PSMA Imaging in the PSA-only Recurrent Setting

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Incidence of BCR after surgery or radiation for clinically localized prostate cancer

- Occurs within 10 y in 20% to 40% of patients after RP, 30% to 50% after RT
- Median time to BCR is typically 2 to 3 y but can occur up to 20 years after primary therapy

National Institutes of Health, National Cancer Institute. https://seer.cancer.gov/statfacts/html/prost.html.

Clinical Dilemmas in men with BCR

- Cannot tell where recurrent disease is located
- Absolute PSA levels tend to correlate with disease burden and risk for metastasis
- Shorter PSADT associated with higher risk of metastases
- Time to BCR is prognostic in most, but not all, studies

Sanda MG, Chen RC, Crispino T, et al.
http://www.auanet.org/guidelines/clinically-localized-prostate-cancer-new-(aua/astro/suo-guideline-2017).
Darwish OM, et al. *Front Oncol*. 2012;2:1-6.
Paller CJ, et al. *Clin Adv Hematol Oncol*. 2013;11:14-23.

Diagnostic Evaluation of Patients With BCR

- No guidelines on frequency of evaluation in men with BCR
- NCCN Guidelines® note:
  - Factors affecting BCR imaging use after RP
    - Risk group before surgery
    - Gleason score
    - Stage
    - Serum PSA
    - PSADT after recurrence
  - Cross-sectional imaging and conventional Tc-99m bone scans are rarely positive in asymptomatic men with PSA < 10 ng/mL
  - Imaging should be performed more frequently when PSADT ≤ 8 mo

NCCN® website.

Table 2. Summary of Main PET/CT Imaging Tracers Studied in Prostate Cancer*

Tracer	Half-life (min)	Cyclotron	Mechanism of action	Excretion	Sensitivity (%)*	Specificity (%)*	FDA Status	Panel Recommendation
C-11 choline	20	Onsite	Cell membrane synthesis	Hepatic	32–93	40–93	• Cleared	May be used for detection of biochemically recurrent small-volume disease in soft tissues
F-18 fluciclovine	110	Regional	Amino acid transport	Renal	37–90	40–100	• Cleared	May be used for detection of biochemically recurrent small-volume disease in soft tissues
F-18 NaF	110	Regional	Adsorption within bone matrix	Hepatic	87–100	62–89	• Cleared	May be used after bone scan for further evaluation of equivocal findings
C-11 acetate	20	Onsite	Lipid synthesis	Lung	59–69	83–98	• Not cleared	May be used in clinical trial or registry
Ga-68 PSMA	68	Generator (no cyclotron)	PSMA analog	Renal	76–86	86–100	• Not cleared	May be used in clinical trial or registry

* Interpret with caution; few studies used biopsy/surgery as gold standard; see *Nuclear Imaging*, above, for references.

Meta analysis: ^{11}C-Choline-PET/CT for Prostate Cancer Biochemical Recurrence

- 18 studies (2,126 patients)
  - Pooled detection rate 62%
- 12 studies (1,270 patients) with adequate data to assess sensitivity and specificity
  - Pooled sensitivity (Sens) 89%
  - Pooled specificity (Spec) 89%
- Local recurrence: Sens 61%, Spec 97%
- Nodal/distant metastasis: 36% detection rate
- Bone metastasis: 25% detection rate

Fanti S, et al. Eur J Nucl Med Mol Imaging. 2016;43:55-69.

^{11}C-Choline-PET/CT Sensitivity by PSA Level

- **Analysis of 358 patients post-RP with BCR (≥ 2 consecutive PSA measurements > 0.2 ng/mL)**
  - **Overall sensitivity /specificity: 85% /93%**
- **Detection rate by PSA level:**
  - **PSA 0.2 to 1 ng/mL: 19%**
  - **PSA 1 to 3 ng/mL: 46%**
  - **PSA > 3 ng/mL: 82%**
- **Package insert for ^{11}C-choline notes reduced sensitivity and specificity in patients with PSA levels < 2.0 ng/mL**

Giovacchini G, et al. *Eur J Nucl Med Mol Imaging.* 2018;37:301-309.
Choline C11 PI 2015.

^{18}F-Fluciclovine (FACBC)

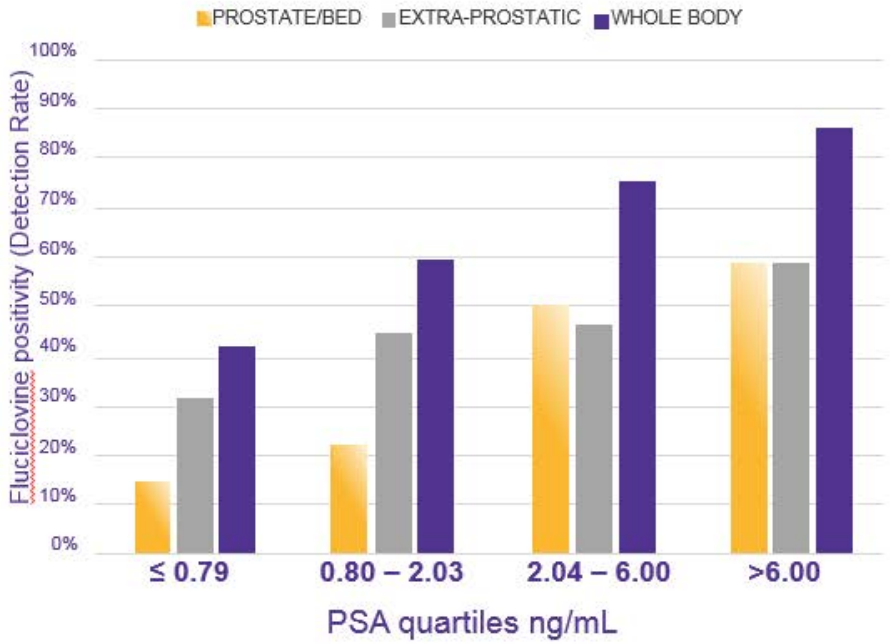
- *anti*-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid
- Synthetic, unnatural alicyclic L-leucine analog accumulates in prostate cancer cells
  - Not metabolized like ^{11}C-methionine
  - Relatively little renal excretion
- Uptake related to functional activity of amino acid transporters, which are upregulated in prostate cancer cells

Multicenter Study of FACBC-PET/CT in Biochemically Recurrent Prostate Cancer

- 596 patients (4 sites) with BCR after RP and/or RT
- PSA median (range): 2.0 (0.05-82.0)
- Endpoints
  - Detection rate stratified by baseline PSA
  - Diagnostic performance vs pathology reference standard (N=143)

