PSMA THERANOSTICS:
CURRENT STATUS AND FUTURE DIRECTIONS

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Theranostics

=

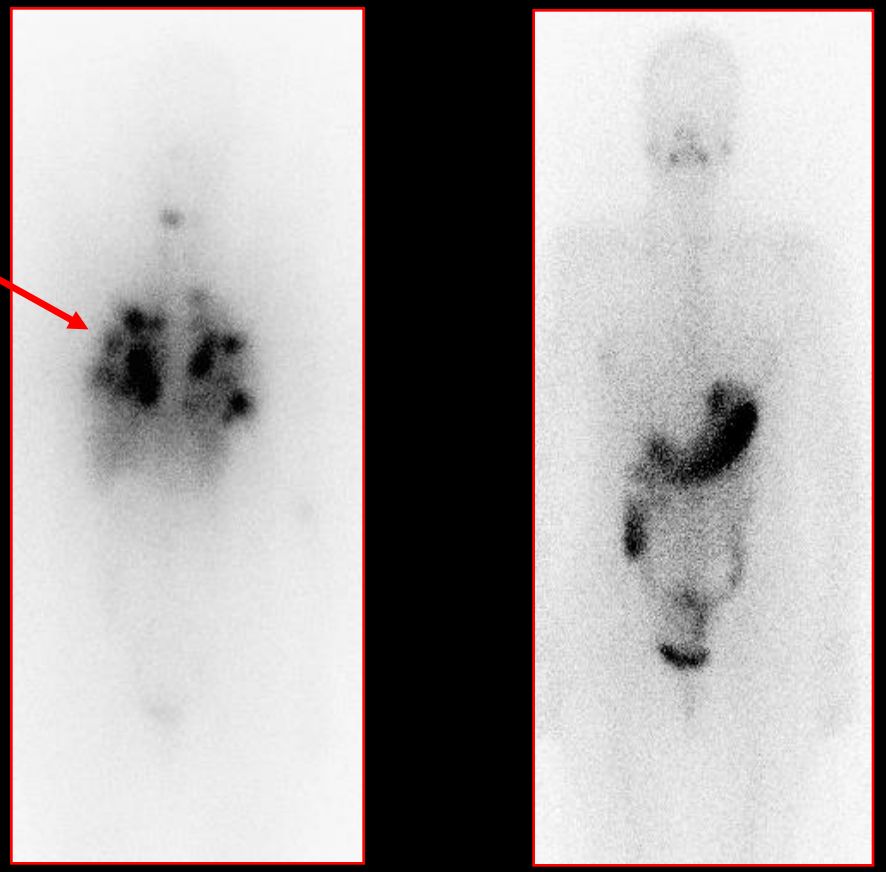
Therapeutics + Diagnostics

The possibility to perform diagnostic imaging and subsequently administer therapies by the means of the “same molecule”

Radioiodine Therapy of Differentiated Thyroid Cancer

"Effective therapy works"

Lung metastases of differentiated thyroid carcinoma



before therapy

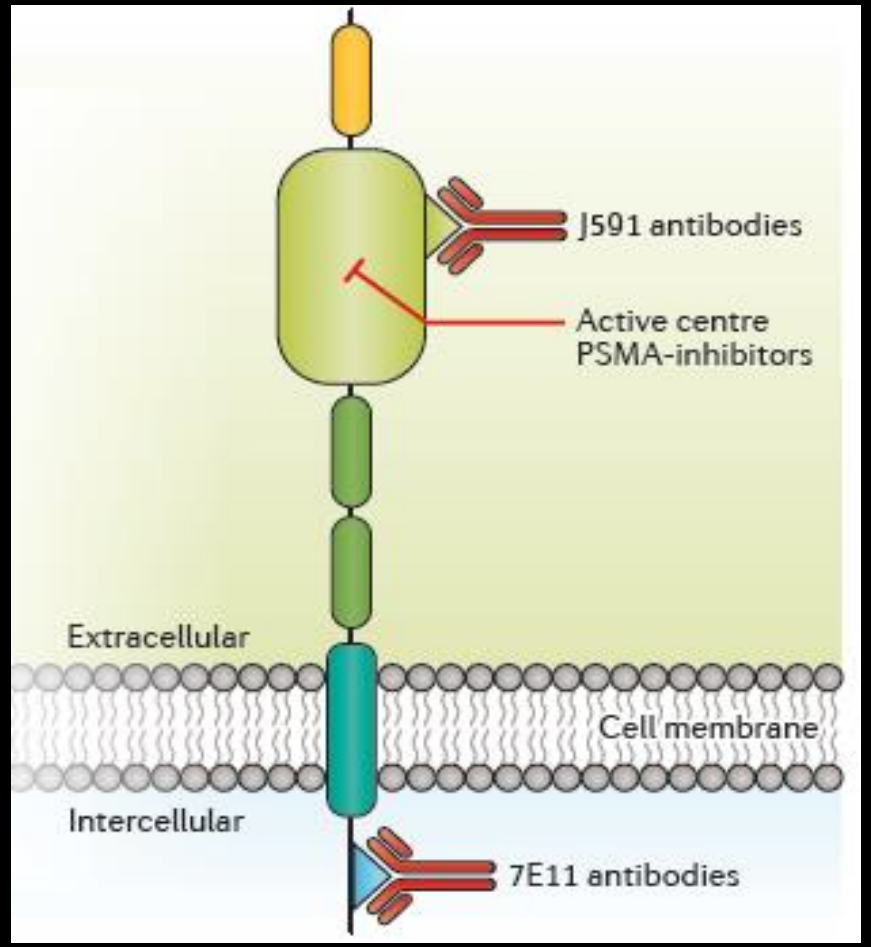
after therapy

PSMA as target for PCa imaging and therapy

Prostate-**S**pecific **M**embrane **A**ntigen

[syn. Glutamate carboxypeptidase II (GCP-II)]

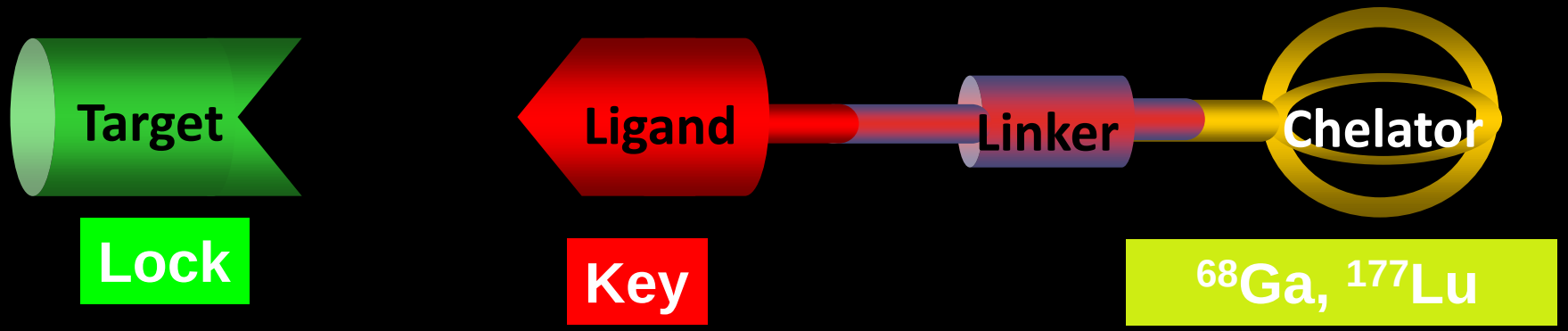
- cell surface protein
- overexpression in >90% of PCa cells
- promising target for imaging and therapy
- development of various PSMA-ligands



Maurer et al., Nat Rev Urol 2016

THERANOSTIC PAIRS
Targeted Molecular Imaging and Therapy
WE TREAT WHAT WE SEE

SCHEMATIC REPRESENTATION OF A DRUG FOR IMAGING AND TARGETED THERAPY



Targets

- Antigens
  e.g. CD20, HER2)
- GPCR e.g. SSTR
- Enzymes & inhibitors
  e.g. PSMA
- Transporters

Molecular Address

- Antibodies, minibodies, Affibodies, SHALs, aptamers
- Regulatory peptides (agonists & antagonists)
- PSMA ligands
- Amino Acids

