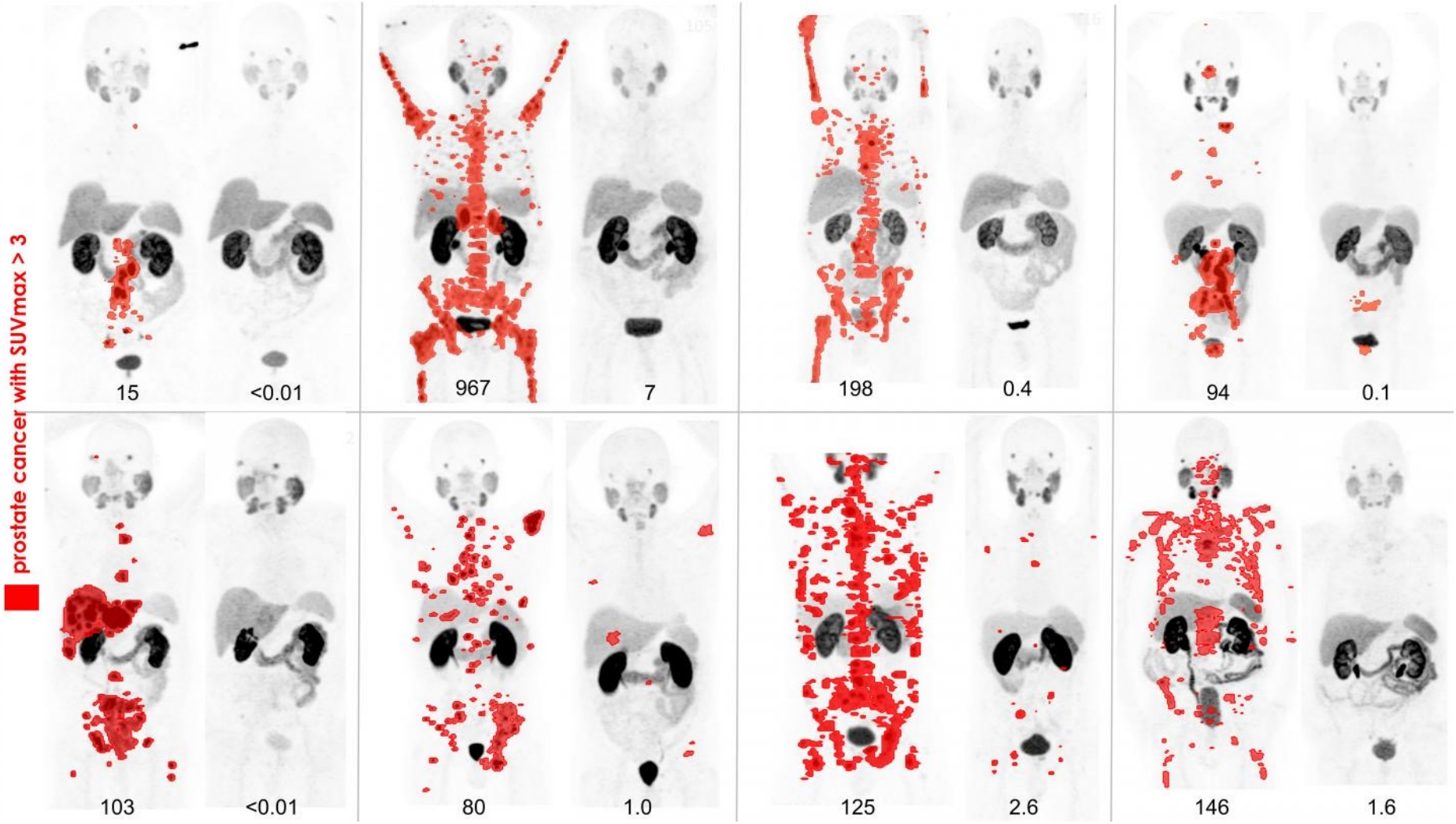
PSMA-Phenotyping

PSMA-ligand therapy



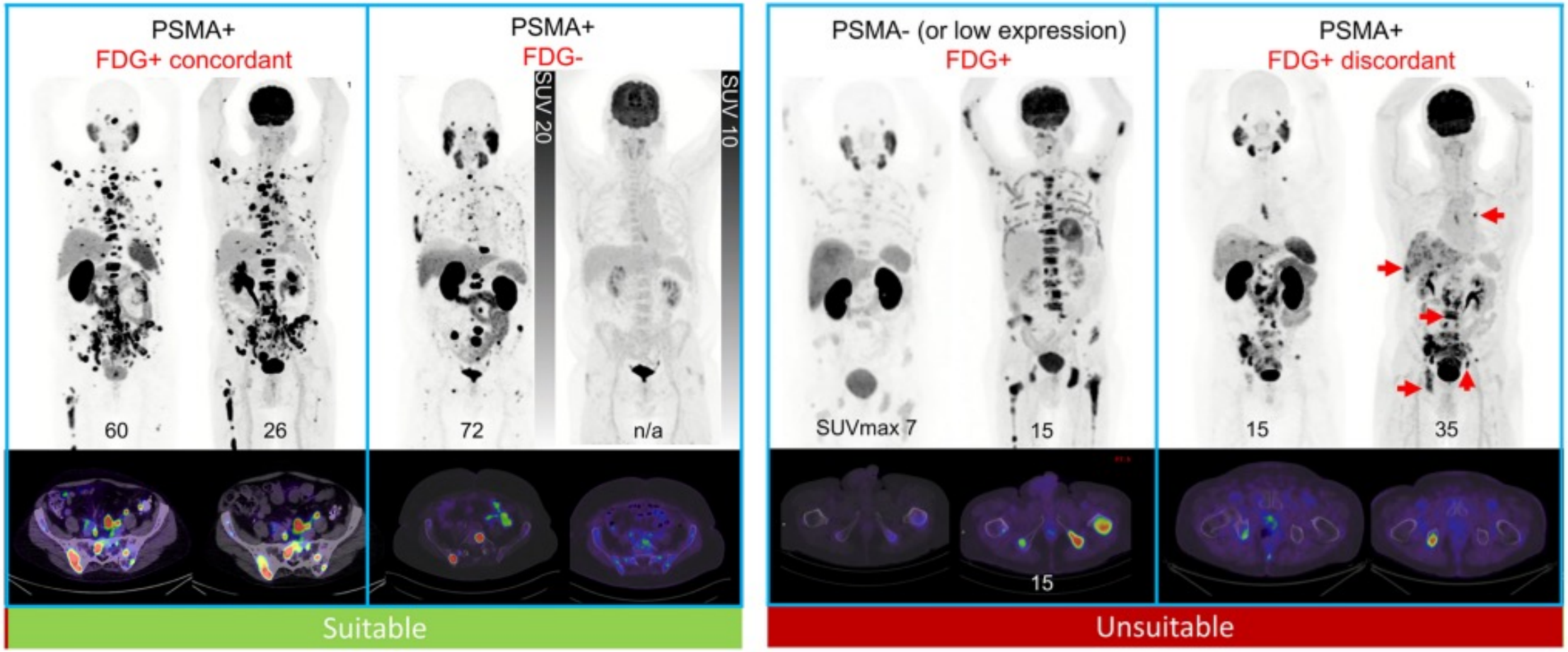
12/13	02/14	05/14	07/14
^{68}Ga-DKFZ-11 PSMA-PET/CT, MIP	^{177}Lu-DKFZ-617 Therapy, geometric mean	^{177}Lu-DKFZ-617 Therapy, geometric mean	^{68}Ga-DKFZ-11 PSMA-PET/CT, MIP

PSMA-ligand therapy



SNMMI Image-of-the-year 2018:
PSMA-Theranostik des fortgeschrittenen metastasierten Prostatakarzinoms

PSMA-ligand therapy



PSMA-ligand therapy

NOVARTIS

Search Menu

Home > News > Novartis Pluvicto™ approved by FDA as first targeted radioligand therapy for treatment of progressive, PSMA positive metastatic castration-resist ...

Novartis Pluvicto™ approved by FDA as first targeted radioligand therapy for treatment of progressive, PSMA positive metastatic castration-resistant prostate cancer

Mar 23, 2022

Ad hoc announcement pursuant to Art. 53 LR

- *FDA also approved complementary diagnostic imaging agent, Locametz®, after radiolabeling with gallium-68 for the identification of PSMA-positive lesions[2]*
- *Metastatic prostate cancer has a 5-year survival rate of less than 30%[3]; mCRPC patients who progress on multiple lines of therapy have limited treatment options*
- *FDA approval was based on pivotal Phase III VISION trial, where patients with pre-treated PSMA-positive mCRPC who received Pluvicto plus standard of care had a statistically significant reduction in risk of death[1]; both alternate primary endpoints of overall survival and radiographic progression free survival were met[1]*
- *Novartis is committed to reimagining medicine in prostate cancer with targeted radioligand therapy - a type of precision cancer treatment combining a targeting compound (ligand) with a therapeutic radioisotope (a radioactive particle)*