Bach-Gansmo T, et al. J Urol. 2017;197:676-683

Fluciclovine in Biochemically Recurrent Prostate Cancer

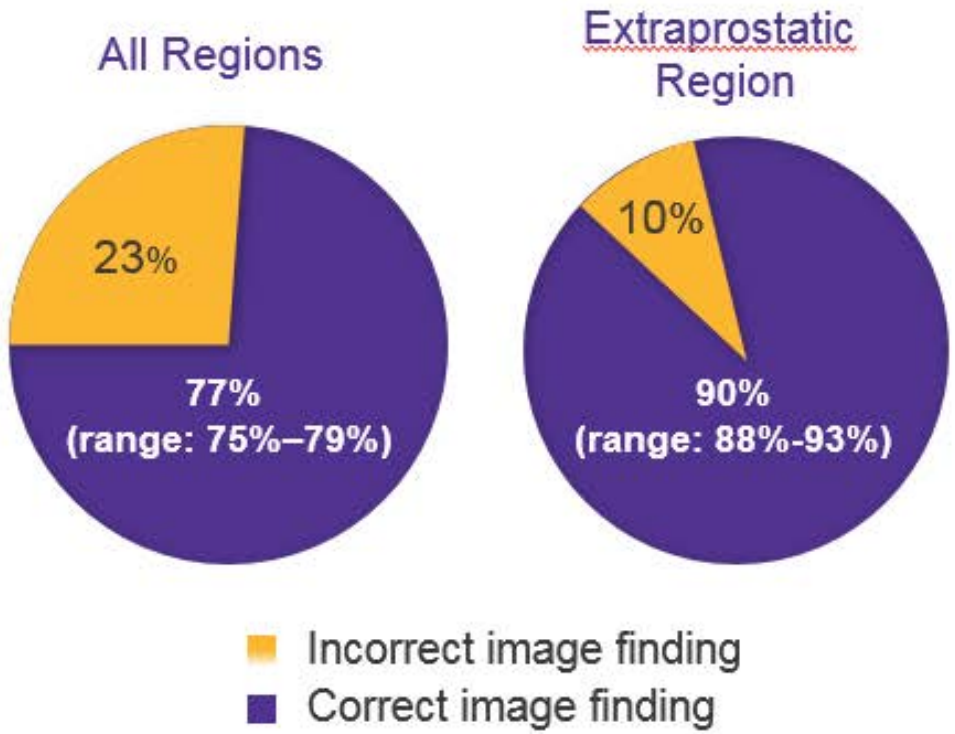


Adapted from Bach-Gansmo, *J Urol*, 2017.

Impact of PSA on fluciclovine (^{18}F) PET/CT detection rate at subject and region levels in combined data set[1]

1. Bach-Gansmo T, Nanni C, Nieh PT, et al. *J Urol*. 2017;197:676-683.

Performance of Axumin (fluciclovine F18) in patients with biochemically suspected recurrent prostate cancer[1]



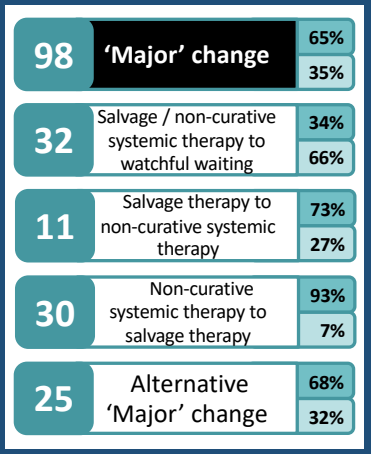
On average, the readers correctly predicted the histology findings for 77% of the images (range: 75%-79%). For the approximately one-third of images with suspicious lesions outside the region of the prostate bed, readers correctly identified the histology finding in an average of 90% of the images (range: 88%-93%).

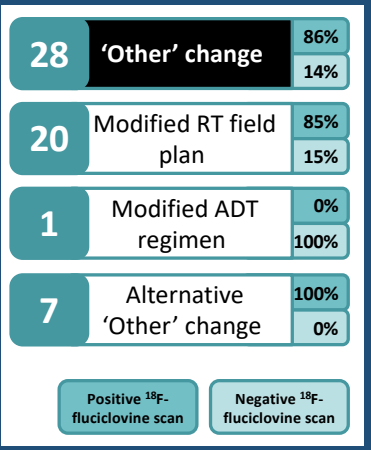
1. Axumin® (fluciclovine F 18) injection [Prescribing Information]. Blue Earth Diagnostics, Ltd; August 2016.

The Impact of Positron Emission Tomography with ^{18}F-Fluciclovine on the Treatment of Biochemical Recurrence of Prostate Cancer: Results from the LOCATE Trial

Gerald L. Andriole,*,† Lale Kostakoglu, Albert Chau,‡ Fenghai Duan,‡ Umar Mahmood, David A. Mankoff,‡ David M. Schuster‡ and Barry A. Siegel‡ on Behalf of the LOCATE Study Group

- ^{18}F-fluciclovine detected lesions in 57% of patients.
  - PSA: 0-0.5ng/mL: 31%
  - >0.5-1.0ng/mL: 50%
  - 1.0-2.0ng/mL: 66%.
- Management plans were revised in **126/213 patients (59%, 95% CI: 52–66)**.
  - 78% were ‘major’ changes involving a change in treatment modality.
  - 70% were informed by positive ^{18}F-fluciclovine PET/CT findings.





0022-5347/19/2012-0322/0
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https://doi.org/10.1016/j.juro.2018.08.050
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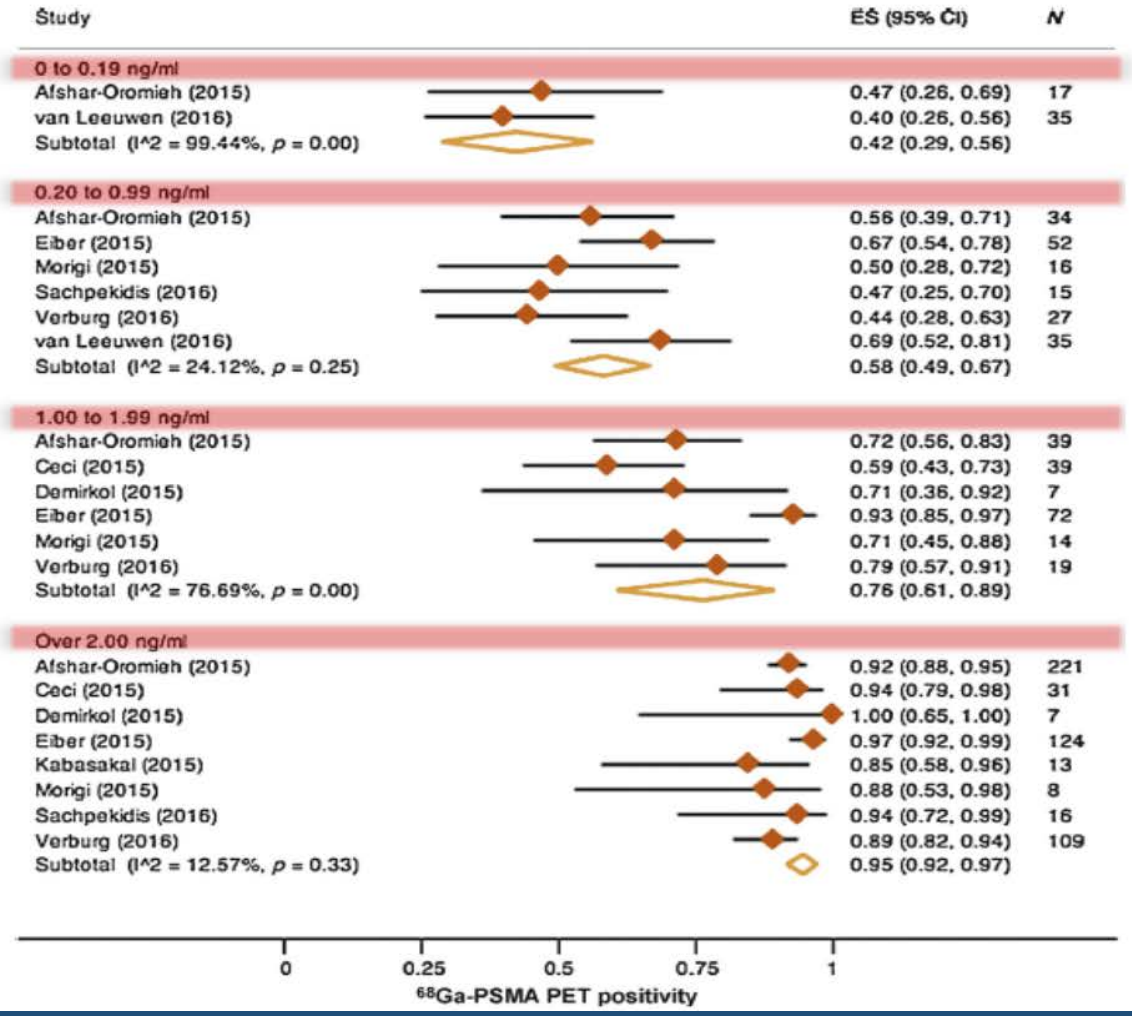
Prostate Specific Membrane Antigen (PSMA)

