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Title:

A comprehensive assessment of ^{68}Ga-PSMA-11 PET in biochemically recurrent prostate cancer: Results from a prospective multi-center study in 2005 patients

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ABSTRACT

We prospectively investigated the performance of the prostate-specific membrane antigen (PSMA) ligand ^{68}Ga-PSMA-11 for detecting prostate adenocarcinoma in patients with elevated prostate-specific-antigen (PSA) after initial therapy.

Methods: ^{68}Ga-PSMA-11 hybrid positron emission tomography (PET) was performed in 2005 patients at the time of biochemical recurrent prostate cancer (BCR) following either radical prostatectomy (RP) (50.8 %), definitive radiation therapy (RT) (19.7 %), or RP with post-operative RT (PORT) (29.6 %). Presence of prostate cancer was assessed qualitatively (detection rate = positivity rate) and quantitatively on a per-patient and per-region basis creating a disease burden estimate from presence or absence of local (prostate/prostate bed), nodal (N1: pelvis) and distant metastatic (M1: distant soft tissue and bone) disease. The primary study endpoint was the positive predictive value (PPV) of ^{68}Ga-PSMA-11 PET/CT confirmed by histopathology.

Results: Following prostatectomy, the scan detection rate increased significantly with rising PSA levels (44.8 % at PSA < 0.25 to 96.2 % at PSA > 10 ng/mL; $p < 0.001$). The detection rate significantly increased with rising PSA levels in each individual region, overall disease burden, prior androgen deprivation, clinical T-stage, and Gleason grading from prostatectomy specimen ($p < 0.001$). Following RT, the detection rate for in-gland prostate recurrence was 64.0 % compared to 20.6 % prostate bed recurrences after RP and 13.3 % following PORT. PSMA-positive pelvic nodal disease was detected in 42.7 % following RP, in 40.8 % after PORT and 38.8 % after RT.

In patients with histopathologic validation the PPV per-patient was 0.82 (146/179). The SUV_{max} of histologically proven true positive lesions was significantly higher than false positive lesions (median 11.0 (IQR 6.3 – 22.2) vs 5.1 (IQR 2.2 – 7.4) $p < 0.001$).

Conclusion: We confirmed a high PPV of ^{68}Ga-PSMA-11 PET in BCR and the PSA level as the main predictor of scan positivity.

Key words:

prostate cancer; prostate-specific membrane antigen (PSMA), disease pattern; hybrid PET;

INTRODUCTION

Biochemical recurrence (BCR) is an independent risk factor of survival outcomes (*1*) following radical prostatectomy (RP) and radiation therapy (RT) for localized prostate cancer. BCR following definitive therapy is common, especially in higher risk disease, and may effect > 50 % of patients long-term (*2,3*). With broadened utilization of newer PSMA-based radioligands to identify disease locations of prostate cancer using PET, the treatment of BCR is rapidly changing to more personalized and targeted approaches (*4*). While a large body of retrospective evidence is available suggesting high accuracy of ^{68}Ga-PSMA-11 (*5,6*), prospective studies including gold-standard histological verification are rare (*7*). The difficulty in obtaining pathological confirmation of PSMA PET positive (suspicious) lesions is related to the high positivity rate at relatively low disease burden and challenges in sampling of small and difficult to reach lesions.

To better comprehensively assess the performance characteristics of ^{68}Ga-PSMA-11 PET, three institutions, the University of Michigan (UM), University of California at Los Angeles (UCLA) and San Francisco (UCSF), combined their prospective trial datasets of patient populations with BCR disease to determine the accuracy of ^{68}Ga-PSMA-11 based on histopathology and identify predictors of PET positivity and patterns of recurrence.

MATERIALS AND METHODS

Patients

The Food and Drug Administration granted the use of ^{68}Ga-PSMA-11 under three investigational new drug applications. Imaging was performed within registered prospective clinical studies assessing the diagnostic performance of ^{68}Ga-PSMA-11 PET in BCR prostate cancer at the UM (ClinicalTrials.gov

NCT03396874), UCLA (NCT02940262) and UCSF (NCT03803475). The respective Institutional Review Boards of each institution approved these study protocols. From February 2018 to December 2020, a total of 2005 patients were enrolled with histologically proven prostate cancer and BCR after prostatectomy with (PORT) or without postoperative radiotherapy (RP) (PSA level > 0.2 ng/mL, > 6 weeks after surgery) or definitive radiotherapy (RT) (PSA nadir + ≥ 2 ng/mL). Patients with other active malignancy within the last 2 years (excluding skin basal cell or cutaneous superficial squamous cell carcinoma that has not metastasized and superficial bladder cancer) were not eligible. Patients following any other interval treatment than androgen deprivation therapy (ADT) were excluded. Prior conventional imaging was not required for study participation. All subjects provided written informed consent.