PSMA-ligand therapy

ORIGINAL ARTICLE

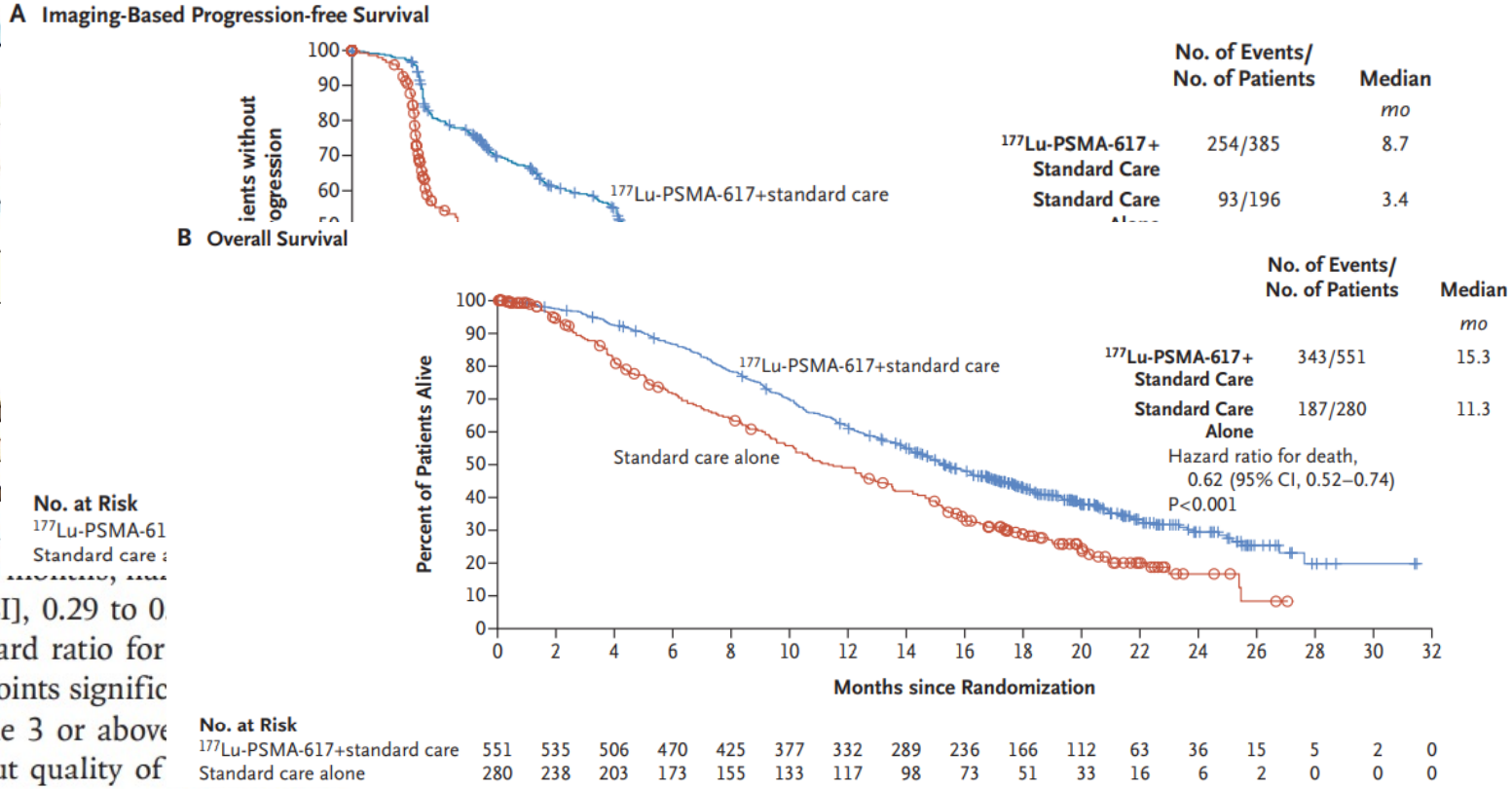
Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Ca

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahba
L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park,
A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan,
R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION I

ABSTRACT

RESULTS

From June 2018 to mid-October 2019, a total of 831 o
underwent randomization. The baseline characteristics of t
between the groups. The median follow-up was 20.9 mon
standard care significantly prolonged, as compared with
aging-based progression-free survival (median, 8.7 vs. 3.4
progression or death, 0.40; 99.2% confidence interval [CI], 0.29 to 0
and overall survival (median, 15.3 vs. 11.3 months; hazard ratio for
95% CI, 0.52 to 0.74; P<0.001). All the key secondary end points signific
^{177}Lu-PSMA-617. The incidence of adverse events of grade 3 or above
with ^{177}Lu-PSMA-617 than without (52.7% vs. 38.0%), but quality of
adversely affected.



PSMA-ligand therapy / ESMO 2023

MADRID 2023 ESMO congress

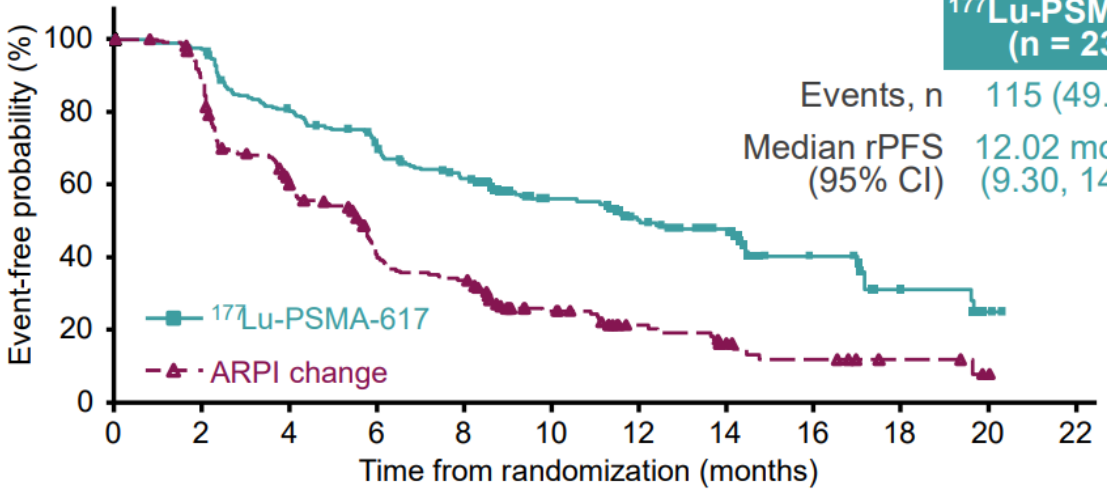
Phase 3 trial of [^{177}Lu]Lu-PSMA-617 in taxane-naive patients with metastatic castration-resistant prostate cancer (PSMAfore)