Reporting Unit

- ^{99m}Tc, ^{111}In
- ^{68}Ga, ^{18}F

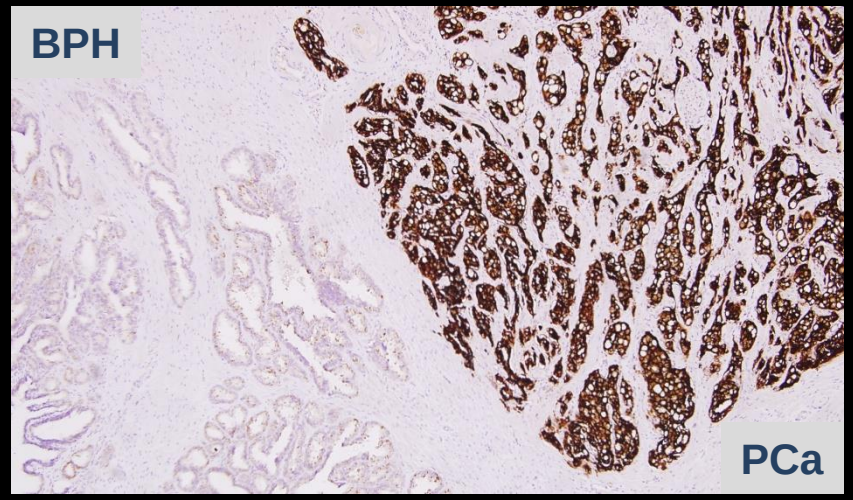
Cytotoxic Unit

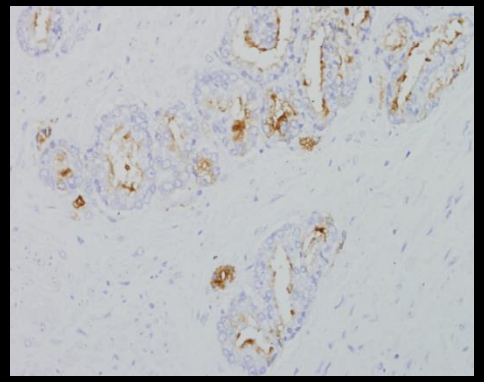
- ^{90}Y, ^{177}Lu
- ^{225}Ac, ^{213}Bi

Courtesy Helmut Mäcke (modified)