^{68}Ga-PSMA-11 PET

The investigational radiotracer ^{68}Ga-PSMA-11 was manufactured as described in the literature from either generator produced ^{68}Ga-$GaCl_3$ (*8,9*) or cyclotron production of Gallium-68 via a liquid target and a General Electric FASTlab synthesis module (*10*). Imaging was performed on dedicated hybrid PET/CT (n = 1886) or PET/MRI (n = 119) scanners according to a standardized imaging protocol (*8*). On average 61 (median 60, interquartile range [IQR] 57 - 65) minutes following intravenous administration of 5.5 (IQR 5.0 – 6.2) mCi of ^{68}Ga-PSMA-11, a static emission scan was performed from the thighs to the vertex. Time-of-flight acquisition was performed in 936/2005 (47 %) scans. Images were reconstructed using iterative ordered subset expectation maximization according to vendor recommendations. UCLA performed a diagnostic 2.5 mm collimation CT scan (200–240 mAs, 120 kV) with intravenous (IV) contrast on either a Siemens Biograph 64 TruePoint or mCT scanner. At UM, CT scans (3 mm collimation) were either low-dose (100 mAs, 120 kV on Siemens Biograph 6 Truepoint) or dose-modulated (Siemens mCT) without IV contrast. The UCSF investigators performed PET/CT (GE

Discovery, Siemens mCT or Philips Vereos scanners) or PET/MRI at 2.5 mm collimation dependent on scanner availability and contraindications. Diagnostic CT was obtained with the use of a standard protocol (80 to 100 mA, 120 kV) before the PET scan with IV contrast for most scans (*7*). All imaging devices received American College of Radiology Accreditation.

Image Data

^{68}Ga-PSMA-11 scans were analyzed locally at each institution according to recent guidelines (*8*) by experienced Nuclear Medicine physicians with access to clinical information, histopathology, and prior imaging studies when available. Any focal ^{68}Ga-PSMA-11 uptake above location-specific background levels was considered PSMA-positive.

Presence of prostate cancer was quantitatively assessed on a per-region (prostate/prostate bed, pelvis, soft tissue, bone) and per-patient basis. Each involved region was added to generate an estimate of the total disease burden (0 = no disease, 1-4: sum of positive regions). Figure 1 indicates the sampled specific disease locations among these 4 regions.

Lesion Validation and Quantification

Lesion validation was based on histopathologic analysis only. For lesions with histopathological verification, the maximum standardized uptake value (SUV_{max}) was obtained. In case that the lesion could be identified with a clear margin on anatomic imaging (either on respective CT or MRI), the maximum lesion diameter (mm) was also recorded.

Statistical Analysis

The PPV of ^{68}Ga-PSMA-11 PET/CT confirmed by histopathology was the primary study endpoint. Receiver operating characteristics (ROC) analysis was used to determine the optimal SUV_{max} threshold to separate benign from malignant foci. For contingency table analyses, chi-squared tests were used to assess hypotheses. For continuous data, the Wilcoxon rank-sum test was applied. Logistic regression was used to study the association between clinically relevant disease parameters, scan characteristics, and scan positivity rates.

RESULTS

Patient Characteristics

Table 1 displays patient characteristics of 2005 enrolled subjects with BCR prostate cancer following either RP (51.2 %), PORT (29.4 %), or definitive RT (19.4 %). Age, initial PSA, PSA nadir, clinical T-stage and T-stage from prostatectomy specimen were similar between groups. As shown in supplemental Table 1, Gleason grade groups derived from 1586 prostatectomy specimen were not significantly different between RP and PORT treated patients ($p = 0.1$). However, the Gleason grade groups at biopsy were significantly higher in 389 patients receiving RT compared to 481 prostatectomy patients ($p < 0.001$).

A large majority of patients treated by radical prostatectomy (RP and PORT) had no interval treatment between initial therapy and scan (83.0 %), while 50.2 % RT treated patients had received ADT. The time interval between initial therapy and scan was significantly shorter for patients with persistent PSA following RP/PORT (18.1 [IQR 4.5 – 72.4] months) vs. patients who achieved undetectable PSA levels after RP/PORT (75.0 [IQR 41.0 – 125.5] months) ($p < 0.001$).