- PSMA is normally expressed by cells in the CNS, normal prostate, proximal renal tubules and salivary gland
- High expression in prostate cancer cells (with further increases when tumors become castration resistant)
- New, small molecule ligands target the extracellular domain of PSMA (unlike Prostascint, which targets the intracellular domain)
- F-18 and Ga-68 agents under investigation

Mauer T, et al. Nat. Rev. Urol. 2016;13:226-235

Performance of ^{68}Ga-PSMA PET for BCR

Detection efficacy stratified by PSA-values

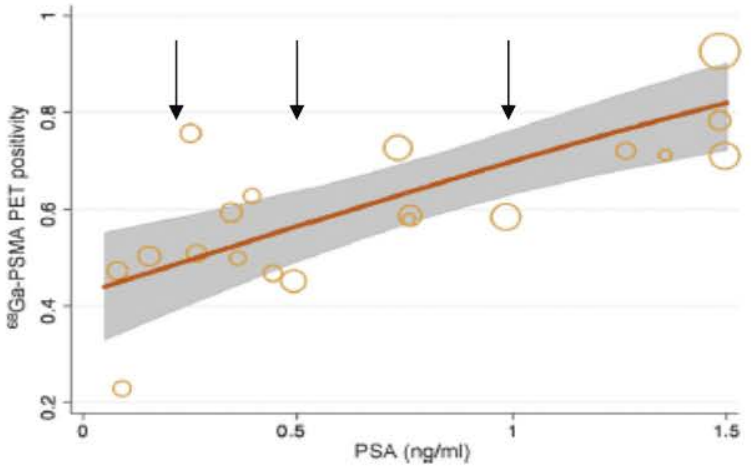


Predicted positivity in meta-regression analysis

48% at 0.2 ng/ml

56% at 0.5 ng/ml

70% at 1.0 ng/ml

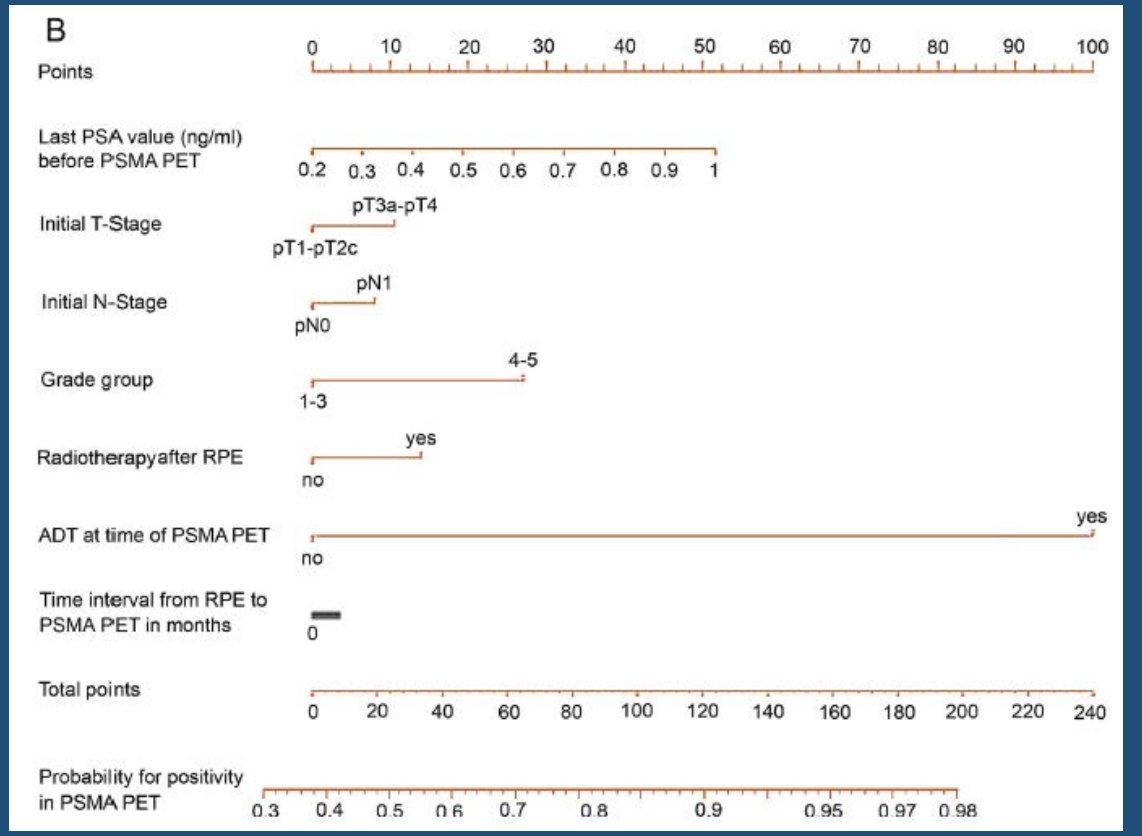


Choline labelled agents:
16% for PSA <1 ng/ml, 26% for PSA <2 ng/ml

Treglia et al, Clin Chem Lab Med 2013

Perrera et al Eur Uro. 2016

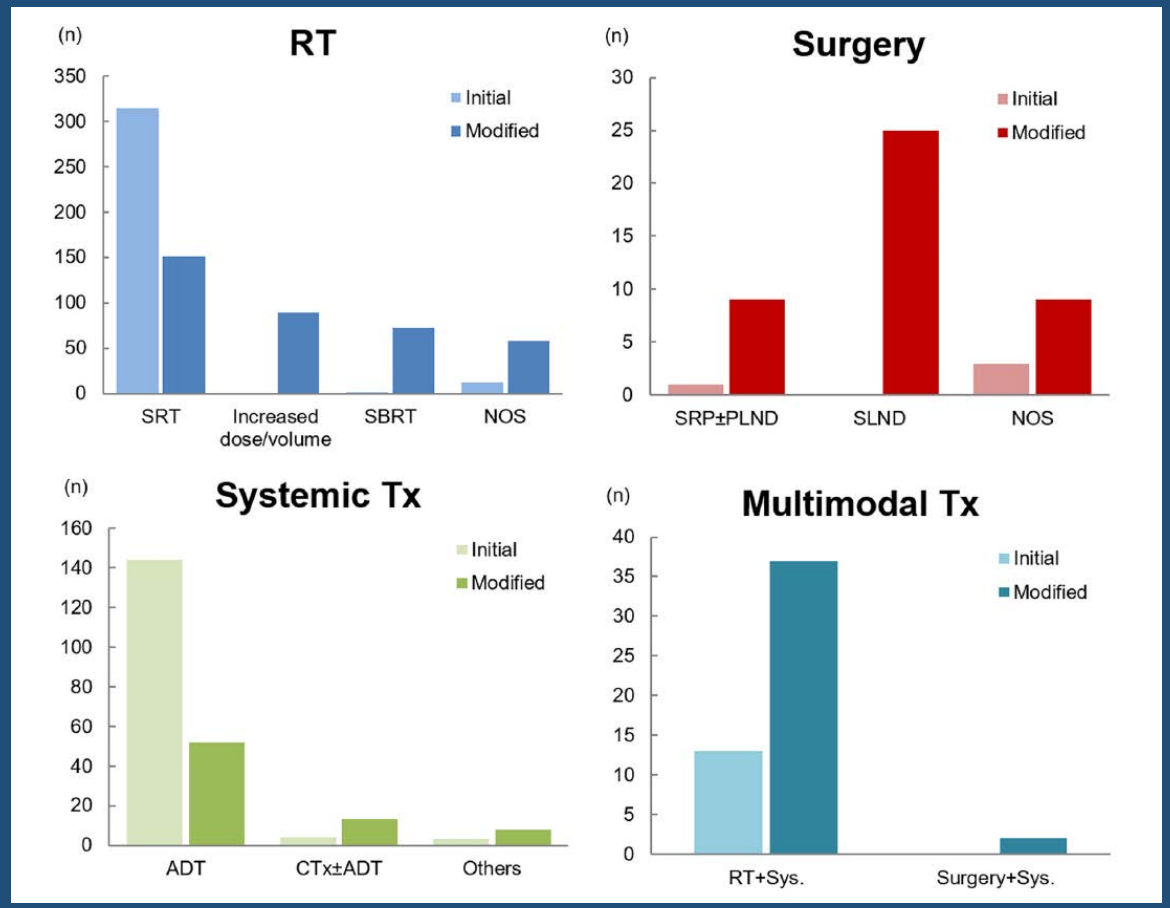
Efficacy, Predictive Factors, and Prediction Nomograms for ^{68}Ga-labeled Prostate-specific Membrane Antigen–ligand Positron-emission Tomography/Computed Tomography in Early Biochemical Recurrent Prostate Cancer After Radical Prostatectomy