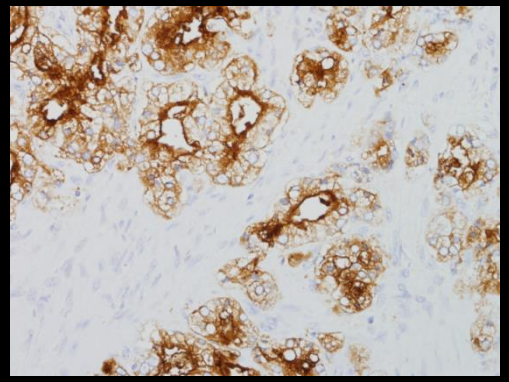
PSMA EXPRESSION IS PROSTATE CANCER SPECIFIC AND INCREASES WITH TUMOR GRADE

# 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

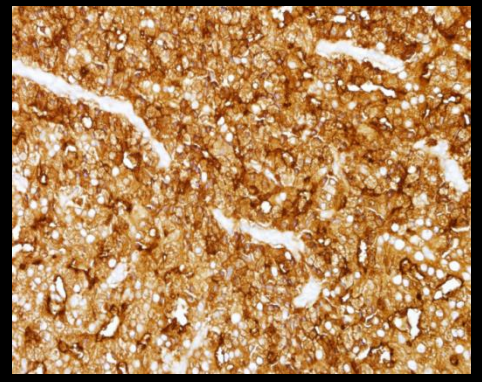




Gleason 3



Gleason 4

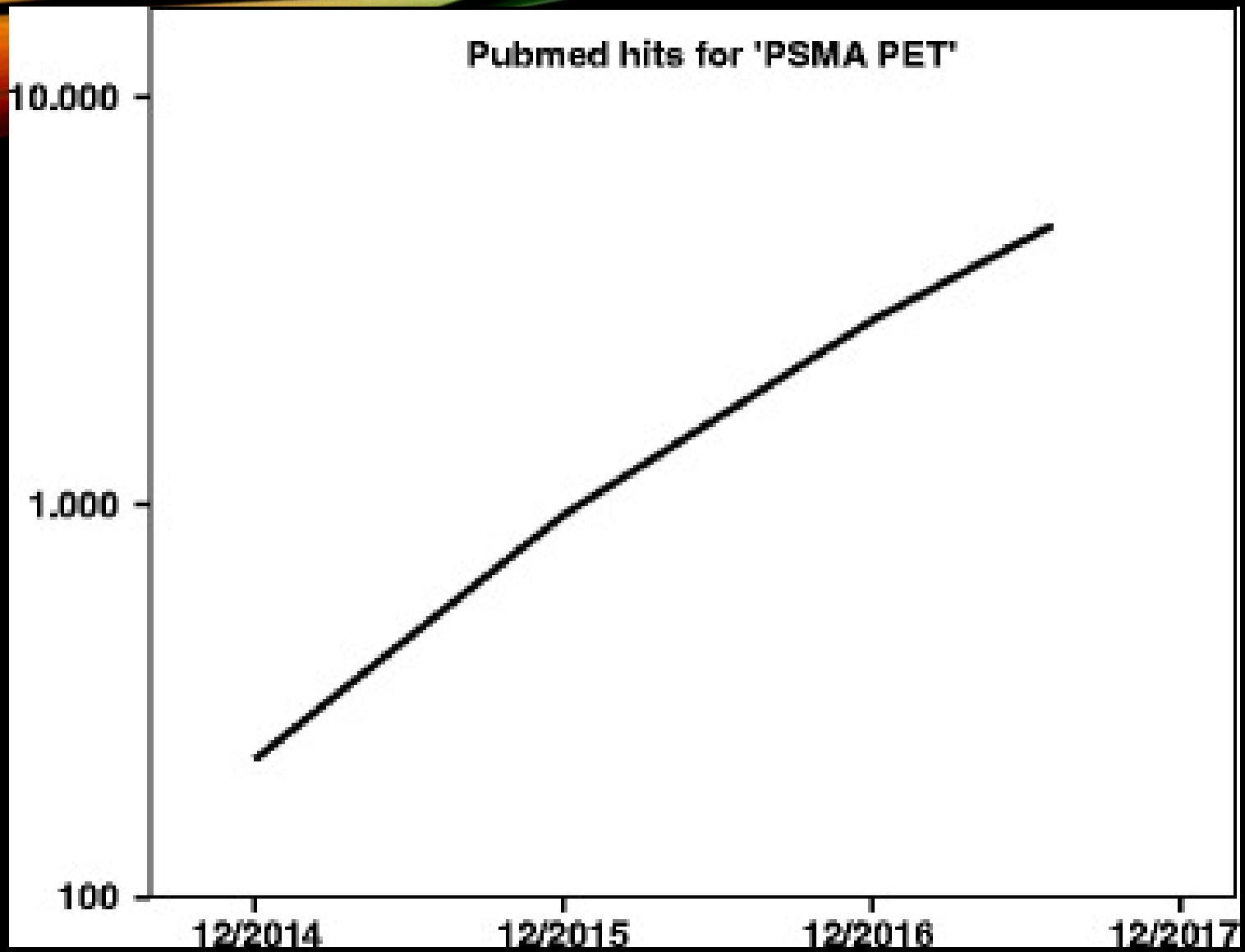


Gleason 5

Courtesy of Dr. Neil Bander New York-Presbyterian Hospital

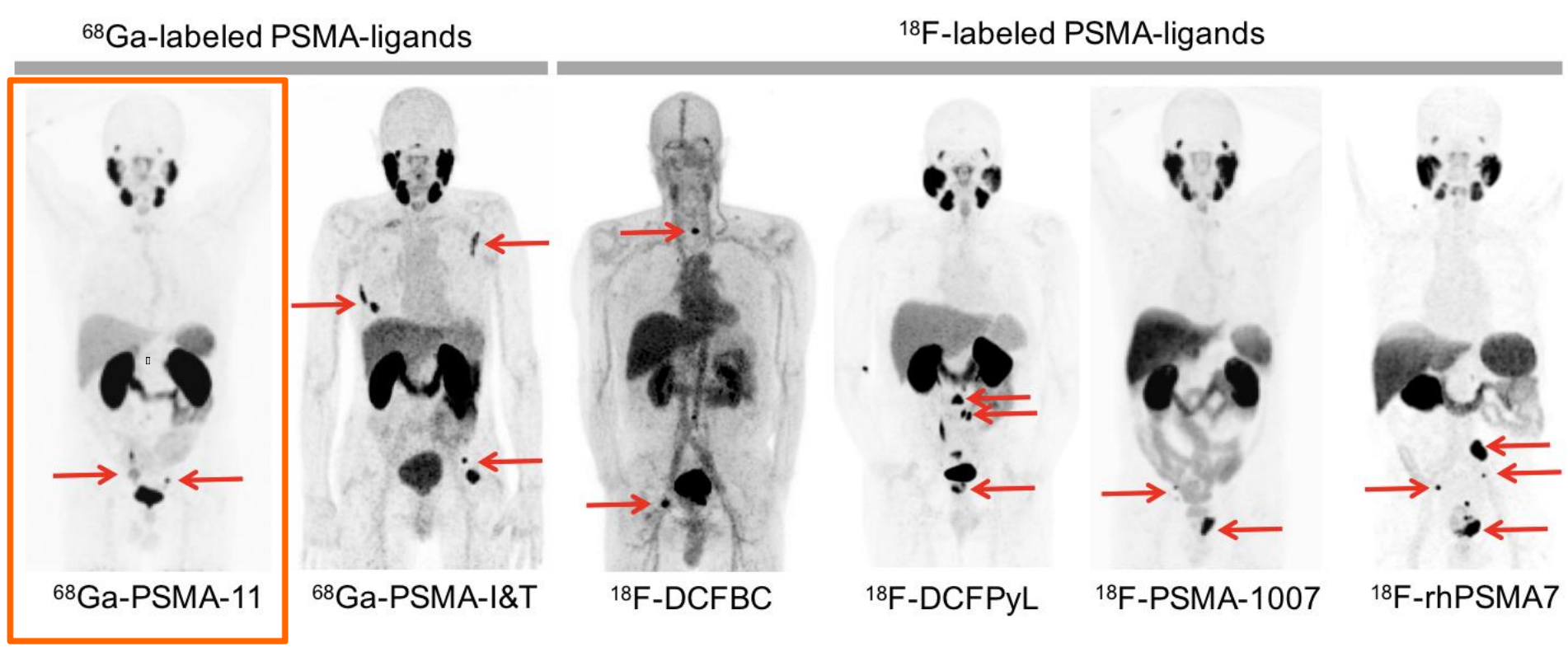
PSMA-based

Diagnostics



Number of results for the search term “PSMA PET” in pubmed.gov with annual publication date restrictions starting from January 2014 until July 2017 (x-axis) and logarithmic depiction of cumulative publications (y-axis)

PSMA-ligands for PET imaging



First report of human application:

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

Biochemical recurrence

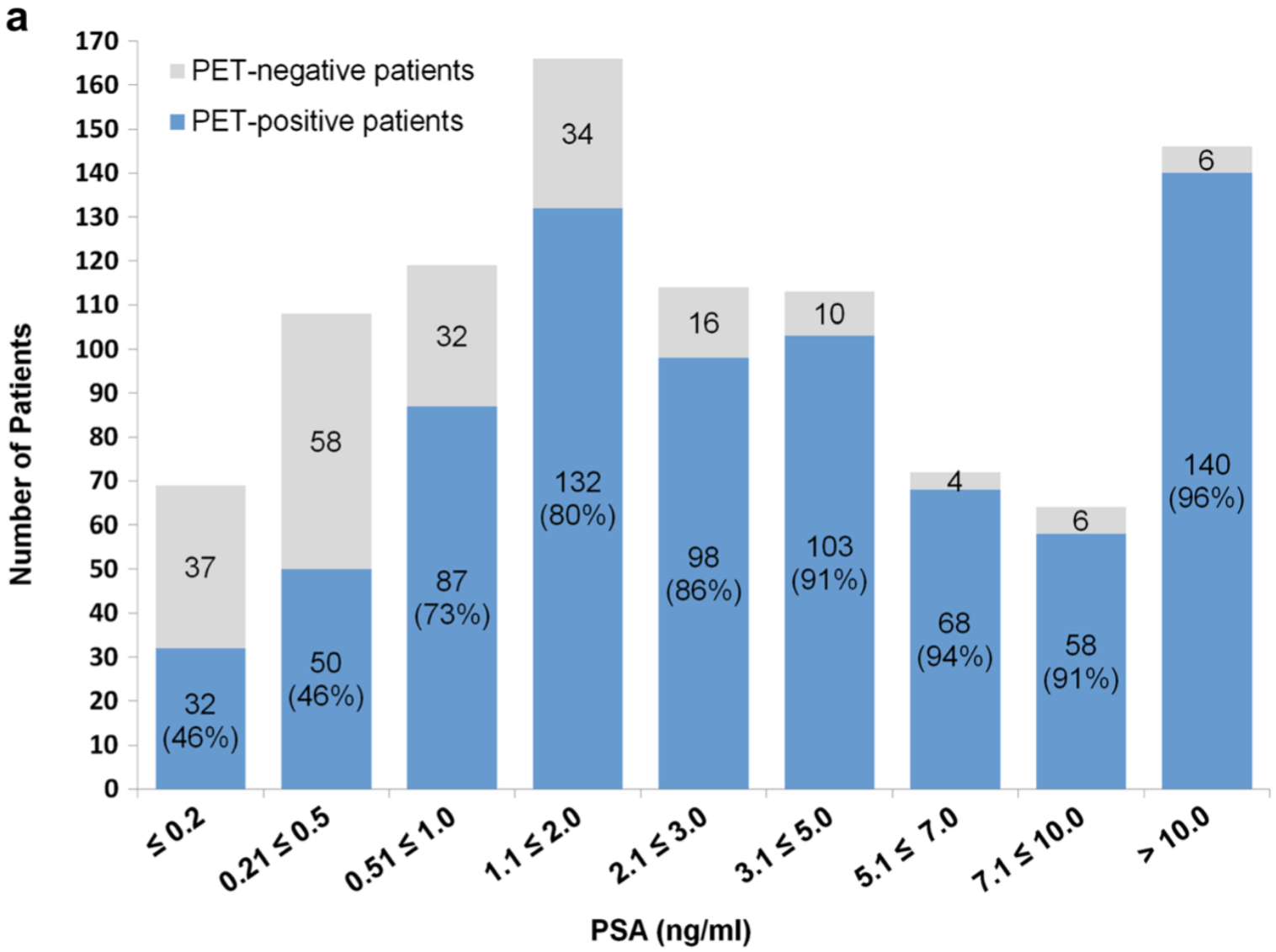


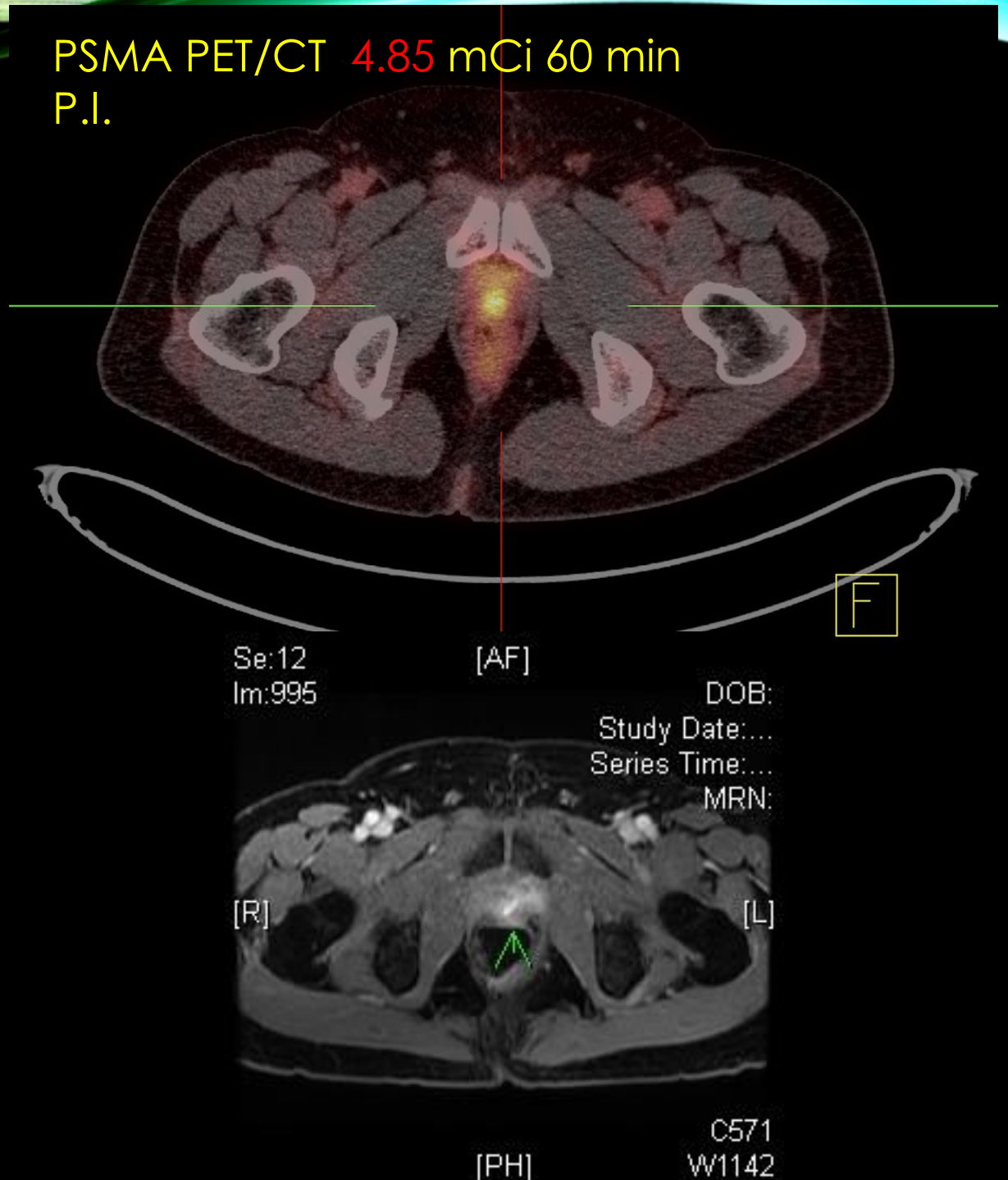
Fig. 1 Probabilities of a pathological ^{68}Ga-PSMA-11 PET/CT scan (*a*) and plot of the rates of pathological PET/CT scans with confidence intervals (*b*) in relation to PSA levels in 971 patients. *Blue columns* Numbers of patients with a pathological PET/CT scan together with the rates which also represent the patient-based sensitivities of ^{68}Ga-PSMA-11 PET/CT in detecting recurrent PCa in relation to PSA level. Amongst all patients with a PSA level less than 0.2 ng/ml, 15 had values less than 0.1 ng/ml