Presenter: Oliver Sartor,*
Mayo Clinic, Rochester, MN, USA

Co-authors: D Castellano, K Herrmann, J de Bono, ND Shore, KN Chi, M Crosby, JM Piulats, A Flechon, XX Wei, H Mahammedi, G Roubaud, H Studentova, S Ghebremariam, E Kpamegan, TN Kreisl, N Delgoshaie, K Lehnhoff, MJ Morris,* K Fizazi,*
on behalf of the PSMAfore investigators
*Contributed equally

rPFS: primary endpoint was met

Primary HR: 0.41 (95% CI: 0.29, 0.56); $p < 0.0001$
Updated HR: 0.43 (95% CI: 0.33, 0.54)



	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median rPFS (95% CI)	12.02 months (9.30, 14.42)	5.59 months (4.17, 5.95)

Number of patients still at risk

234	216	174	150	125	82	64	45	20	10	2	0
234	197	126	79	65	36	21	12	8	4	1	0

PSMA-ligand therapy / new approach

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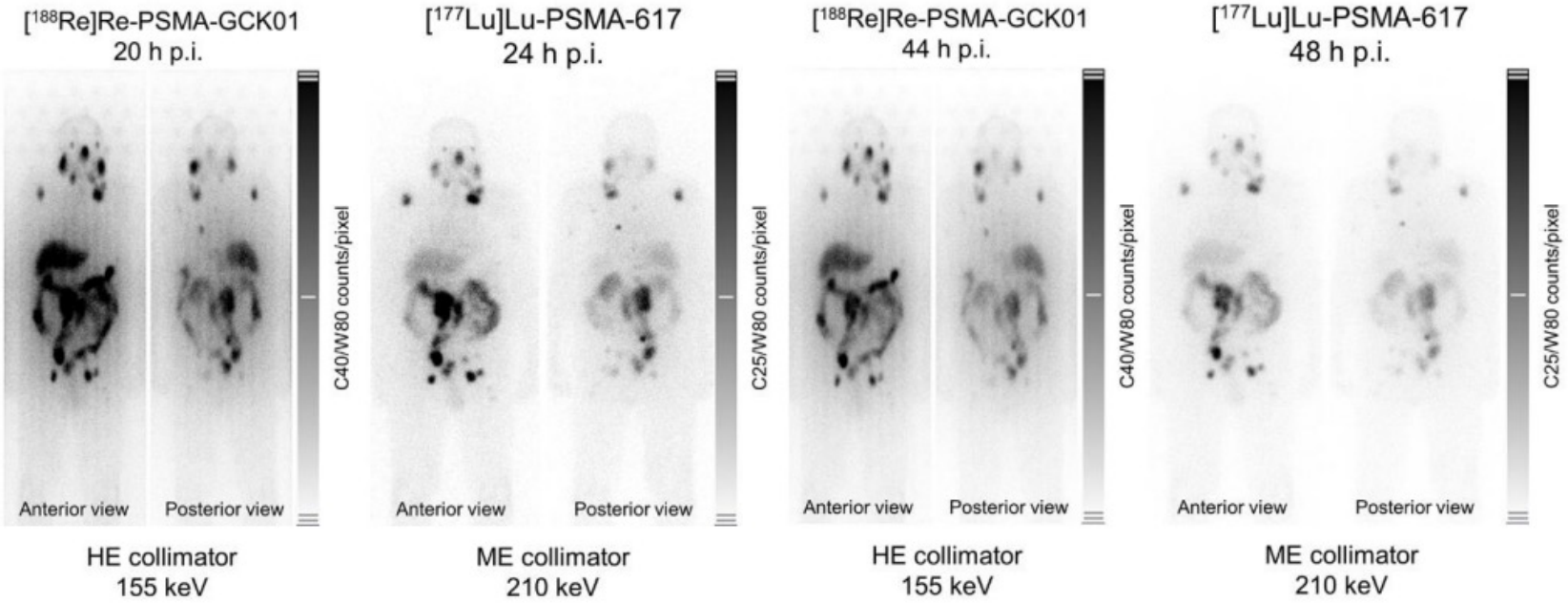
PSMA-GCK01 - A Generator-Based ^{99m}Tc-/^{188}Re-Theranostic Ligand for the Prostate-Specific Membrane Antigen

