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PSMA-PET identifies PCWG3 target populations with superior accuracy and reproducibility when compared to conventional imaging: a multicenter retrospective study

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Short title

PSMA PCWG3

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ABSTRACT

Background: Prostate-specific membrane antigen (PSMA)-ligand positron-emission-tomography (PSMA-PET) is potentially useful for screening of castration resistant prostate cancer (CRPC) clinical trial target populations.

Aim: We investigated the impact of PSMA-PET on Prostate Cancer Clinical Trials Working Group 3 (PCWG3) clinical subtype classification when compared to conventional imaging (CI).

Methods: Multicenter retrospective study enrolling patients with *(a)* PSMA-PET for CRPC, *(b)* PSA values ≥1 ng/mL and *(c)* CI, i.e. CT plus bone scan or whole-body MRI. Clinical PCWG3 subtype was determined for PET vs. CI by three blinded readers.

Results: 67 patients were included and PSMA-PET led to up-staging in 15% (10/67) of patients, of these 6/10 (60%) had CI non-metastatic CRPC. PSMA-PET resulted in down-staging in 15% (10/67) of patients. Agreement for PET vs. CI PCWG3 clinical subtype was 0.81 vs. 0.51, 0.74 vs. 0.47, 0.95 vs. 0.72, or 0.59 vs. 0.66 for local, nodal, bone, or visceral disease, respectively.

Conclusion: PSMA-PET demonstrated major concordance with CI for per-patient PCWG3 clinical subtype and should be implemented in future CRPC clinical trial screening procedures.

Keywords

CRPC; PCWG; Positron Emission Tomography (PET); prostate cancer; PSMA

MANUSCRIPT

INTRODUCTION

Prostate cancer is the second leading cause of cancer mortality in men worldwide (*1*). Patients initially respond to hormonal therapy but eventually develop potentially fatal castration resistant disease (CRPC) (*2*). In 2016, the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) summarized CRPC clinical trial recommendations, defining five clinical CRPC target populations based on pattern of spread, ranging from non-metastatic (nmCRPC) to visceral metastatic CRPC. PCWG3 recommends conventional imaging (CI), i.e. bone scan (BS), CT and/or whole-body MRI (wbMRI) as standard imaging modalities (*3*). Since PCWG3, positron emission tomography with small-molecule ligands that bind to cell-surface prostate-specific membrane antigen (PSMA-PET) have been introduced widely. In patients with biochemical recurrence and low PSA level, PSMA-PET proved superior accuracy for recurrent prostate cancer staging (*4*) also when compared to recently approved Fluciclovine PET (*5*). PSMA-PET further localized metastases in more than half of patients with nmCRPC by CI (*6*) and detected higher tumor load in CRPC patients with bone metastases on previous bone scan (BS) (*7*). We therefore hypothesize that PSMA-PET offers more accurate and reproducible identification of PCWG3 CRPC clinical trial target populations and will lead to considerable stage migration when compared to CI.

MATERIAL AND METHODS

Study Design and Participants

Datasets from 1140 CRPC patients at three participating high-volume PET Centers (University of Bologna; University Hospital Essen; Technical University Munich) were

retrospectively screened for patients with prostate cancer who had: *(a)* PSMA-PET between January 2014 and January 2019, *(b)* PSA values ≥1 ng/mL at the time of PET in accordance with PCWG3 (*3*) and *(c)* BS and CT or wbMRI within 3 months of the PSMA-PET without changes of therapy between the staging modalities. Patient flow is demonstrated in Figure 1. Approval was obtained by the University of Duisburg-Essen ethics committee (18-8153-BO). All patients gave written consent to undergo PSMA-PET. The prerequisite to obtain informed consent for inclusion in this retrospective analysis was waived by the ethics committee.

CRPC Subtypes and Stage Migration

PCWG3 clinical subtypes were, by ascending stage: 1) nmCRPC; 2) locally recurrent disease only; 3) nodal spread (±local relapse); 4) bone disease (±local and/or nodal disease) and 5) visceral disease (±local and/or nodal disease and/or bone disease). Upstaging was defined as any shift to a higher stage number, down-staging was defined as any shift to a lower stage number.