Detection Rate

Given differences of the PSA entry criteria following definitive RT, scan detection rates for RT below PSA 2.0 ng/mL were not available. The scan positivity rate was 78.0 % for the entire population, but was not evenly distributed among treatment groups (n = 712, 67.1 % for RP; n = 590, 83.1 % for PORT; n = 422, 95.9 % for RT).

Table 2 displays the detection rate for all 3 therapy groups separated by PSA ranges. A significant increase of the detection rate with rising PSA levels was seen for RP ($p < 0.001$) and PORT treated patients ($p < 0.001$). In a subcohort of 777 patients treated by prostatectomy with lower PSA levels (< 1.0 ng/mL) at the time of scan, the detection rate was significantly higher in PORT (n = 208; 71.6 %) treated vs. RP treated (n = 569; 52.7 %) patients ($p < 0.001$). In the same subcohort, the detection rate was also higher in patient with interval ADT (71.2 %) vs. without ADT (54.4 %, $p < 0.02$). The detection rate was positively correlated with the Gleason grade groups obtained from prostatectomy specimen (n = 1586 of [999 RP, 587 PORT]; $p < 0.001$), clinical T-stage (n = 670 [242 RP, 160 PORT, 242 RT]; $p < 0.01$), but not with Gleason grade groups at initial prostate biopsy (n = 870 [291 RP, 190 PORT, 289 RT]; $p = 0.86$).

Given the high detection rate for patient treated by RT (roughly 95 % at any PSA range), no significant relationship of the PSA with the detection rate was found (Table 2). When considering the entire patient population (n = 2005), the regional detection rates for local failure (prostate or prostate bed) (supplemental Table 2; $p < 0.001$), pelvic nodal disease (supplemental Table 3; $p < 0.001$), distant metastatic disease in soft tissue (supplemental Table 4; $p < 0.001$), and bone (supplemental Table 5; $p < 0.001$) increased significantly with PSA levels.

Lesion Validation per Histopathology

The supplemental Table 6 summarizes the patient characteristics of positive scans with (n = 179) or without (n = 1360) histopathological analyses of PSMA-positive lesions. Risk parameters (PSA, PSA nadir, clinical T-stage, Gleason grade groups, locoregional and distant metastatic disease extent) and scan parameters were similar between groups. The average lesion-based PPV was 0.82 for the entire histopathologically assessed population (Table 3). Tissue samples were obtained by either needle biopsy (75 %) or surgical resection (25 %). Given varying accessibility and risk of specific lesion locations, the number of samples obtained decreased from prostate gland/prostate bed (43 %), over soft tissues (26 %) to pelvic lymph nodes (24 %) and bone (7 %). The region-specific PPV increased from 0.72 in pelvic lymph nodes to 0.83 in the prostate/prostate bed as well as bone, and 0.88 in soft tissue lesions. Most false positive (FP) lesions (n = 33) were noted in the prostate region including 10 foci (after RT) in the prostate gland, and 4 lesions in the prostate bed as well as one in a seminal vesicle. Other common locations were pelvic lymph nodes (n = 9) and soft tissue lesions (n = 8) including extra-pelvic lymph nodes/masses, inguinal lymph nodes and one benign neoplasm (supplemental Table 7).

On a per patient basis, the available SUV_{max} of 141 true positive (TP) lesions was significantly higher (median 11.0, IQR 6.3 – 22.2) than for 30 FP (median 5.1, IQR 2.2 – 7.4) lesions ($p < 0.001$), while the maximum size of lesions was similar between groups (TP: 1.3 (0.8 – 2.13); FP: 1.05 IQR 0.75 – 2.13). ROC analysis as function of lesion SUV_{max} resulted in an area under the ROC curve of 0.77. At the optimal SUV_{max} threshold (7.5) for differentiating malignant from benign findings, the sensitivity was 69 % and the specificity was 80 %."

Disease Burden and Pattern

As shown in supplemental Table 8, involvement of a single region was the most common outcome except for patients with a PSA ≥ 10 ng/mL. Nonetheless, the rate of multi-region involvement increased steadily with rising PSA levels in the entire patient population as we as for each individual treatment group (RP, PORT, RT) ($p < 0.001$).