- 67 y/o male, s/p RRP at 2015/04/30, stage PT2cN0M0, initial PSA 7.81 ng/ml. GS:3+3

- PSA rising after op:

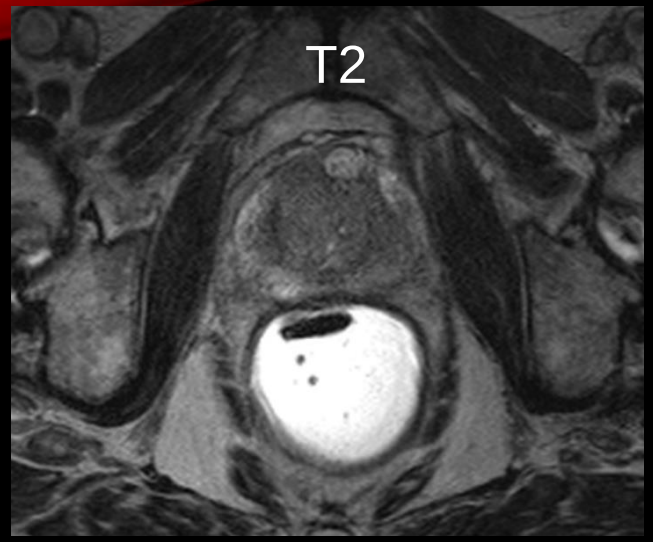
5.48(2015/4/30)--> 0.23(6/8)--> 0.13(7/8)--> 0.27(10/5) --> 0.24(2016/3/31)--> 0.22(7/5)-->0.27(7/25)-->0.3(9/16)-->0.38(10/24) -->0.32(12/13) -->0.38(2017/1/16)--> 0.39(3/8) --> 0.5 (20170406) --> 0.41 (2017/4/25)

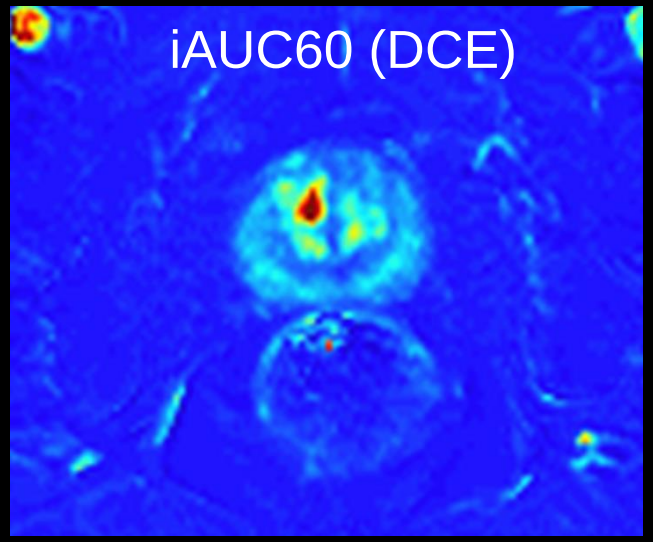
- PSMA PET: Increased uptake at prostate fossa, corresponding to enhanced lesion at posterior wall of anastomosis site of MRI->Recurrent prostate cancer can be confirmed