Imaging Procedures

^{68}Ga-PSMA-11 PET was acquired in accordance with the international guideline as part of a PET/CT (n=52) or PET/MRI (n=15) examination (*8*). Of 67 examinations, 58 (87%) were performed with radiographic contrast enhancement. Attenuation correction was based on the diagnostic CT (PET/CT) or a separate Dixon-based sequence (PET/MRI).

PET imaging. Patients received, on average, 137 MBq (range: 111-159 MBq) of ^{68}Ga-PSMA-11. Image acquisition was started after an average of 64 minutes (range: 51-68 minutes) post injection. The PET was reconstructed by ordered subset expectation

maximization-based algorithms. Data from the CT or MRI scan were used for attenuation correction.

CT imaging. Full-dose CT scan was acquired from the skull base to the mid-thigh. Automatic dose modulation was applied with a tube voltage of 120 kV (200-240 mAs). Iodinated i.v. contrast was given 70 seconds before image acquisition.

MRI imaging. wbMRI examinations were performed on an integrated 3 Tesla PET/MRI scanner using high channel surface coils. The field of view was from the skull base to the mid-thigh and protocol consisted of first a simultaneous PET and 3D Dixon VIBE sequences for scatter correction, a diffusion-weighted sequence with b-values of 50, 500 and 1000, then a standardized wbMRI protocol including an axial T1-weighted VIBE sequence after administration of gadolinium.

BS imaging. An average of 683 MBq (range: 606-947 MBq)^{99m}Tc-DPD or ^{99m}Tc-HDP was given intravenously. Delayed whole-body imaging was performed 2 to 4 h post tracer injection (matrix size of 128 × 128 or 256 × 256). SPECT imaging was obtained depending on the recruiting Center's protocol.

Image Interpretation

Clinical PCWG3 subtype was determined for PET versus CI by three blinded readers using published criteria after dedicated reader training (*9*–*11*). PET datasets included PSMA PET with CT or MRI; CI datasets included CT and BS (n=52) or wbMRI (n=15). Datasets were read separately and independently after anonymization and randomization with more than two weeks' time between PET vs. CI reading sessions. Readers were familiar with the patients' most recent PSA value and prior treatments but were blinded to other imaging

findings and clinical data. OsiriX MD (Pixmeo SARL, Switzerland) was used for the central readings. Consensus (positive vs. negative) was determined by majority vote.

Statistical Analysis

For continuous data mean ± SD, median and inter-quartile range (IQR) were reported, while categorical variables were described using absolute and relative (%) frequencies. PSMA-PET and CI positivity rate for the localization of site of disease was determined on a patient basis stratified by PSA at the time of the scan. Association between categorical variables including ISUP grade group, T stage, N stage, D'Amico risk group, chemotherapy naïve, first and second line of therapy were evaluated with Pearson's X^2 test or Fischer's exact test. Due to an asymmetric distribution of PSA, its association with PSMA or CI positivity was assessed with the non-parametric Mann-Whitney Test. When the effect of categoric variables was assessed against a symmetric continuous variable (SUV_{max}), a linear model with ANOVA was used. Interobserver agreement was determined by Fleiss' κ and interpreted by the criteria of Landis and Koch (12). Statistical analysis was conducted with Stata statistical software version 13 (StataCorp, College Station, TX) and a p value lower than 0.05 was considered significant.

RESULTS

Patient Characteristics

Sixty-seven patients were included (Technical University of Munich, 35 [52%]; University Hospital Essen, 24 [36%]; University of Bologna, 8 [12%]). Patient characteristics are given in Table 1. Median PSA level at the time of PSMA-PET was 53.2 ng/mL (IQR 5.8-334.6 ng/mL). Within 3 months before or after PSMA-PET or as part of the PSMA-PET

assessment, 52/67 (78%) patients had CT and BS, 15/67 (22%) had wbMRI. Median time between PSMA-PET and CI was 1 month (IQR 0-2). Median PSA level at the time of CI was 28.7 ng/mL (IQR 3.0-7.5) in the wbMRI group and 122.3 ng/mL (IQR 28.3-388.8) in the CT/BS group. Regarding previous therapies, 41/67 (61%) patients were abiraterone/enzalutamide/apalutamide naïve and 41/67 (61%) chemotherapy naïve; 12/67 (18%) were previously treated with radium-223.