Figure 2 displays the rate of observed disease at encountered locations indicating differences between treatment groups. The supplemental video material highlights the rising disease burden at each region and location per PSA level. Following RT, the most likely positive single region was the prostate (252/394, 64.0 %), while nodal metastatic disease was the predominant location for RP (435/1018, 42.7 %) and PORT (301/593, 50.8 %)). Among pelvic lymph nodes, predominant locations were central pelvic nodes (internal/external/common iliac including obturator), followed by presacral and all other pelvic nodal stations. The probability for bilateral disease involvement increased with PSA levels in all 3 treatment groups (RP and RT: $p < 0.001$; PORT: $p < 0.05$). When considering only patients with PSA levels ≥ 2 ng/mL, the rate of locoregional disease (prostate/bed and/or pelvic lymph nodes) was similar between treatment groups (supplemental Table 9).

As shown in supplemental Table 10, distant metastatic disease increased with rising PSA levels, though it was unequally distributed among treatment groups and disease location (soft tissue vs. bone). Soft tissue metastases (supplemental Table 4), including the frequently encountered retroperitoneal lymph node metastases, were more often found following PORT (188/593, 31.7 %) compared to RP (154/1018, 15.1 %) at any PSA level. Similar results were noted for osseous metastases (PORT: 162/593, 27.3 % vs. RP (162/1018, 15.9 %) (supplemental Table 5). When osseous disease was detected, the most common locations were pelvic, thoracic and spinal lesions.

DISCUSSION

As reviewed in recent a large retrospective cohort (*11*) and prior meta-analyses (*6,12*), a substantial body of evidence exists to support the use of ^{68}Ga-PSMA-11 in BCR prostate cancer. However, this evidence is mostly derived from retrospective studies while prospective data are rare (*7*).

We present the largest prospectively obtained patient population of ^{68}Ga-PSMA-11 PET in BCR prostate cancer following initial therapy with curative intent. It comprises the highest number of histologically confirmed PSMA-positive lesions and largest prospective dataset assessing scan detection rates, particularly at the most relevant PSA range below 1.0 ng/mL following RP and cases of biochemical failure following primary radiotherapy.

The primary endpoint of the study was the PPV, and not the sensitivity and specificity of the test. This approach was required because histopathological verification is typically only obtained from PSMA-positive lesions. By limiting the analysis of diagnostic efficacy to histopathologically proven PSMA-positive lesions, we avoided uncertainties related to less stringent clinical endpoints, often referred to as composite endpoints.

The results indicated a high PPV similar to other prospectively obtained data obtained with ^{68}Ga-PSMA-11 (*7*) and ^{18}F-DCFPyL (*13*), however slightly lower compared to retrospective single center data as recently reviewed (*14*). The discrepancy may be related to differences in patient populations with unknown proportions of sampling errors. Furthermore, tissue sampling is often obtained from equivocal findings. Histopathological sampling was overrepresented following RT compared to RP or

PORT. In contrast to Fendler et al. (*15*), the probability of FP results was similar in all treatment groups, thus not elevated in the setting of prostate lesions after RT. In our cohort FP assessments were more likely with lower SUV_{max} values while the average lesion size of FP and TP lesions was comparable, indicating that simple sampling errors (due to smaller lesion size) could not be attributed to explain a higher FP rate of low uptake lesions. However, the individual reader threshold to define positive lesions may have influenced the probability of a TP outcome. While we cannot exclude this possibility, inter-reader agreement with ^{68}Ga-PSMA-11 is generally high (*16*). While the selected SUV_{max} threshold of 7.5 differentiated malignant from benign findings with moderate sensitivity and a specificity, the large overlap between the SUV_{max} of TP and FP lesions limits this threshold to reliably predict prostate cancer.

A large body of evidence exists to support a strong relationship between lesion detection rates and PSA levels in BCR prostate cancer (*7*). Our data show a scan positivity rate of 44.8 % at PSA below 0.25 and 50.5 % between PSA 0.25 and 0.5 for patients following RP. These data are in line with the literature obtained from retrospective analyses (*11,12,17*). The correlation of PSMA-scan positivity and PSA have relevant clinical implications. First, it is well established that success of salvage RT (SRT) post-RP is related to the pre-SRT PSA level (*18*). Patients with high pre-SRT PSA (> 2 ng/mL) have very high rates of recurrence post-SRT. In contrast, patients with PSA levels close to 0.2, more than 75 % of patients treated with SRT have long-term durable tumor control (*19*). Additionally, the finding that the pattern of spread post-RP with a rising PSA demonstrates increased nodal, distant, and multi-region disease, further helps explain the findings from RTOG 9601. This trial showed a large overall survival benefit from the addition of hormone therapy at PSA levels > 1.5 ng/mL post-RP, but no improvement in

metastases or survival for patients treated with early SRT (*20*). This may be due to the benefit of ADT in patients with metastatic disease, and men with a pre-salvage PSA > 1.5 ng/mL have a high probability of already harboring regional and distant metastatic disease.