EUROPEAN UROLOGY 73 (2018) 656–661

Impact of ^{68}Ga-PSMA PET on the Management of Patients with Prostate Cancer: A Systematic Review and Meta-analysis

15 Studies
54% Treatment change

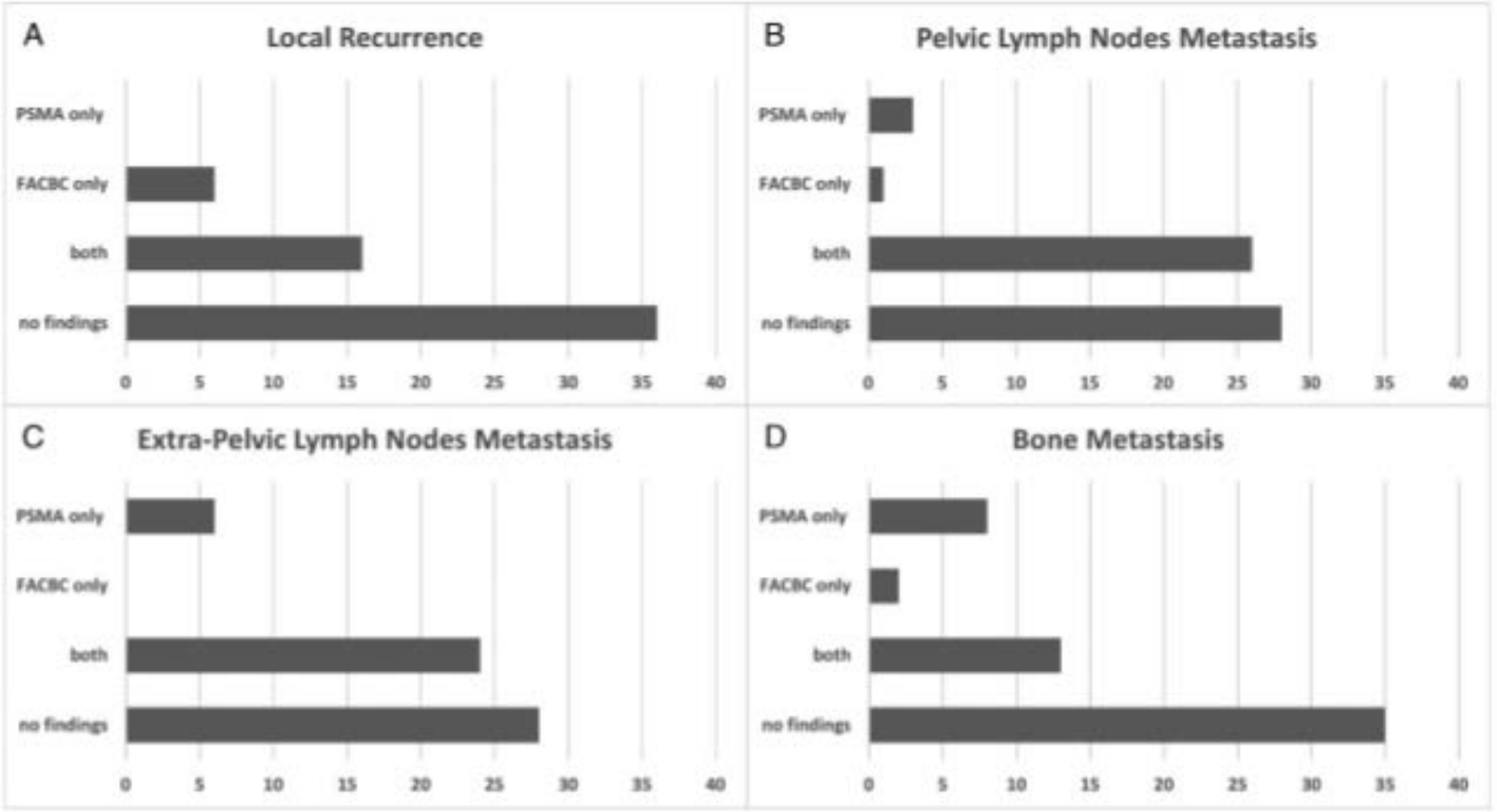


EUROPEAN UROLOGY 74 (2018) 179–190

A Prospective Head-to-Head Comparison of ^{18}F-Fluciclovine With ^{68}Ga-PSMA-11 in Biochemical Recurrence of Prostate Cancer in PET/CT

Results: The overall detection rate for PCa recurrence was 79.3% in ^{18}F-fluciclovine and 82.8% in ^{68}Ga-PSMA-11 ($P = 0.64$). Local recurrence was detected in 37.9% on ^{18}F-fluciclovine and in 27.6% on ^{68}Ga-PSMA-11 ($P = 0.03$). Local pelvic lymph node recurrence was detected on ^{18}F-fluciclovine versus ^{68}Ga-PSMA-11 in 46.6% versus 50%, in extrapelvic lymph node metastases in 41.4% versus 51.7% and in bone metastases in 25.9% versus 36.2%. Lesion-based analysis showed identical findings in local pelvic lymph nodes in 39.7%, in extrapelvic lymph nodes in 22.4%, and in bone metastases in 13.8%.