Lesion Detection

Overall CI was positive in 87% (58/67), PSMA-PET in 92% (62/67) of patients. Positivity rate of CT, BS and wbMRI was 96% (50/52), 90% (47/52) and 47% (7/15), respectively. The probability of detecting any lesion was associated with PSA level at time of the scan (p=0.032 for PSMA-PET and p=0.002 for CI). PSMA-PET versus CI disease burden is shown in (Figure 2). Details on lesion size and SUV are given in Supplemental Table 1.

PCWG3 Subtype

CI PCWG3 clinical subtype was non-metastatic, local, nodal, bone, or visceral disease for 13% (9/67), 0% (0/67), 6% (4/67), 58% (39/67), or 22% (15/67), respectively (Supplemental Table 2 and 3).

Up- or down-staging by PSMA-PET is given in Supplemental Table 4. Overall, PSMA-PET and CI subtype were discordant in 20/67 (30%) of patients. PSMA-PET led to up-staging in 10/67 (15%) patients, 4 of these with migration from nodal or bone to visceral disease, 6 of these with shift from non-metastatic to locally recurrent (n=2), nodal (n=3), or bone (n=1) disease. PET led to down-staging in 10/67 (15%) patients, 7 of these had CI visceral disease in lungs (n=5), liver (n=2) or adrenal (n=1) and 3 had bone involvement ruled out by PSMA-

PET. Lesion validation in 7 patients demonstrated both true negative (n=2, 25%) versus false negative (n=3, 38%) PSMA-PET interpretation (Supplemental Table 5).

There was a statistically significant association between higher D'Amico risk group and PSMA-PET down-staging compared to CI (p=0.003); PSA at time of PET or number of systemic therapies were not significantly associated with stage migration.

Interobserver Agreement

Agreement for PET vs. CI PCWG3 clinical subtype was 0.81 vs. 0.51, 0.74 vs. 0.47, 0.95 vs. 0.72, or 0.59 vs. 0.66 for local, nodal, bone, or visceral disease, respectively. Agreement for nmCRPC was 0.46 for PET and not measurable for CI (n=0) (Supplemental Table 6 and 7).

DISCUSSION

PSMA-PET previously demonstrated unprecedented accuracy for tumor localization in patients with prostate cancer biochemical recurrence and non-metastatic castration-resistant disease (*4*,*6*). Diagnostic value was validated by histopathology, management changes and survival in several trials (*4*,*6*,*13*–*15*). Imaging is essential for identification of CRPC clinical trial target populations. However, the impact of PSMA-PET on CRPC PCWG3 staging remains unknown. Here we assess in a retrospective multi-center study the potential shift in PCWG3 clinical subtype by PSMA-PET when compared to CT with BS or wbMRI. Majority of patients had advanced disease (80% with CI bone and/or visceral metastases) with previous CRPC systemic therapy. PSMA-PET demonstrated higher reproducibility, except for visceral disease, and detected additional lesions especially in patients with PSA ≤15 ng/mL leading to up-staging of CI non-metastatic CRPC. On the other hand, PET demonstrated somewhat

lower reproducibility and did not detect organ lesions leading to down-staging in patients with CI visceral disease (*16*–*19*). Lesion validation indicated false downstaging by PSMA-PET in part of the patients. False negative interpretation for dedifferentiated organ metastases is a known limitation of PSMA-PET. While previously reported high accuracy in biochemical recurrence and non-metastatic CRPC cohorts suggest true findings by PSMA-PET, a systematic lesion validation has not been performed in the presented patients.

Overall, PSMA-PET was concordant with CI CRPC subgroups in more than two third of patients, especially in patients with bone metastatic disease. Both PET and CI detected multifocal disease in almost all patients with more advanced disease (PSA >15 ng/mL). Here we demonstrate that PSMA-PET is a highly reproducible staging tool for advanced CRPC with high concordance with CI. Our findings encourage a shift in the current CRPC imaging choice: PSMA-PET should be included in future CRPC clinical trial entry and potentially also endpoint assessments. Implementation with careful assessment of visceral lesions is expected to improve patient selection thereby increasing probability of trial success and reproducibility of findings. Follow-up PSMA-PET will generate exploratory analyses e.g. for CRPC outcome prediction.

Limitations of our study include its retrospective single-center design, small sample size, the lack of systematic follow-up, heterogeneous imaging modalities, use of the CT and wbMRI part of a PSMA-PET examination and PSMA-PET versus CI readings by the same reader group.