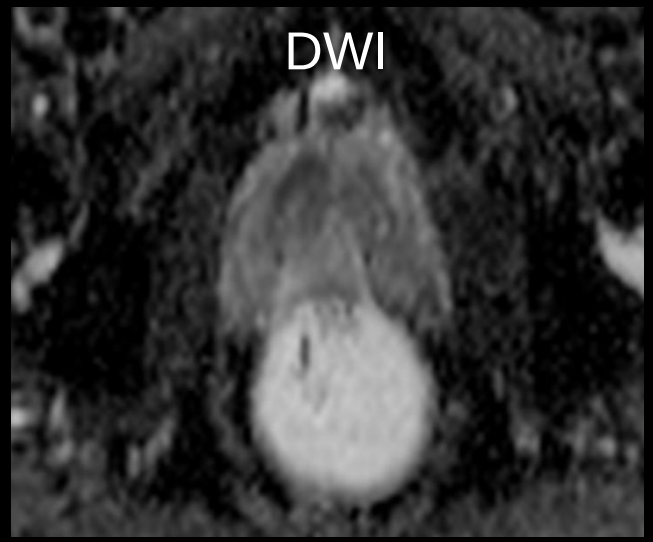


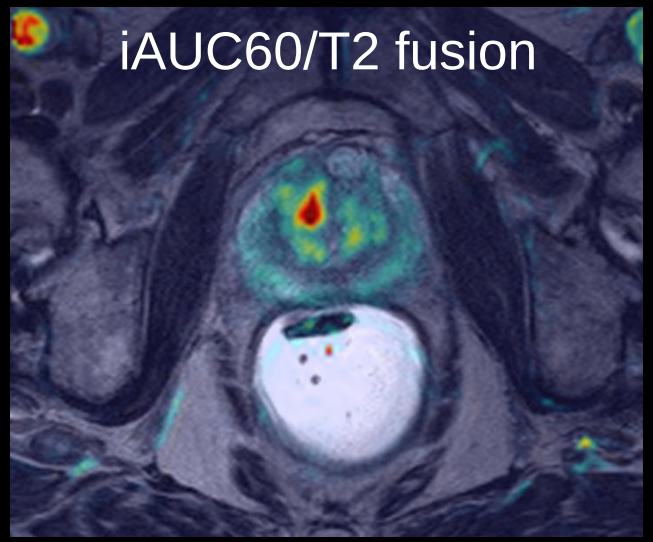
Local detection

mpMRI for detection of PCa

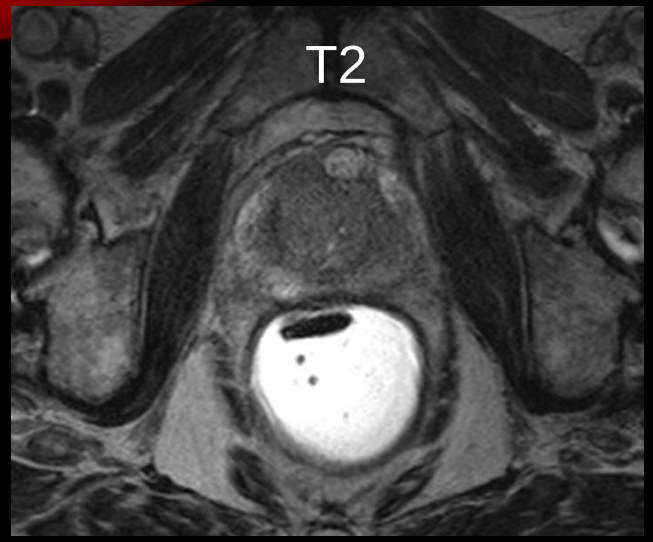


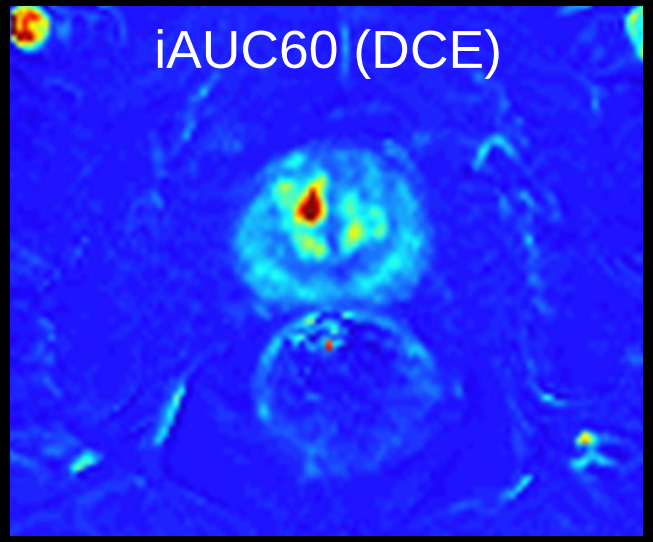


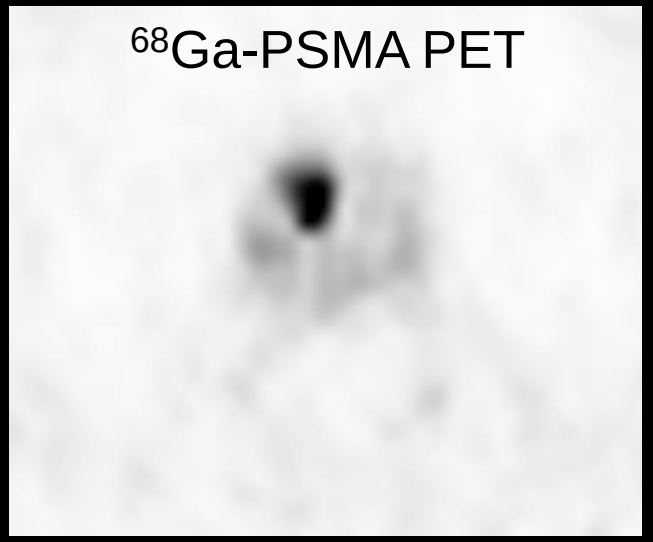


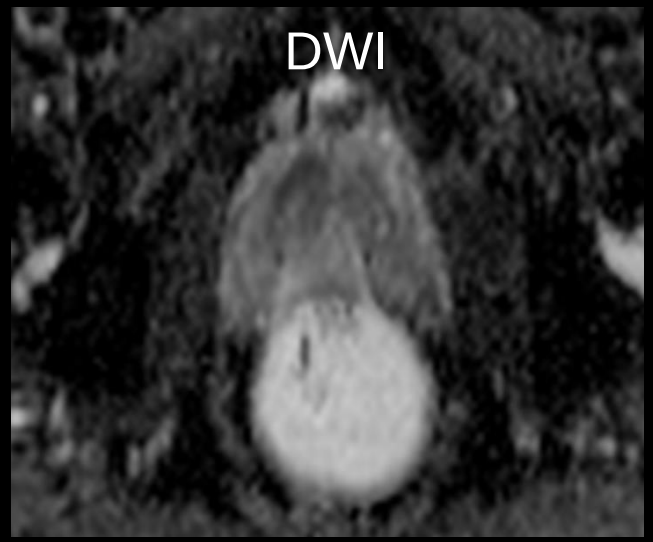


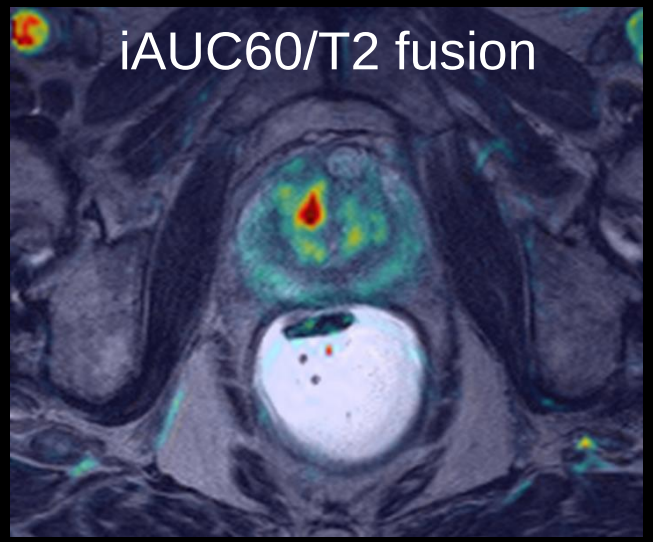
^{68}Ga-PSMA PET/mpMRI for detection of PCa

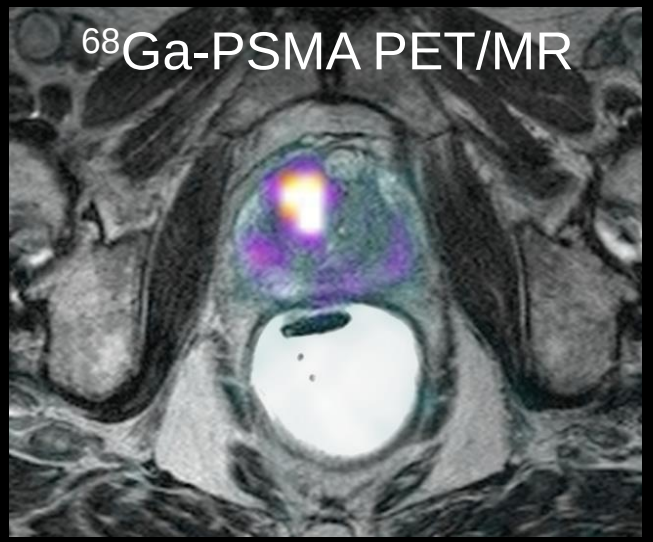












^{68}Ga-PSMA PET/mpMRI for local detection

53 patients examined by preoperative ^{68}Ga-PSMA PET/mpMRI

Evaluation using PIRADS (mpMRI) or 5-point Likert-scale (PET)

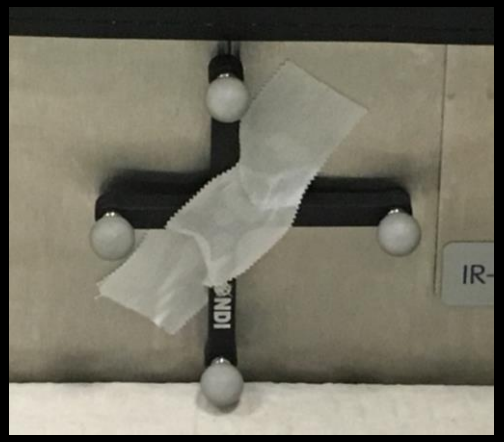
Patient basis	Detection rate (95% CI)	p (to mpMRI)
mpMRI	66 (52-78)	
PET	92 (82-98)	**p<0.001**
PET/mpMRI	98 (89-100)	**p<0.001**

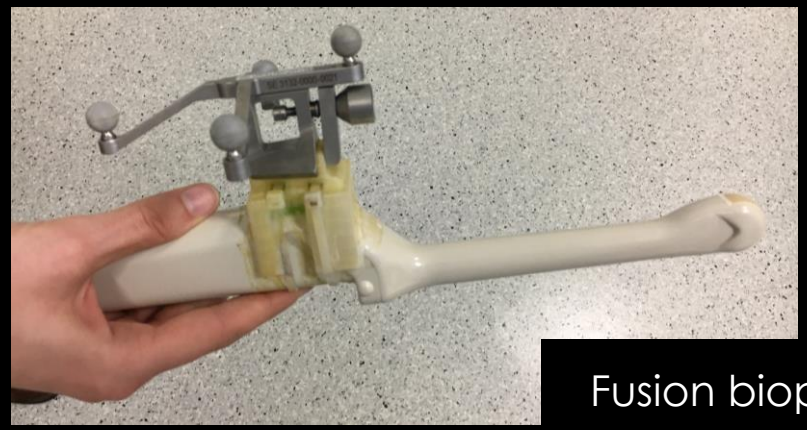
Sextant basis	Sens. (95% CI)	Spec. (95% CI)	AUC (95% CI)	p (to mpMRI)
mpMRI	43 (33-53)	98 (94-100)	0.73 (0.66-0.80)	
PET	64 (56-72)	94 (86-98)	0.83 (0.78-0.87)	**p=0.003**
PET/mpMRI	76 (68-82)	97 (90-99)	0.88 (0.84-0.92)	**p<0.001**