Conclusions: The advantage of ^{18}F-fluciclovine is detecting curable localized disease in close anatomical relation to the urinary bladder, whereas ^{68}Ga-PSMA-11 fails because of accumulation of activity in the urinary bladder. ^{18}F-fluciclovine is almost equivalent to ^{68}Ga-PSMA-11 in detecting distant metastases of PCa recurrence.


A
Local Recurrence
PSMA only
FACBC only
both
no findings
0 5 10 15 20 25 30 35 40
B
Pelvic Lymph Nodes Metastasis
PSMA only
FACBC only
both
no findings
0 5 10 15 20 25 30 35 40
C
Extra-Pelvic Lymph Nodes Metastasis
PSMA only
FACBC only
both
no findings
0 5 10 15 20 25 30 35 40
D
Bone Metastasis
PSMA only
FACBC only
both
no findings
0 5 10 15 20 25 30 35 40

^{18}F-fluciclovine PET-CT and ^{68}Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial

Findings Between Feb 26, 2018, and Sept 20, 2018, 143 patients were screened for eligibility, of whom 50 patients were enrolled into the study. Median follow-up was 8 months (IQR 7–9). The primary endpoint was met; detection rates were significantly lower with ^{18}F-fluciclovine PET-CT (13 [26%; 95% CI 15–40] of 50) than with PSMA PET-CT (28 [56%; 41–70] of 50), with an odds ratio (OR) of 4·8 (95% CI 1·6–19·2; p=0·0026) at the patient level; in the subanalysis of the pelvic nodes region (four [8%; 2–19] with ^{18}F-fluciclovine *vs* 15 [30%; 18–45] with PSMA PET-CT; OR 12·0 [1·8–513·0], p=0·0034); and in the subanalysis of any extrapelvic lesions (none [0%; 0–6] *vs* eight [16%; 7–29]; OR non-estimable [95% CI non-estimable], p=0·0078).

Interpretation With higher detection rates, PSMA should be the PET tracer of choice when PET-CT imaging is considered for subsequent treatment management decisions in patients with prostate cancer and biochemical recurrence after radical prostatectomy and low PSA concentrations (≤2·0 ng/mL). Further research is needed to investigate whether higher detection rates translate into improved oncological outcomes.

www.thelancet.com/oncology Published online July 30, 2019 http://dx.doi.org/10.1016/S1470-2045(19)30415-2

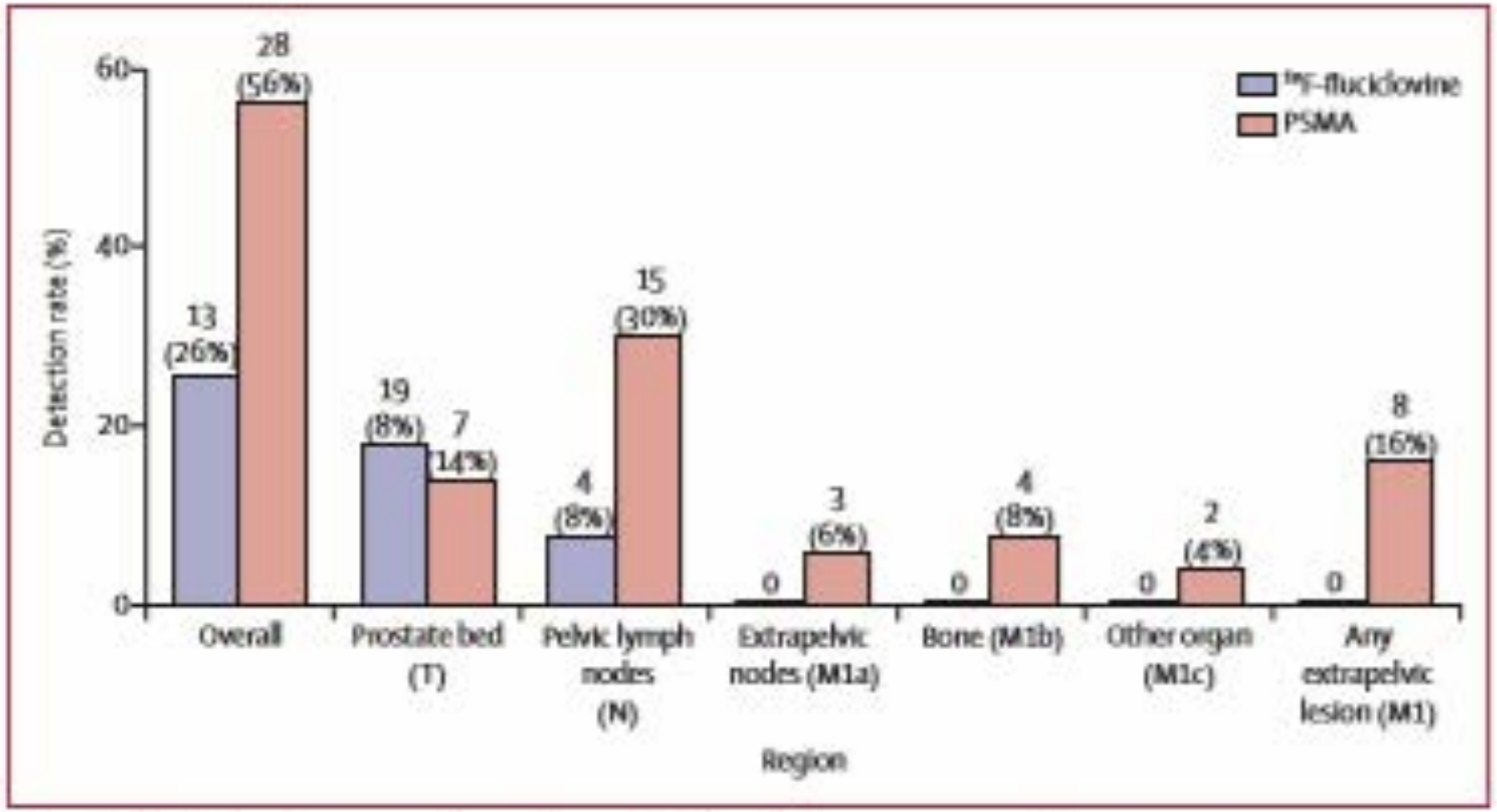


Figure 2: Detection rates per region and per patient (majority consensus reads)
PSMA=prostate-specific membrane antigen.