In conclusion, PSMA-PET was highly reproducible and resulted in PCWG3 subtype migration in 30% of patients, especially in patients with CI non-metastatic disease. Subtypes were concordant in 70% of patients, especially in patients with PSA >15 ng/mL or bone

metastatic disease. PSMA-PET should be implemented in future CRPC clinical trial entry procedures.

KEY POINTS

- Question: Is PSMA-ligand PET accurate and reproducible in identifying CRPC clinical trial target populations as compared to conventional imaging and according to PCWG3 clinical subtypes?
- Pertinent Findings: In this retrospective multicenter study PSMA-ligand PET was highly reproducible and resulted in PCWG3 subtype migration in 30% of patients, especially in patients with non-metastatic disease at conventional imaging. Subtypes were concordant in 70% of patients, especially in patients with PSA >15 ng/mL or bone metastatic disease.
- Implications for Patient Care: PSMA-ligand PET should be implemented in future clinical trial entry procedures for patients with castration-resistant prostate cancer.

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FIGURES

FIGURE 1. Consort diagram for patient selection.

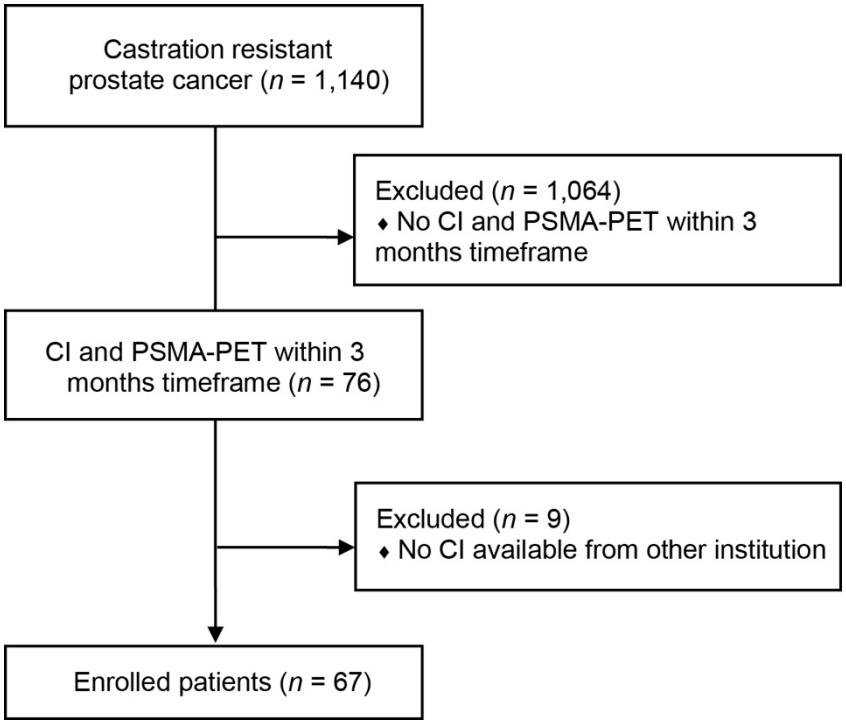
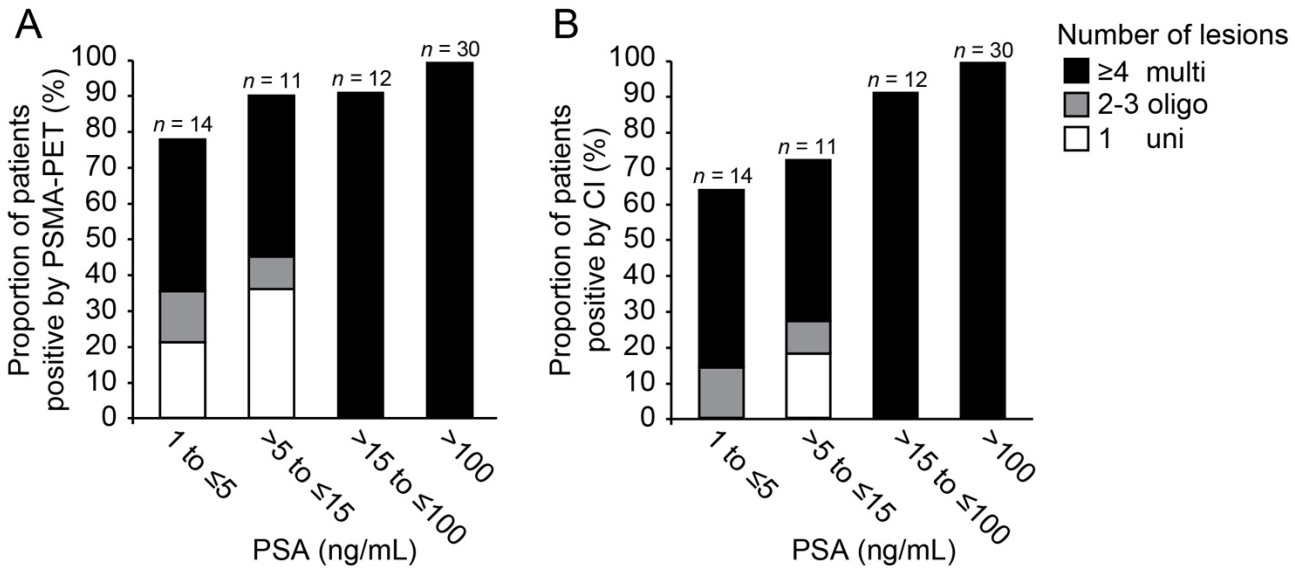