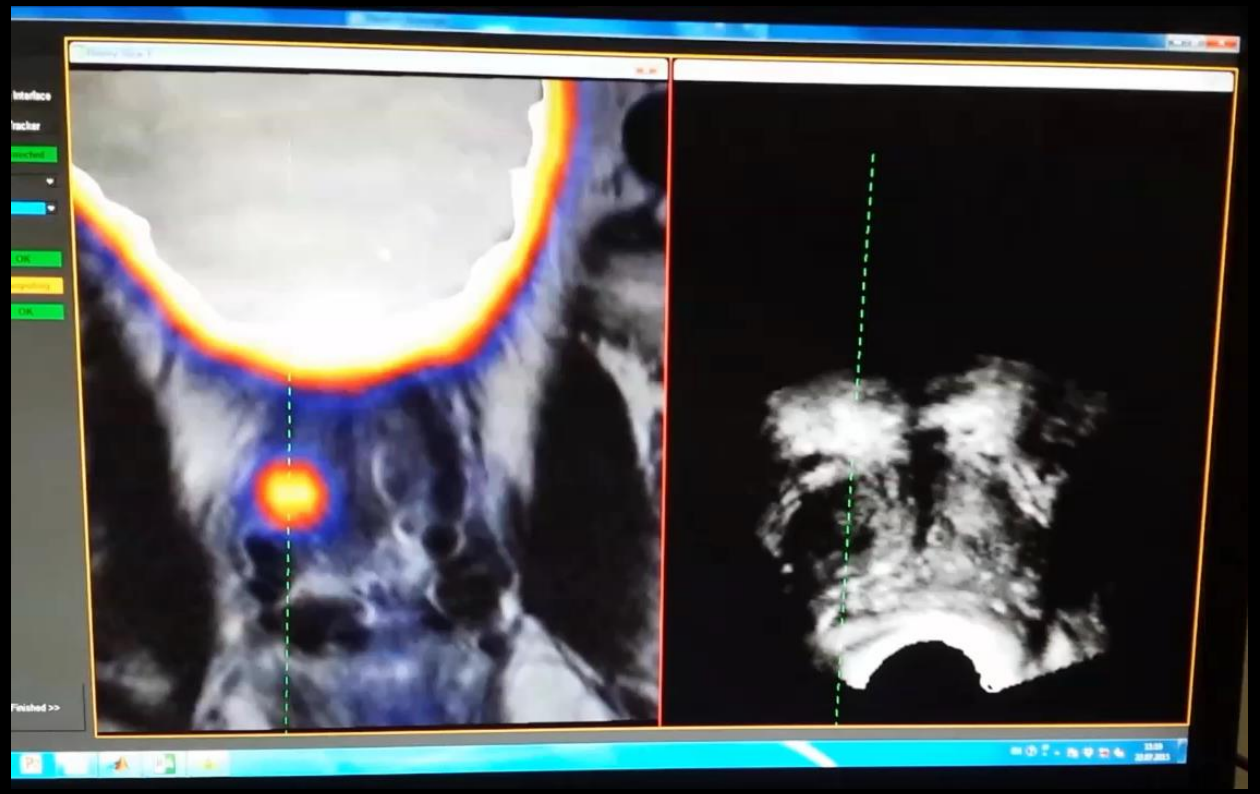
Eiber et al., Eur Urol 2016

^{68}Ga-PSMA-PET/MRI for fusion biopsy (CAMP/TUM)

- Enables fusion of MR, PET/MR to TRUS (optical tracking)
- Facilitates targeted biopsies of suspicious lesions
- Disadvantages: special equipment necessary, not commercial (yet)

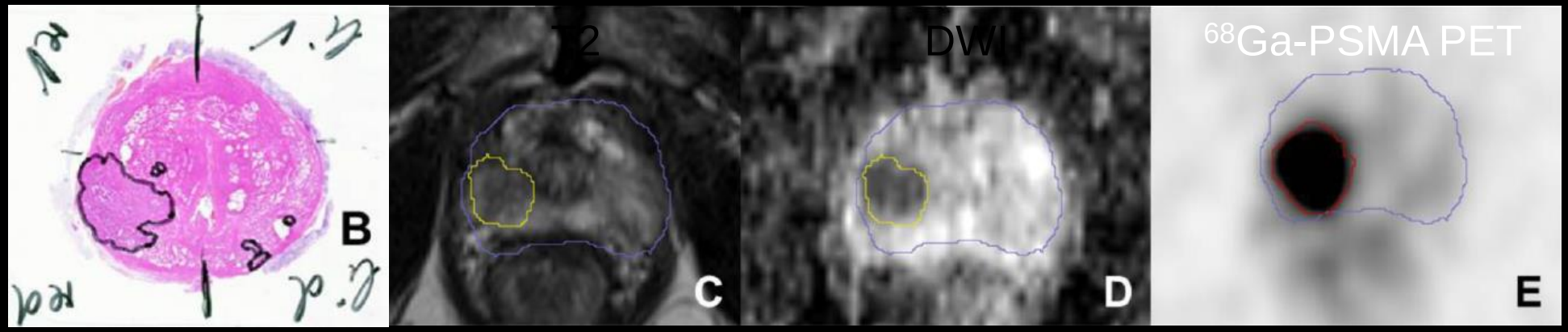




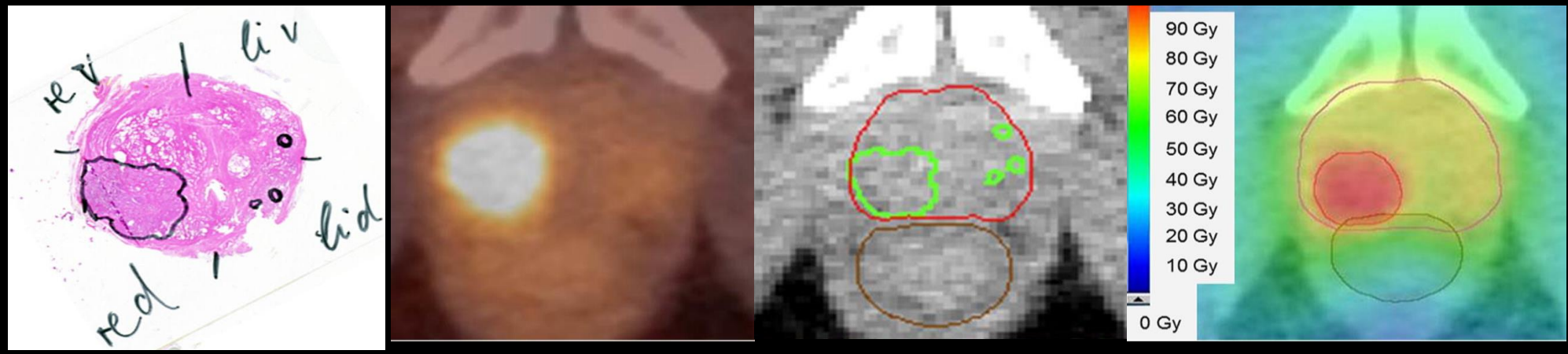


Fusion biopsy system at MRIU/TUM, developed by Department of Computer Aided Medical Procedures, CAMP/TUM (Prof. Navab); Zettinig et al. IJCARS, 2015