Jens Cardinale, Frederik L. Giesel, Christina Wensky, Hendrik G. Rat

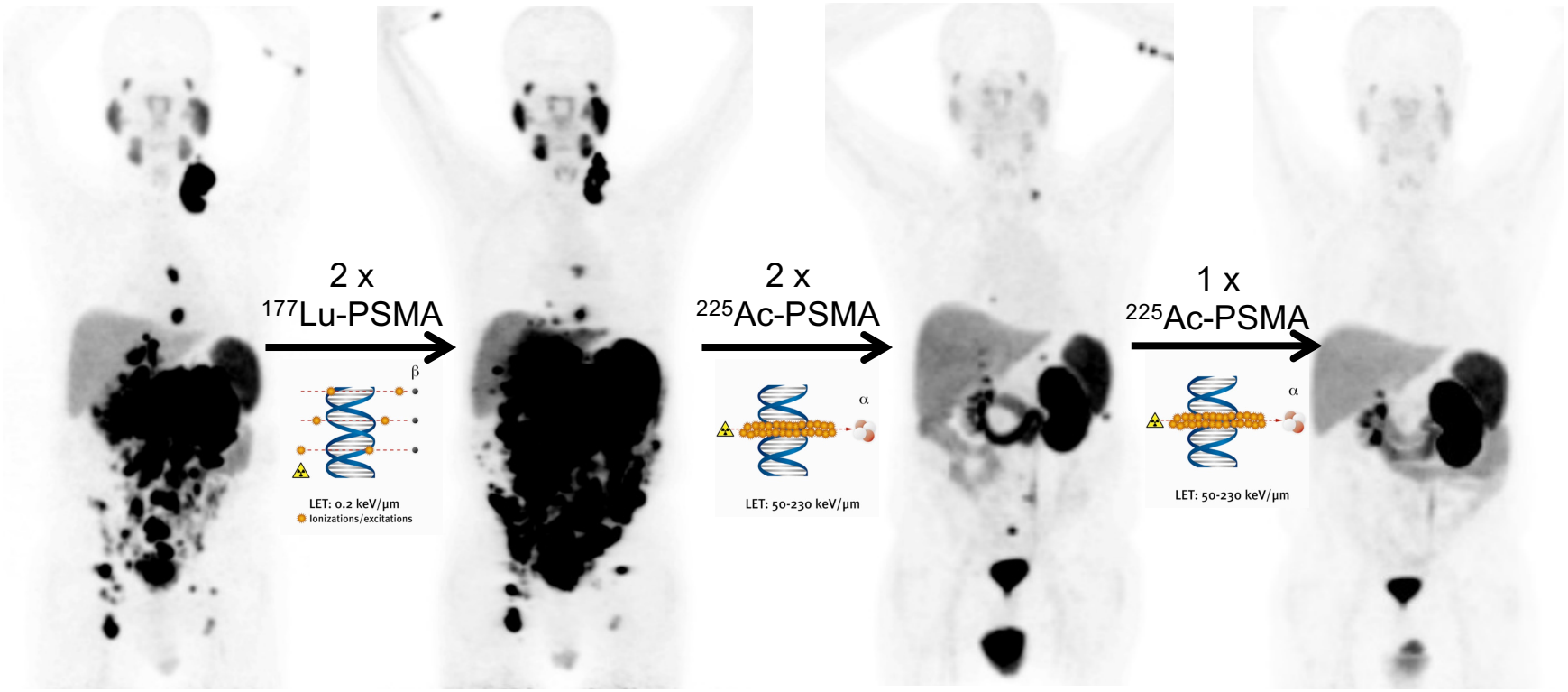
Journal of Nuclear Medicine February 2023, jnumed.122.264944; DOI: https://dc



PSMA-ligand therapy (225Ac-PSMA)