FIGURE 2. PSMA-PET (A) and CI (B) positivity rate on patient basis stratified by PSA and number of lesions.



TABLES

TABLE 1. Patient characteristics (n=67).

	Mean ± SD	**Median**	**IQR**
Age (years)	72 (7)	72	67 – 76
PSA PET (ng/mL)	289.0 (638.1)	53.2	5.8 – 334.6
∆ date PET - date CI (months)	1.0 (1.5)	1.0	0 – 2.0
	Frequency		**%**
≥T3a	34/49		69
N1	20/42		48
ISUP Grade Group ≥4	35/54		65
High-risk (D'Amico stratification)	52/60		87
Previous therapies			
Prostatectomy	43/67		64
External beam radiation therapy	7/67		10
Salvage radiation therapy	29/67		43
Hormonal therapy	67/67		100
Docetaxel	25/67		37
Cabazitaxel	4/67		6
Abiraterone/Enzalutamide/Apalutamide	25/67		37
Radium-223	11/67		16
Palliative RT	12/67		18
Hormonal therapy at the time of the scan	36/67		54
PET/MRI	15/67		22
PET/CT	52/67		78

CI, conventional imaging.

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL TABLE 1. Lesions size and SUV_{max} on a patient-basis categorized by Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE).

	Mean size in cm (IQR)			Mean SUV_{max} (IQR)	
	CT (n=52)	**wbMRI (n=15)**	**PSMA-PET (n=67)**	**PSMA-PET (n=67)**	
T/Tr	2.5 (2.3-3.6)		2.4 (1.6-3.3)	12 (9-19)	
N1	1.7 (1.1-2.5)	1.7 (1.1-2.4)	1.3 (0.7-1.7)	16 (11-24)	
M1a	1.2 (0.9-1.9)	1.2 (0.9-1.8)	1.3 (0.8-1.6)	17 (12-29)	p<0.001
M1b				30 (23-43)	
M1c	3.1 (1.5-4.6)	0.7	3.2 (1.7-4.3)	21 (14-24)	

SUPPLEMENTAL TABLE 2. Comparison between PSMA-PET and CI for whole-body CRPC staging categorized by PCWG3 clinical subtype. PROMISE stage is given in parenthesis.

	All patients (n=67)		CT/BS cohort (n=52)			wbMRI cohort (n=15)	
	PET (%)	**CI (%)**	**PET (%)**	**CT (%)**	**BS (%)**	**PET (%)**	**MRI (%)**
Non-metastatic	5 (7)	9 (13)	2 (4)	2 (4)	5 (10)	3 (20)	8 (53)
Local (T/Tr only)	3 (5)	0	0	0	0	3 (20)	0
Nodal (N1/M1a ± T/Tr)	7 (10)	4 (6)	2 (4)	2 (4)	0	5 (33)	3 (20)
N1 only	3 (5)	3 (4)	0	0	0	3 (20)	2 (13)
M1a only	2 (3)	3 (4)	1 (2)	1 (2)	0	1 (7)	1 (7)
Bone (any M1b)	40 (60)	39 (58)	38 (73)	35 (67)	47 (90)	2 (13)	2 (13)
Visceral (any M1c)	12 (18)	15 (22)	10 (19)	13 (25)	0	2 (13)	2 (13)

BS, bone scan; CI, conventional imaging.