^{68}Ga-PSMA-PET/MRI for planning of local therapy



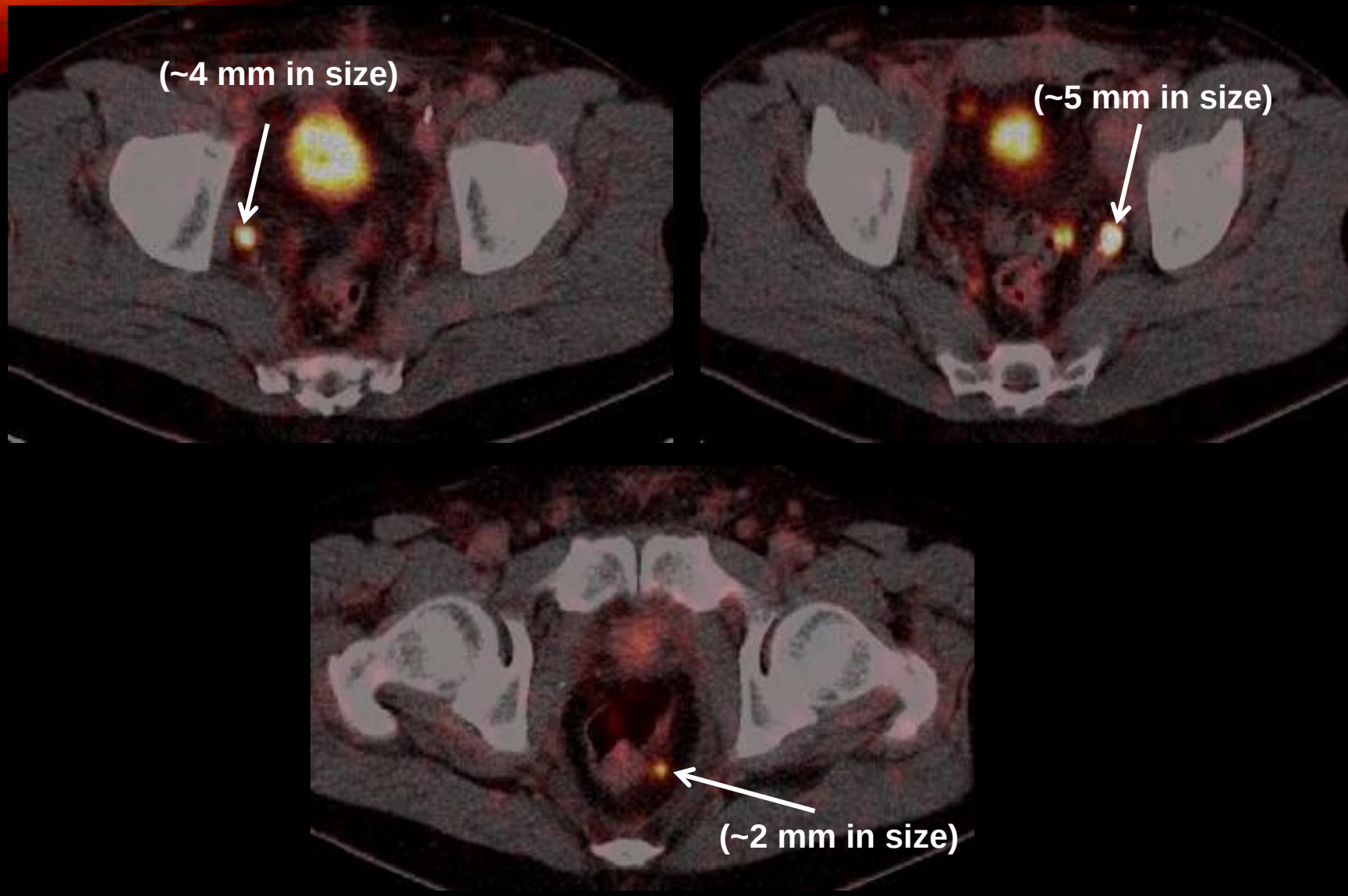
Zamboglou et al., Theranostics 2017



→ ^{68}Ga-PSMA-PET helpful for planning of local boost radiation

Zamboglou et al., Radiother Oncol 2017

Lymph nodes



METASTATIC PELVIC AND PERIRECTAL NODES

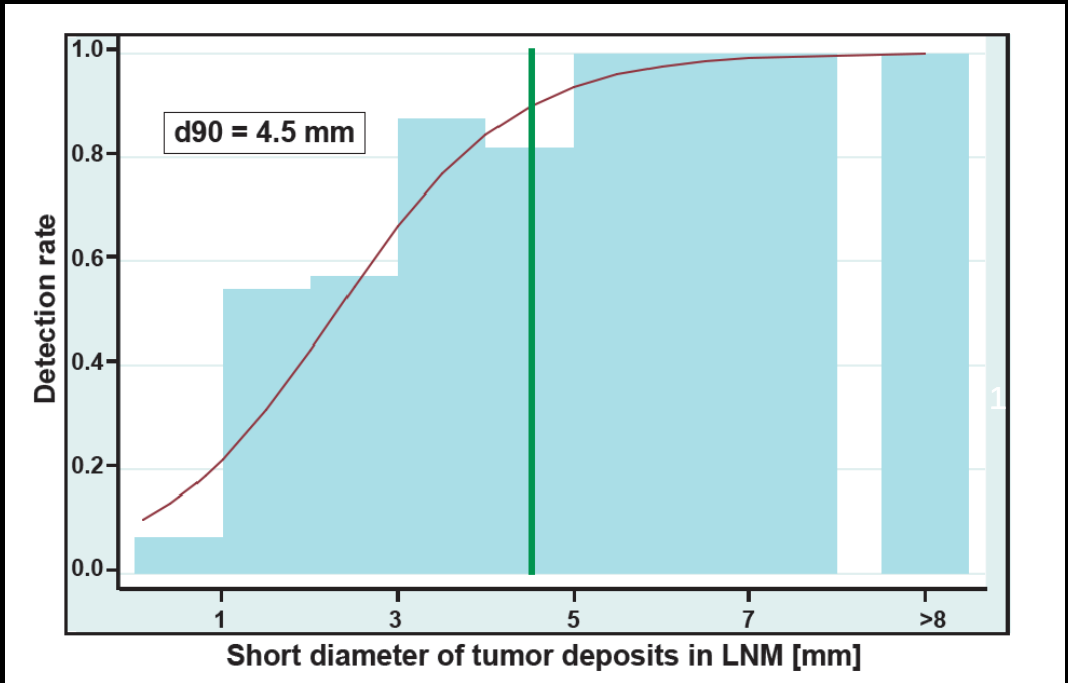
LN-Staging: ^{68}Ga-PSMA PET superior to CT/MRI

Table 2. *LN detection in 130 patients and 734 templates*

	Pt Histology LN Metastasis	Template Histology LN Metastasis
	Morphological	
% Sensitivity	43.9	28.2
% Specificity	85.4	97.1
% Accuracy	72.3	86.1
% PPV	58.1	64.7
% NPV	76.8	87.7
	PSMA-PET	
% Sensitivity	65.9	73.5
% Specificity	98.9	99.2
% Accuracy	88.5	95.1
% PPV	96.4	94.5
% NPV	86.3	95.2

Maurer et al., J Urol 2016

LN-Staging: ^{68}Ga-PSMA PET not perfect!

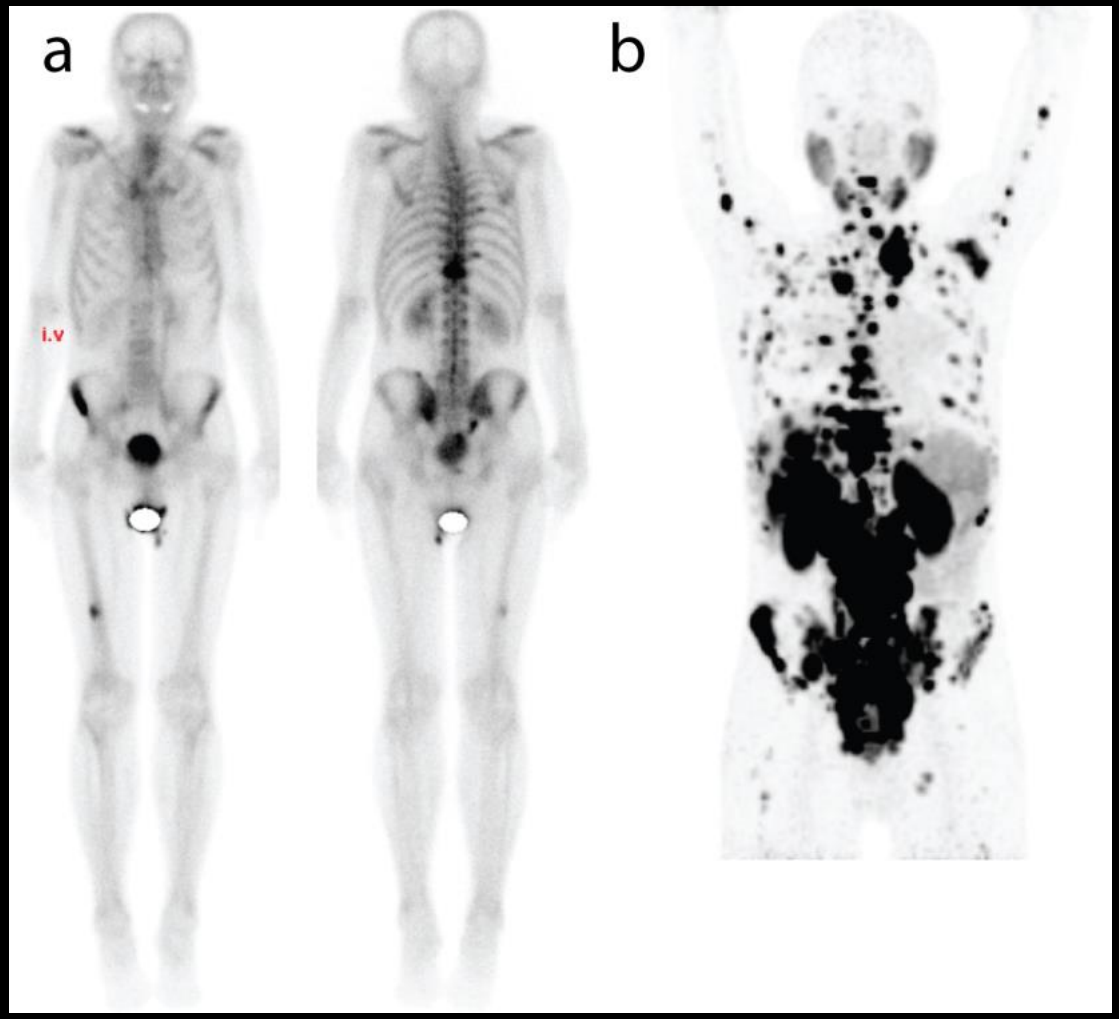


- Detection rate of metastatic LN lesions by ^{68}Ga-PSMA PET requires certain size (50%/90% at short axis diameters of ≥2.3mm/≥4.5mm)[1-3]
- CT/MRI: criterion for malignancy size >8-10mm[4]

[1]Jilg et al., Theranostics 2017; [2]Vinsensia et al., J Nucl Med. 2017;
[3]Maurer et al., J Urol 2016; [4]Hovels et al., Lancet Oncol 2017

Bone

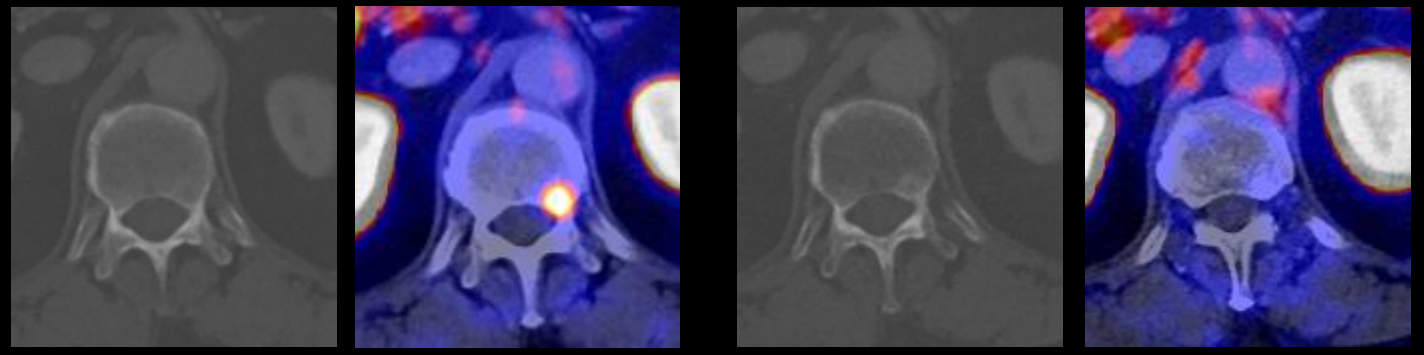
Bone staging: ^{68}Ga-PSMA PET vs. bone scintigraphy (BS)