^{225}Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer

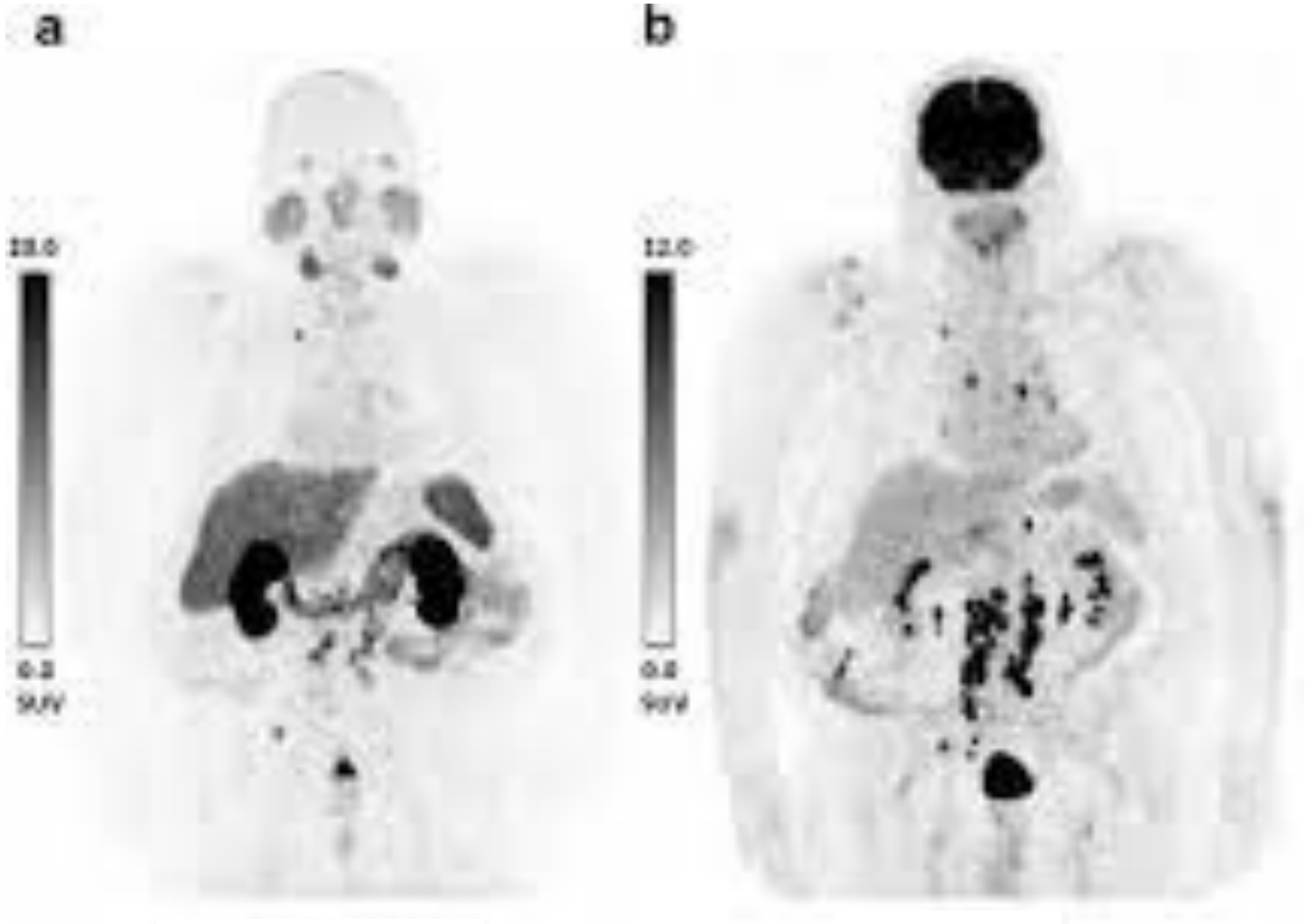
Clemens Kratochwil*[1], Frank Bruchertseifer*[2], Frederik L. Giesel[1], Mirjam Weis[2], Frederik A. Verburg[3], Felix Mottaghy[3], Klaus Kopka[4], Christos Apostolidis[2], Uwe Haberkorn[1], and Alfred Morgenstern[2]



6/2015	9/2015	2/2016	4/2016
PSA = 294 ng/ml	PSA = 419 ng/ml	PSA = 3.5 ng/ml	PSA < 0.1 ng/ml