This study has several limitations. Technical parameters might have been confounding factors and could have potentially introduced a bias. ^{18}F-fluciclovine uptake time was shorter than that recommended by guidelines.[16] This might have affected pelvic image quality via higher blood pool activity at the time of imaging, and thus T and N staging, but not the extrapelvic (M) staging. Some ^{18}F-fluciclovine PET-CT scans were done without intravenous CT-contrast application. However, the

PSMA readers had recorded a higher number of PSMA scan reads than the ^{18}F-fluciclovine readers had recorded of ^{18}F-fluciclovine scan reads. This difference is probably because of the more frequent clinical use of PSMA, especially in Europe. However, care was taken to select

F-18 DCFPyL: Study in Metastatic Prostate Cancer

- 9 pts with suspected PC recurrence imaged with 18FDCFPyL PET/CT
  - 139 sites positive with ^{18}F-DCFPyL uptake (138 definite, 1 equivocal) for metastases vs 45 lesions (30 definite, 15 equivocal) identified by conventional imaging modalities (CIM)
  - Large proportion of negative or equivocal lesions on CIM would be positive on ^{18}F-DCFPyL (0.72; 95% CI, 0.55-.084)
  - Few negative lesions on ^{18}F-DCFPyL would be positive on CIM (0.03; 95% CI, 0.01-0.07)

Rowe, SP, et al Mol. Imaging Biol. 2016; 18:411-419

Table 1: Patient Characteristics

	All included		BR post RP only*		BR post RT only*	
Variable	**Value**	**n**	**Value**	**n**	**Value**	**n**
Age (years)	69.1±6.5	130	68.4±6.3	92	70.8±6.9	35
Body weight (kg)	87.4±14.4	130	86.9±14.4	92	87.7±13.5	35
Height (cm)	177.3±6.8	130	176.9±6.8	92	177.5±6.6	35
Injected activity (MBq)	369.2±47.2	130	367.8±47.1	92	371.1±46.0	35
Uptake time (min)	120.4±1.5	130	120.5±1.7	92	120.2±0.6	35
Inclusion criteria†						
Known PC after radical prostatectomy with BR	94 (72.3%)	130	92 (100%)	92	0 (0.0%)	35
Known PC after radiation therapy with BR	37 (28.5%)	130	0 (0.0%)	92	35 (100%)	35
PSA at baseline (ng/mL)	5.20±6.50	130	3.03±3.40	92	11.11±8.94	35
PSA doubling time (months)	12.2±11.8	113	12.0±12.3	78	12.9±11.1	32
Treatment history†						
Surgery	94 (72.3%)	130	92 (100%)	92	0 (0.0%)	35
Radiotherapy†	45 (34.6%)	130	7 (7.6%)	92	35 (100%)	35
Brachytherapy	27 (60.0%)	45	0 (0.0%)	7	26 (74.3%)	35
External beam	20 (44.4%)	45	5 (71.4%)	7	13 (37.1%)	35
IMRT	4 (8.9%)	45	2 (28.6%)	7	2 (5.7%)	35
Proton	1 (2.2%)	45	0 (0.0%)	7	1 (2.9%)	35
Radium-223	0 (0.0%)	45	0 (0.0%)	7	0 (0.0%)	35
ADT	62 (47.7%)	130	39 (42.4%)	92	22 (62.9%)	35
Chemotherapy	1 (0.8%)	130	1 (1.1%)	92	0 (0.0%)	35

Values are presented as mean ± std. dev. or proportions. PC: prostate cancer; BR: biochemical recurrence; RP: radical prostatectomy; RT: radiation therapy; ADT: Androgen deprivation therapy; IMRT: Intensity-modulated radiation therapy. *Inclusion criteria; †Categories are not mutually exclusive.

Journal of Nuclear Medicine, published on April 12, 2019 as doi:10.2967/jnumed.119.226381

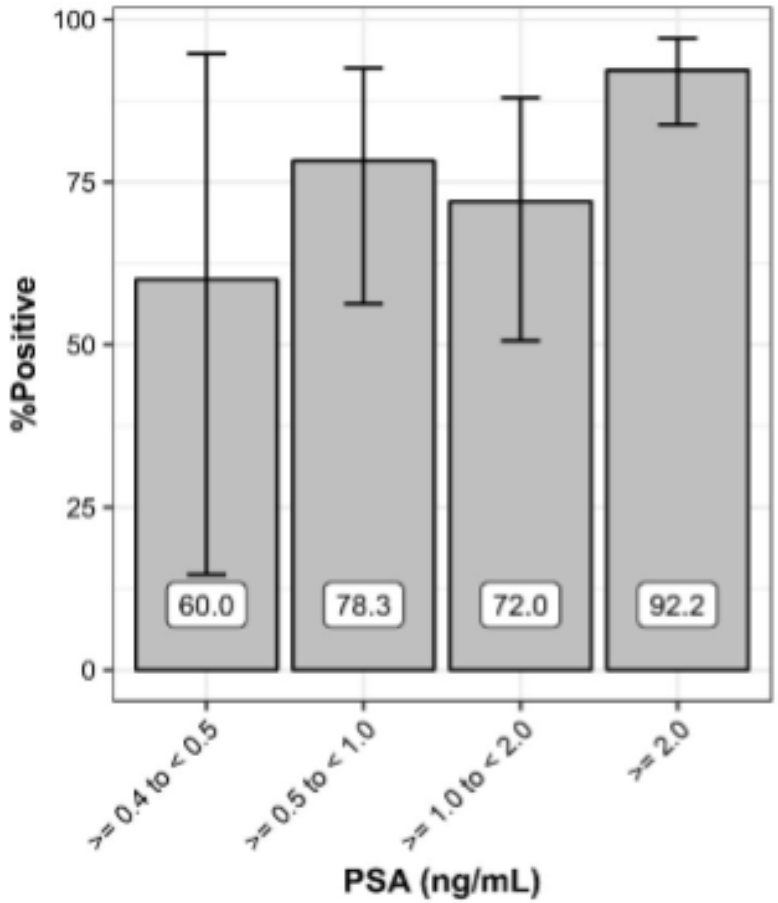


Figure 2. Proportion of positive scans based on PSA levels. Error bars represent 95% confidence interval.