SUPPLEMENTAL TABLE 3. Comparison between non-contrast CT (n=8) and contrast-enhanced CT (n=44) for whole-body CRPC staging categorized by PCWG3 clinical subtype. PROMISE stage is given in parenthesis.

	Non-contrast PET/CT (n=8)		**Contrast-enhanced PET/CT (n=44)**	
	PET (%)	**CT (%)**	**PET (%)**	**CT (%)**
Non-metastatic	0	2 (25)	2 (5)	0
Local (T/Tr only)	0	0	0	0
Nodal (N1/M1a ± T/Tr)	1 (13)	0	1 (2)	2 (5)
N1 only	0	0	0	0
M1a only	1 (13)	0	0	1 (2)
Bone (any M1b)	5 (63)	5 (63)	33 (75)	30 (68)
Visceral (any M1c)	2 (25)	1 (13)	8 (18)	12 (27)
Overall positivity	8 (100)	6 (75)	42 (95)	44 (100)

SUPPLEMENTAL TABLE 4. PSMA-PET impact on PCWG3 clinical subtype. n patients are listed in each cell. No change for PET vs. CI is given in grey cells.

		PSMA-PET				
	n=67	**(1) nonmetastatic**	**(2) local**	**(3) nodal**	**(4) bone**	**(5) visceral**
CI	**(1) nonmetastatic**	**3**	2*	3*	1*	0
	(2) local	0	**0**	0	0	0
	(3) nodal	0	0	**3**	0	1*
	(4) bone	2†	0	1†	**33**	3*
	(5) visceral	0	1†	0	6†	**8**

* PET upstaging; † PET downstaging

SUPPLEMENTAL TABLE 5. Lesion validation in patients with visceral lesions at CI and down-staging at PSMA-PET.

Patient	PSMA-PET stage		CI stage		Visceral disease site with CI	Type of validation	Validation result for PSMA-PET
	PROMISE	PCWG3	PROMISE	PCWG3			
Essen 13	T0N1M1ab	Bone disease	T0N0M1abc	Visceral disease	Lung	NA	-
Essen 21	TrN0M0	Local disease	T0N0M1abc	Visceral disease	Lung	Imaging	False negative
Essen 27	T0N1M1ab	Bone disease	T0N0M1bc	Visceral disease	Lung	NA	-
TUM 03	T0N1M1b	Bone disease	T0N0M1abc	Visceral disease	Adrenal	NA	-
TUM 07	TrN0M1b	Bone disease	TrN0M1abc	Visceral disease	Liver	Imaging	False negative
TUM 21	T0N1M1ab	Bone disease	T0N0M1bc	Visceral disease	Lung	Imaging	False negative
					Liver		True negative
TUM 34	T0N1M1ab	Bone disease	T0N1M1abc	Visceral disease	Lung	Imaging	True negative

Notes: NA=not available

- **SUPPLEMENTAL TABLE 6.** Raw readers findings of all patients for CI (A) and for PSMA-PET (B).

SUPPLEMENTAL TABLE 6A

	Imaging modality	r1_T/Tr	r2_T/Tr	r3_T/Tr	consensus_T/Tr	r1_N	r2_N	r3_N	consensus_N	r1_Bone	r2_Bone	r3_Bone	consensus_Bone	r1_Visceral	r2_Visceral	r3_Visceral	consensus_visceral
patient 001	BS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
patient 003	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 005	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 007	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 009	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 011	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 013	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 015	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 018	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 021	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 030	BS	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
patient 033	BS	0	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0
patient 037	BS	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
patient 041	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 044	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 046	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 048	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 050	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 052	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 054	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 056	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 058	BS	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
patient 060	BS	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0
patient 062	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 064	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 066	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 068	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 070	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 072	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 074	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 076	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 078	BS	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0
patient 080	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 082	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 084	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 086	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 088	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 090	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0