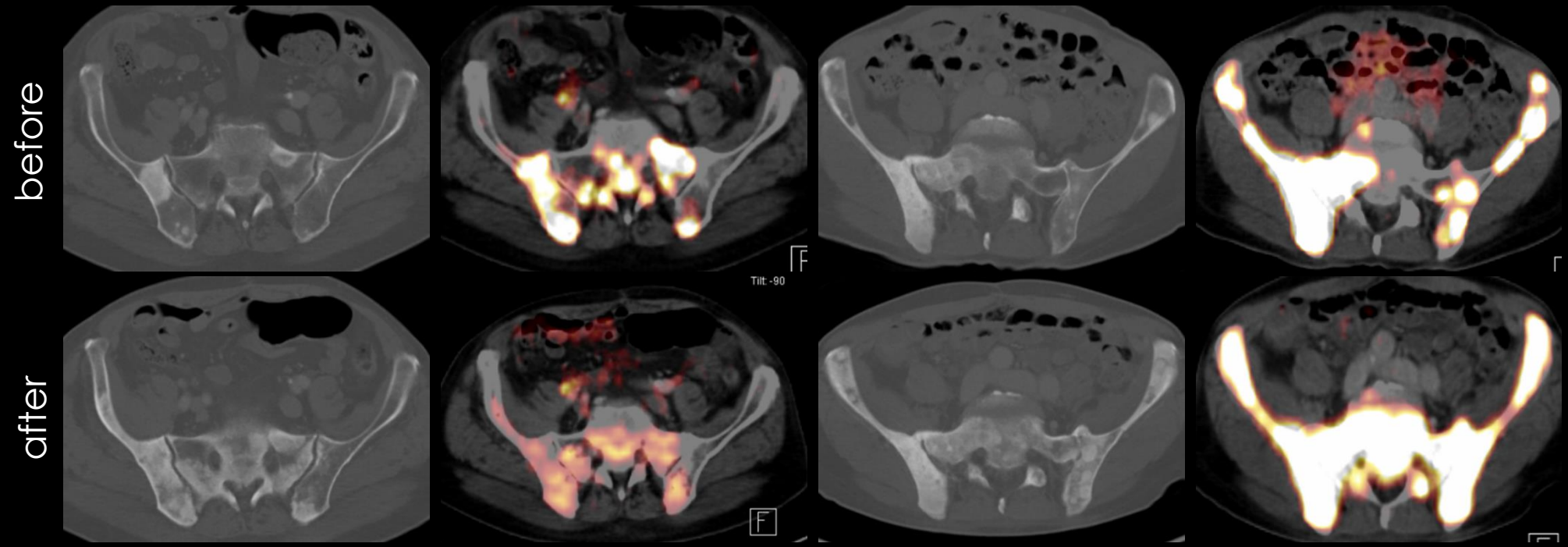


Pyka et al, EJNMMI 2016

Metastatic PCa

mCRPC: Treatment response evaluation by ^{68}Ga-PSMA PET

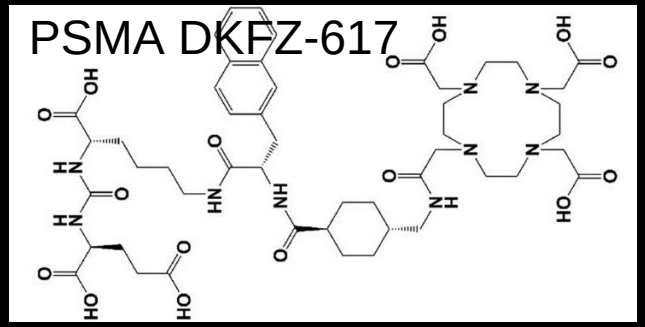




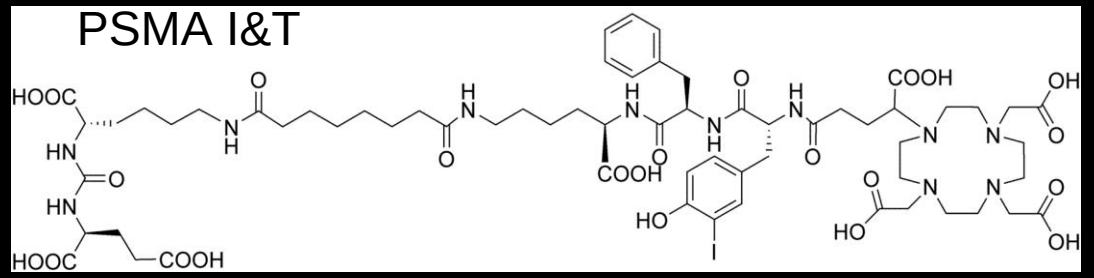
PSMA-based Therapeutics

^{177}Lu-PSMA-radioligand therapy (PRLT)

Theranostic PSMA-ligands for endoradiotherapy using ^{177}Lu



Benešová et al., JNM 2015



Weineisen et al, JNM 2015

Increasing number of retrospective case series , e.g. [1] [2] [3] [4]

- 50% PSA decline in 30-60% of patients
- rare event of grade III/IV toxicities

[1] Ahmadzadehfar et al, Oncotarget 2016, [2]Kratochwil et al, JNM 2016, [3]Rahbar et al, JNM 2016,[4]Baum RP et al, JNM 2016

^{177}Lu-PSMA-radioligand therapy: safety

Table 2. Safety of ^{177}Lu-PSMA radioligand therapy in the literature.

		Hematotoxicity CTCAE grade 3/4				
Reference	n	Hb (%)	WBC (%)	Plt (%)	Xerostomia	Nonhematologic AE
Ahmadzadehfar et al.[64]	10	10	0	0	0	mild nausea, fatigue
Rahbar et al.[66]	28	11	0	0	14	mild nausea
Ahmadzadehfar et al.[65]	24	9	0	0	8.7	mild nausea
Baum et al.[67]	56	0	0	0	3.5	na
Kratochwil et al.[72]	30	3.3	0	3.3	6.7	mild nausea, fatigue
Rahbar et al.[73]	82	2.8	0	0	8.5	mild nausea
Heck et al.[74]	22	0	0	0	37	fatigue, appetite loss
Rahbar et al.[69]	145	10	3	4	8	mild nausea
Bräuer et al.[75]	59	18	3	3	25	nausea, fatigue

Abbreviations: CTCAE: common toxicity criteria of adverse events, Hb: haemoglobin, WBC: white blood cells, Plt: platlets.

Rahbar et al, Molecular Imaging 2018

EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT)

- Indications:

Patients with metastatic, castration-resistant prostate cancers (mCRPC) who have exhausted or are ineligible for approved alternative options and **with adequate uptake of PSMA ligands on the basis of a pre-therapy imaging study** can be considered for treatment.

- Adequate uptake? A baseline ^{68}Ga-PSMA-11 PET SUVmax at dominant sites of tumor involvemnt to be at least 1.5 times the SUVmean of liver. [Hofman MS et al. *Lancet Oncol. 2018*]

https://doi.org/10.1007/s00259-019-04485-3

(LuPSMA trial): a single-centre, single-arm, phase 2 study [31]

- mCRPC cases, progressive disease after standard Tx
- **57%** achieved a PSA decline of 50% or more; objective response by imaging in nodal or visceral disease was reported in **82%** of patients with measurable disease
- **Grade 1 dry mouth in 87% patients**, grade 1 or 2 transient nausea in 50%, and grade 1 or 2 fatigue in 50% of patients [4]. The most common toxic effects possibly related to 177Lu-PSMA-617 were grade 3 lymphocytopenia in eleven (37%), **grade 3 anaemia in four (13%), and grade 3 or 4 thrombocytopenia in four (13%) patients**. In summary, data indicate a favorable safety profile for 177Lu-PSMA RLT.
- Median PSA PFS and OS were 7.6 mo and 13.5 mo.

Lancet Oncol 2018; 19: 825–33

Conclusion

- PSMA Theranostics: A paradigm of precision medicine in mCRPC - a visible lesion is a treatable lesion
- PSMA PET imaging: Gatekeeper for PSMA-directed-RLT of metastatic Pca; monitoring the effect of systemic treatment
- PSMA-directed-RLT: Favorable safety profile, xerostomia is a main concern; 50% achieved a PSA decline of 50% or more; OS benefit?
- 30% patients may undergo disease progression with Lu177-PSMA-RLT, Ac225-PSMA-RLT could be a surrogate – combination protocol may have better outcome