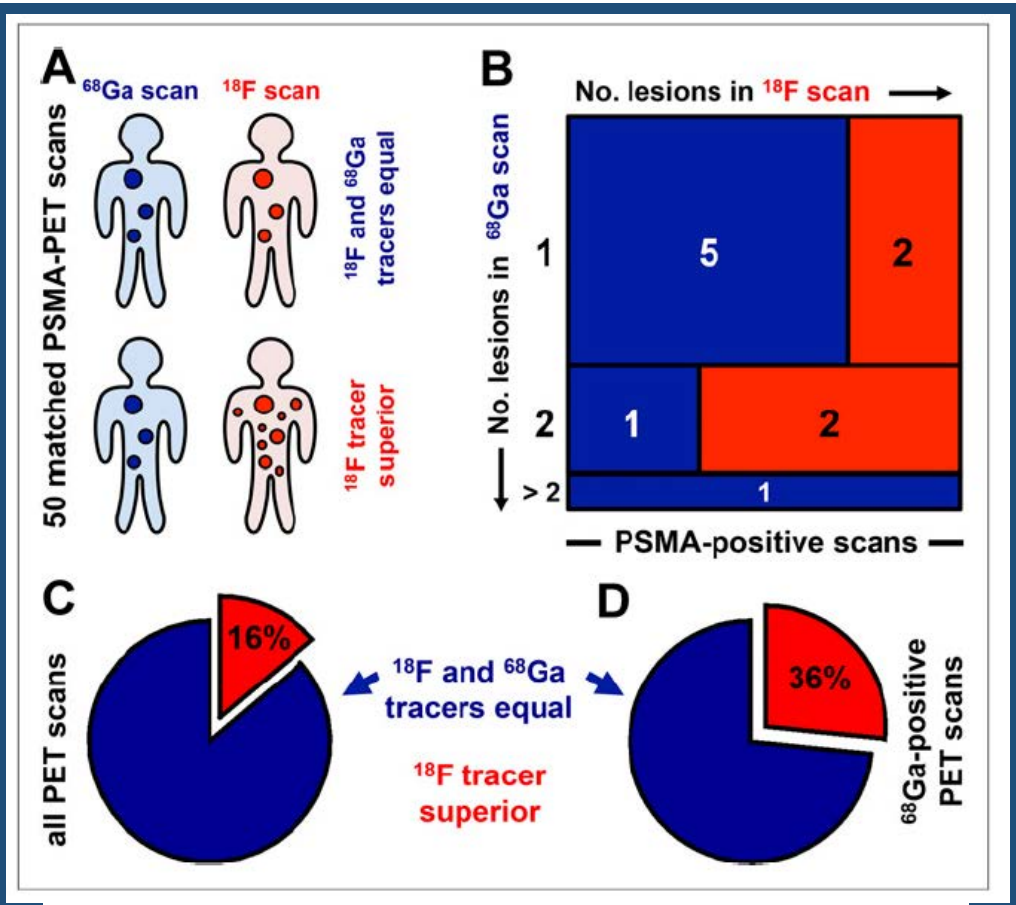
Journal of Nuclear Medicine, published on April 12, 2019 as doi:10.2967/jnumed.119.226381

Table 3: Changes in Treatment Intent, Disease Stage, Investigation, Decision-Making or Management Plan

	All included		BR post RP only*		BR post RT only*	
Variable	Value	n	Value	n	Value	n
Change in treatment intent	36 (65.5%)	55	21 (56.8%)	37	13 (86.7%)	15
To Palliative	18 (50.0%)	36	10 (47.6%)	21	6 (46.2%)	13
To Curative	18 (50.0%)	36	11 (52.4%)	21	7 (53.9%)	13

Journal of Nuclear Medicine, published on April 12, 2019 as doi:10.2967/jnumed.119.226381

PSA-Stratified Performance of ^{18}F- and ^{68}Ga-PSMA PET in Patients with Biochemical Recurrence of Prostate Cancer



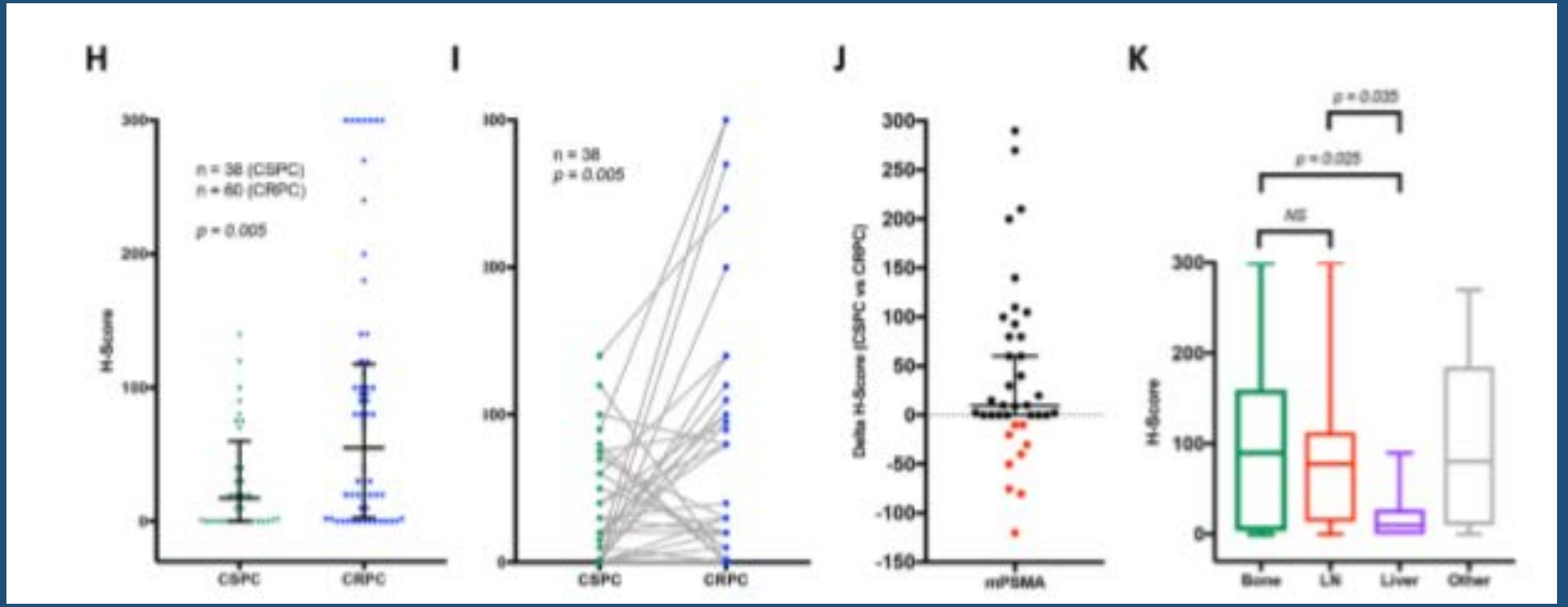
J Nucl Med 2017; 58:947–952
DOI: 10.2967/jnumed.116.185538

Prostate-specific Membrane Antigen Heterogeneity and DNA Repair Defects in Prostate Cancer

Please cite this article in press as: Paschalis A, et al. Prostate-specific Membrane Antigen Heterogeneity and DNA Repair Defects in Prostate Cancer. Eur Urol (2019), https://doi.org/10.1016/j.eururo.2019.06.030