patient 092	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 094	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 096	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 098	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 100	BS	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0
patient 102	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 104	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 106	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 108	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 110	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 112	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 114	BS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
patient 116	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 118	BS	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 002	CT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
patient 004	CT	0	1	0	0	0	0	0	0	1	1	1	1	1	0	0	0
patient 006	CT	0	0	0	0	0	1	0	0	1	1	1	1	0	0	0	0
patient 008	CT	0	0	0	0	0	1	0	0	1	1	1	1	0	0	0	0
patient 010	CT	0	0	0	0	0	1	0	0	1	1	1	1	1	1	1	1
patient 012	CT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
patient 014	CT	0	1	0	0	0	1	0	0	1	1	1	1	0	0	0	0
patient 016	CT	0	0	0	0	0	1	0	0	1	1	1	1	0	0	0	0
patient 019	CT	0	0	0	0	0	1	1	1	1	1	1	1	0	1	1	1
patient 022	CT	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1
patient 031	CT	0	1	0	0	1	1	1	1	1	1	1	1	1	1	0	1
patient 034	CT	0	0	0	0	1	1	1	1	1	1	1	1	1	1	0	1
patient 038	CT	0	0	0	0	0	1	0	0	1	1	0	1	1	1	0	1
patient 042	CT	0	0	0	0	0	1	0	0	1	1	1	1	1	1	0	1
patient 045	CT	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	0
patient 047	CT	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 049	CT	0	1	0	0	0	0	0	0	1	1	1	1	0	1	0	0
patient 051	CT	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 053	CT	0	0	0	0	0	1	0	0	1	1	1	1	0	1	1	1
patient 055	CT	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
patient 057	CT	0	1	0	0	0	1	0	0	1	1	1	1	0	0	0	0
patient 059	CT	1	1	1	1	0	0	0	0	1	1	0	1	0	0	0	0
patient 061	CT	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
patient 063	CT	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 065	CT	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 067	CT	1	0	0	0	1	1	0	1	1	1	1	1	0	0	0	0
patient 069	CT	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0

patient 071	CT	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 073	CT	0	0	0	0	1	0	0	0	1	1	1	1	1	1	1	1
patient 075	CT	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1
patient 077	CT	1	1	1	1	0	1	0	0	1	1	1	1	1	0	0	0
patient 079	CT	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0
patient 081	CT	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 083	CT	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 085	CT	1	1	0	1	0	0	0	0	1	1	1	1	0	0	0	0
patient 087	CT	0	0	0	0	1	1	0	1	1	1	1	1	0	0	0	0
patient 089	CT	0	0	0	0	0	1	0	0	1	1	1	1	0	0	0	0
patient 091	CT	1	1	0	1	0	1	0	0	1	1	1	1	0	0	0	0
patient 093	CT	1	1	0	1	0	1	0	0	1	1	1	1	0	0	0	0
patient 095	CT	1	1	0	1	0	0	0	0	1	1	1	1	0	0	0	0
patient 097	CT	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 099	CT	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 101	CT	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
patient 103	CT	0	0	0	0	0	0	1	0	1	1	1	1	1	1	0	1
patient 105	CT	0	0	0	0	1	1	0	1	1	1	1	1	0	0	0	0
patient 107	CT	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 109	CT	0	0	0	0	0	0	1	0	1	1	1	1	0	0	0	0
patient 111	CT	0	0	0	0	0	1	1	1	1	1	1	1	0	0	0	0
patient 113	CT	0	0	0	0	1	1	0	1	1	1	1	1	0	0	0	0
patient 115	CT	0	0	0	0	1	1	1	1	0	0	0	0	1	1	1	1
patient 117	CT	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 119	CT	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 017	wbMRI	0	0	0	0	1	1	0	1	1	1	1	1	0	0	0	0
patient 020	wbMRI	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 023	wbMRI	0	0	0	0	1	1	0	1	1	1	1	1	0	0	0	0
patient 024	wbMRI	0	0	0	0	1	1	0	1	0	0	0	0	1	0	0	0
patient 025	wbMRI	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
patient 026	wbMRI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
patient 027	wbMRI	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
patient 028	wbMRI	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
patient 029	wbMRI	0	0	0	0	1	1	0	1	1	1	1	1	1	0	0	0
patient 032	wbMRI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
patient 035	wbMRI	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0
patient 036	wbMRI	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0
patient 039	wbMRI	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
patient 040	wbMRI	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 043	wbMRI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