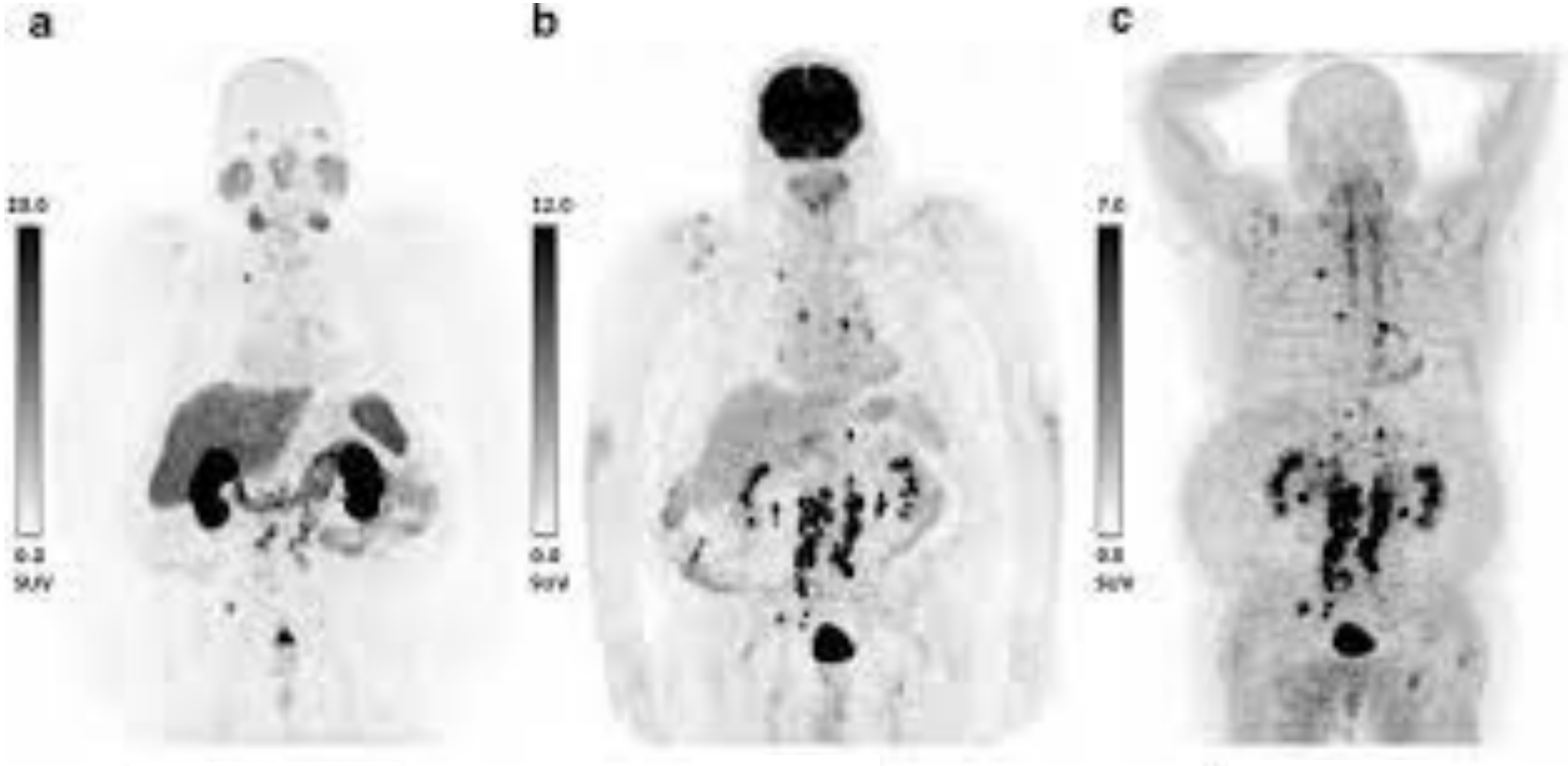
Kratochwil C et al.; JNM 2018

PSMA-negative phenotyp



^{68}Ga-PMSA-11 ^{18}F-FDG

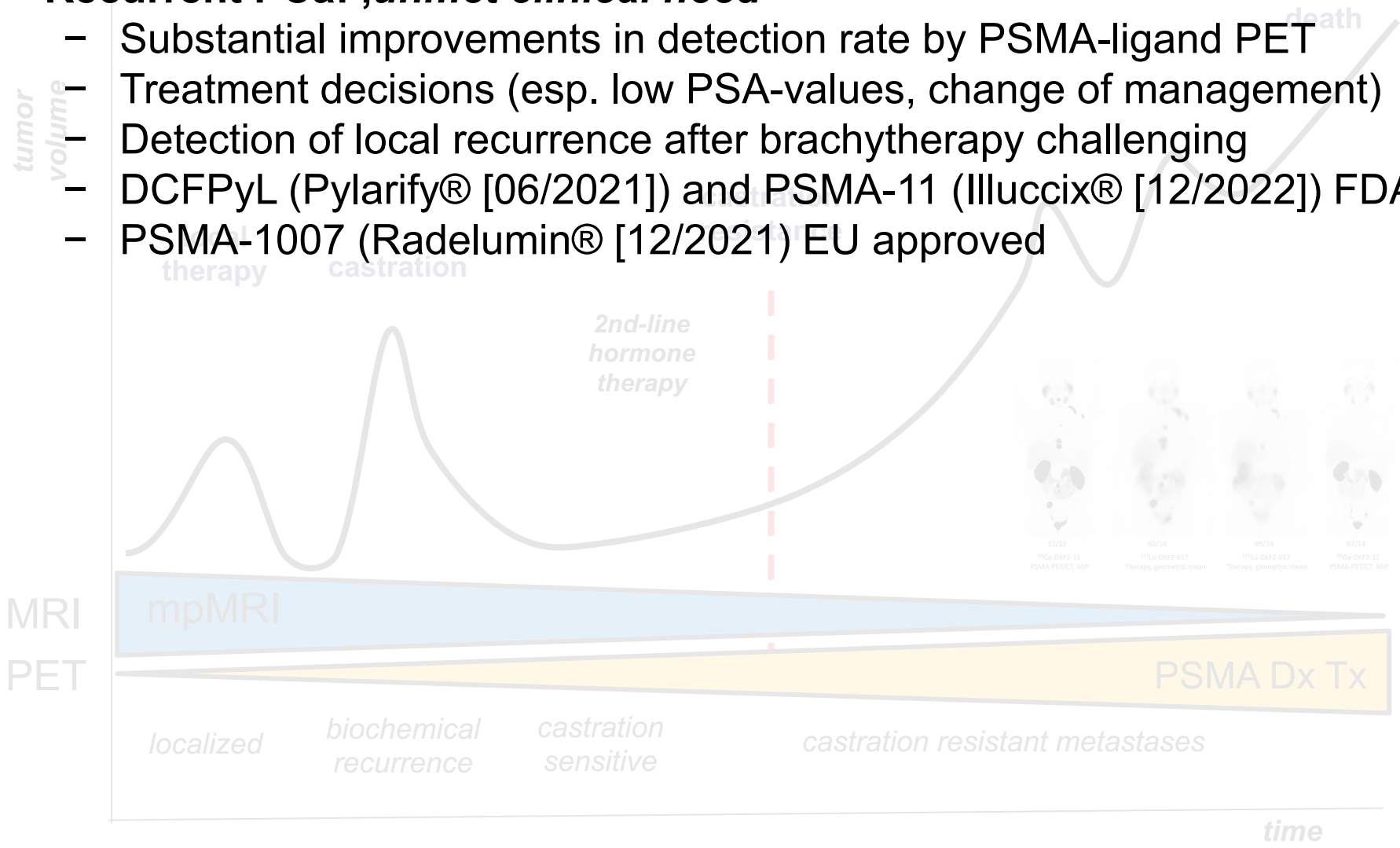
PSMA-negative phenotyp



^{68}Ga-PMSA-11 ^{18}F-FDG ^{68}Ga-FAPI

Summary

- **Recurrent PCa: ‚*unmet clinical need*‘**
  - Substantial improvements in detection rate by PSMA-ligand PET
  - Treatment decisions (esp. low PSA-values, change of management)
  - Detection of local recurrence after brachytherapy challenging
  - DCFPyL (Pylarify® [06/2021]) and PSMA-11 (Illuccix® [12/2022]) FDA approved