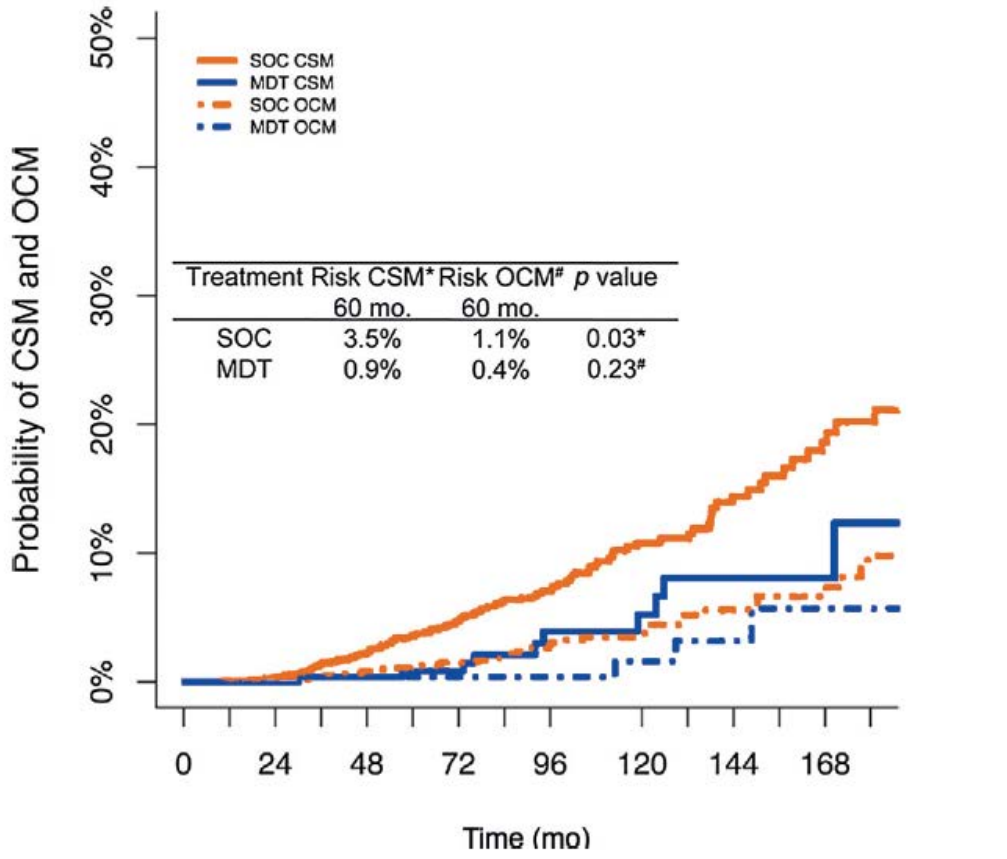
Design, setting, and participants: Membranous PSMA (mPSMA) expression was scored immunohistochemically from metastatic castration-resistant PC (mCRPC) and matching, same-patient, diagnostic biopsies, and correlated with next-generation sequencing (NGS) and clinical outcome data.

Conclusions: Membranous PSMA expression is upregulated in some but not all PCs, with mPSMA expression demonstrating marked inter- and intrapatient heterogeneity. DDR aberrations are associated with higher mPSMA expression and merit further evaluation as predictive biomarkers of response for PSMA-targeted therapies in larger, prospective cohorts.


H
n = 38 (CSPC)
n = 60 (CRPC)
p = 0.005
H-Score
CSPC
CRPC
I
n = 38
p = 0.005
CSPC
CRPC
J
Delta H-Score (CSPC vs CRPC)
mPSMA
K
p = 0.035
p = 0.025
NS
H-Score
Bone
LN
Liver
Other

Standard of Care Versus Metastases-directed Therapy for PET-detected Nodal Oligorecurrent Prostate Cancer Following Multimodality Treatment: A Multi-institutional Case-control Study

T. Steuber [a], *C. Jilg* [b], *P. Tenns* ... *Zilli* [e],



Treatment	Risk CSM* 60 mo.	Risk OCM# 60 mo.	*p* value
SOC	3.5%	1.1%	0.03*
MDT	0.9%	0.4%	0.23#

https://doi.org/10.1016/j.euf.2018.02.015
2405-4569/© 2018 European Association of Urology.

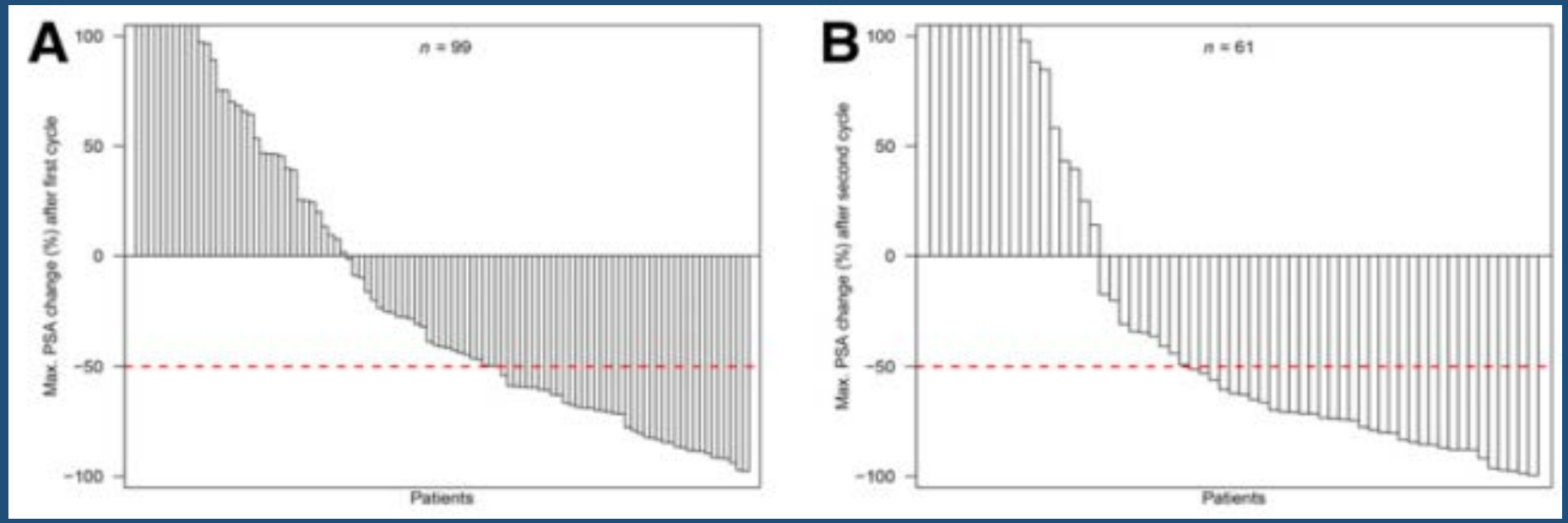
PSMA: Other potential uses

- Primary detection
- Monitor results of focal therapy or XRT
- Primary staging, eg, high-risk
- Therapy

German Multicenter Study Investigating ^{177}Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients

Kambiz Rahbar*[1], Hojjat Ahmadzadehfar*[2], Clemens Kratochwil[3], Uwe Haberkorn[3], Michael Schäfers[1], Markus Essler[2], Richard P. Baum[4], Harshad R. Kulkarni[4], Matthias Schmidt[5], Alexander Drzezga[5], Peter Bartenstein[6], Andreas Pfestroff[7], Markus Luster[7], Ulf Lützen[8], Marlies Marx[8], Vikas Prasad[9], Winfried Brenner[9], Alexander Heinzel[10], Felix M. Mottaghy[10], Juri Ruf[11], Philipp Tobias Meyer[11], Martin Heuschkel[12], Maria Eveslage[13], Martin Bögemann[14], Wolfgang Peter Fendler†[6], and Bernd Joachim Krause†[12,15]

J Nucl Med 2017; 58:85–90



First cycle

Second Cycle

PET scans for Biochemical Recurrence

- Detection rate dependent on PSA level
- FACBC seems to be more sensitive than Choline
- PSMA-based scans not approved in US
  - Possibly more sensitive for non-LR
- PET scans change treatment decisions
- Unknown whether such treatment changes make a difference in ultimate outcomes
- PSMA theranostic application under evaluation