SUPPLEMENTAL TABLE 6B

	Imaging modality	r1_T/Tr	r2_T/Tr	r3_T/Tr	consensus_T/Tr	r1_N	r2_N	r3_N	consensus_N	r1_Bone	r2_Bone	r3_Bone	consensus_Bone	r1_Visceral	r2_Visceral	r3_Visceral	consensus_visceral
patient 001	PSMA-PET	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	1
patient 002	PSMA-PET	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0
patient 003	PSMA-PET	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1
patient 004	PSMA-PET	1	1	1	1	0	0	0	0	1	1	1	1	1	0	0	0
patient 005	PSMA-PET	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0
patient 006	PSMA-PET	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 007	PSMA-PET	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 008	PSMA-PET	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0
patient 009	PSMA-PET	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
patient 010	PSMA-PET	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0
patient 011	PSMA-PET	0	0	0	0	1	1	1	1	0	0	0	0	1	1	1	1
patient 012	PSMA-PET	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
patient 013	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 014	PSMA-PET	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1
patient 015	PSMA-PET	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0
patient 016	PSMA-PET	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0
patient 017	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 018	PSMA-PET	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
patient 019	PSMA-PET	0	0	1	0	1	1	1	1	0	0	0	0	1	1	1	1
patient 020	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 021	PSMA-PET	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
patient 022	PSMA-PET	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
patient 023	PSMA-PET	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
patient 024	PSMA-PET	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
patient 025	PSMA-PET	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0
patient 026	PSMA-PET	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 027	PSMA-PET	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
patient 028	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 029	PSMA-PET	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	0
patient 030	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	1	1	1
patient 031	PSMA-PET	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0
patient 032	PSMA-PET	1	0	0	0	0	1	0	0	1	1	1	1	0	0	0	0
patient 033	PSMA-PET	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0
patient 034	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	1	0	0
patient 035	PSMA-PET	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 036	PSMA-PET	0	0	0	0	0	0	0	0	1	1	1	1	0	0	1	0
patient 037	PSMA-PET	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 038	PSMA-PET	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	0
patient	PSMA-	0	0	0	0	0	1	0	0	1	1	1	1	0	1	0	0

039	PET																
patient 040	PSMA-PET	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0
patient 041	PSMA-PET	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0
patient 042	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 043	PSMA-PET	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
patient 044	PSMA-PET	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 045	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 046	PSMA-PET	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0
patient 047	PSMA-PET	1	1	1	1	0	0	0	0	1	1	1	1	0	0	0	0
patient 048	PSMA-PET	1	1	1	1	1	1	0	1	1	1	1	1	0	0	0	0
patient 049	PSMA-PET	0	0	0	0	1	1	1	1	0	0	0	0	1	1	0	1
patient 050	PSMA-PET	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 051	PSMA-PET	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 052	PSMA-PET	0	0	0	0	1	0	1	1	1	1	1	1	0	0	0	0
patient 053	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
patient 054	PSMA-PET	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
patient 055	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
patient 056	PSMA-PET	0	0	0	0	0	1	0	0	1	1	1	1	0	0	0	0
patient 057	PSMA-PET	0	1	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 058	PSMA-PET	0	0	0	0	1	0	0	0	1	1	1	1	0	0	0	0
patient 059	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	1	1	1
patient 060	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 061	PSMA-PET	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0
patient 062	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 063	PSMA-PET	0	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 064	PSMA-PET	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0
patient 065	PSMA-PET	0	0	1	0	1	1	1	1	1	1	1	1	0	0	0	0
patient 066	PSMA-PET	1	1	1	1	1	1	0	1	1	1	1	1	0	0	0	0
patient 067	PSMA-PET	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1

Notes: r1=reader 1; r2=reader 2; r3=reader 3; Tr=local; N=lymph node; 0=negative for prostate cancer lesions; 1=positive for prostate cancer lesions.

SUPPLEMENTAL TABLE 7. Interobserver agreement for visual image interpretation (PSMA-PET and CI) with 95% confidence intervals in parentheses.

	nmCRPC	Local disease	Nodal disease	Bone disease	Visceral disease
CI	-	0.51 (0.41-0.62)	0.47 (0.37-0.58)	0.72* (0.62-0.82	0.66* (0.56-0.77)
PSMA-PET	0.46 (0.32-0.60)	0.81* (0.68-0.95)	0.74* (0.60-0.87)	0.95* (0.81-1.10)	0.59 (0.46-0.73)

Notes: *=substantial to almost perfect agreement