  - PSMA-1007 (Radelumin® [12/2021) EU approved



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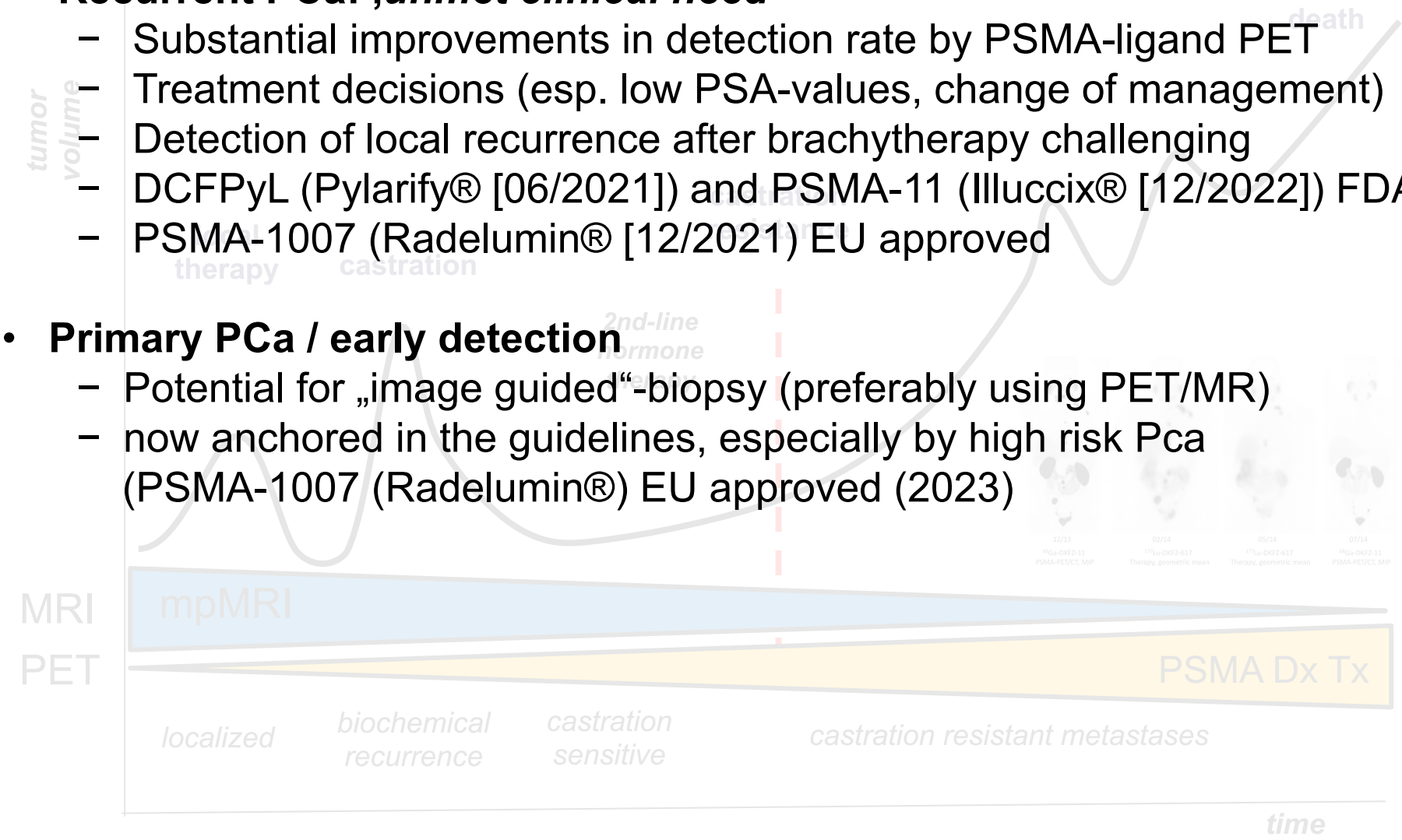
- **Primary PCa / early detection**
  - Potential for „image guided“-biopsy (preferably using PET/MR)
  - now anchored in the guidelines, especially by high risk Pca (PSMA-1007 (Radelumin®) EU approved (2023)



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- **PSMA-ligand therapy**
  - Last line therapy / FDA approval (Pluvicto®[03/2022])
  - Phase-II/III trials are ongoing (2nd / 3nd PSMA-ligand therapies)

Thanks !

frederik@egiesel.com