Prior conventional imaging (CT abdomen/pelvis and bone scan) was not required for participation in this study, mainly due to the fact that conventional imaging is often non-contributing in biochemically recurrent prostate cancer and therefore increasingly omitted as part of standard of care (*16,21*). However, since available prior conventional imaging was allowed to contribute to scan interpretations, such information may have been a potential source of bias.

In our patient population, we noted substantial differences in the pattern of PSMA-positive disease across PSA ranges and treatment groups as highlighted in supplemental video materials. However, these differences may wholly be based on a pronounced selection bias. We emphasize that the risk of recurrent prostate cancer and the location and extent of metastatic disease is dependent on many factors not assessed in this trial. Confounding factors include differences in risk at the time of diagnosis, heterogeneity and interval advances in therapeutic techniques within treatment groups, and variations in disease management following initial therapy. Furthermore, the observed rate of recurrent and metastatic disease per region in each treatment group does not provide information about the overall rate of recurrent prostate cancer as scans were exclusively performed in patients expected to present with recurrent disease. Nonetheless, the study offers insights about the relationship of initial risk factors (Gleason score, initial PSA, PSA nadir, age), interval treatment (ADT) and PSA outcome at the time of scan with ^{68}Ga-PSMA-11 scan findings.

CONCLUSION

Our prospective multi-center trial confirmed that ^{68}Ga-PSMA-11 PET is an accurate and effective modality to identify BCR prostate cancer. Our data indicate specific recurrent disease pattern for initial therapy approaches and PSA ranges. Half of all scans performed at PSA levels below 0.5 ng/mL resulted positive opening the door for PSMA-targeted focal therapy approaches at an early time point of disease recurrence. While the knowledge of the disease location is of great importance for salvage therapy planning, it remains to be seen whether PSMA image-guided (focal) therapy of BCR prostate cancer can improve outcomes.

DISCLOSURES

JCA reports prior consulting activities for Advanced Accelerator Applications, Blue Earth Diagnostics, Curium Pharma, GE Healthcare, EXINI, IBA RadioPharma, Janssen Pharmaceuticals, Lantheus, POINT biopharma, Progenics, Radiomedix, Telix Pharmaceuticals outside of the submitted work.

DES received personal fees from Janssen, AstraZeneca, Blue Earth, and Boston Scientific, and funding from Janssen.

MP reports prior consulting activities for Bayer, and received grant funding from Endocyte/Novartis, Blue Earth Diagnostics, Progenics, the Michigan Prostate SPORE (NIH/NCI 5P50CA186786), and the Department of Radiology of the University of Michigan.

PJHS received funding from the Department of Radiology of the University of Michigan, and grants from Endocyte/Novartis, and GE Healthcare.

TAH served received grant funding from the National Cancer Institute (R01CA212148, R01CA235741), the Prostate Cancer Foundation (2017 Young Investigator Award and 2019 VAlor Challenge Award 18CHAL03), Advanced Accelerator Applications and Philips, and served as a consultant for Ipsen, Blue Earth Diagnostics, Curium.

ZR received personal fees from AstraZeneca and Dendreon, grant funding from AstraZeneca, the Prostate Cancer Foundation (2018 Young Investigator Award), the Michigan Prostate SPORE (NIH/NCI 5P50CA186786).

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Key points

QUESTION: Diagnostic efficacy of ^{68}Ga-PSMA-11 in biochemical recurrent prostate cancer?

PERTINENT FINDINGS: Compared with histopathology, ^{68}Ga-PSMA-11 PET provides a high positive predictive value to identify biochemically recurrent prostate cancer loco-regionally and in distant metastases. The scan detection rate increases with PSA levels and PSA-dependent within individual regions. Higher detection rates are noted with increasing overall disease burden, prior androgen deprivation therapy, higher clinical T-stage and Gleason grade group ratings following prostatectomy.

IMPLICATIONS FOR PATIENT CARE: ^{68}Ga-PSMA-11 PET provides a high diagnostic value in biochemically recurrent prostate cancer.

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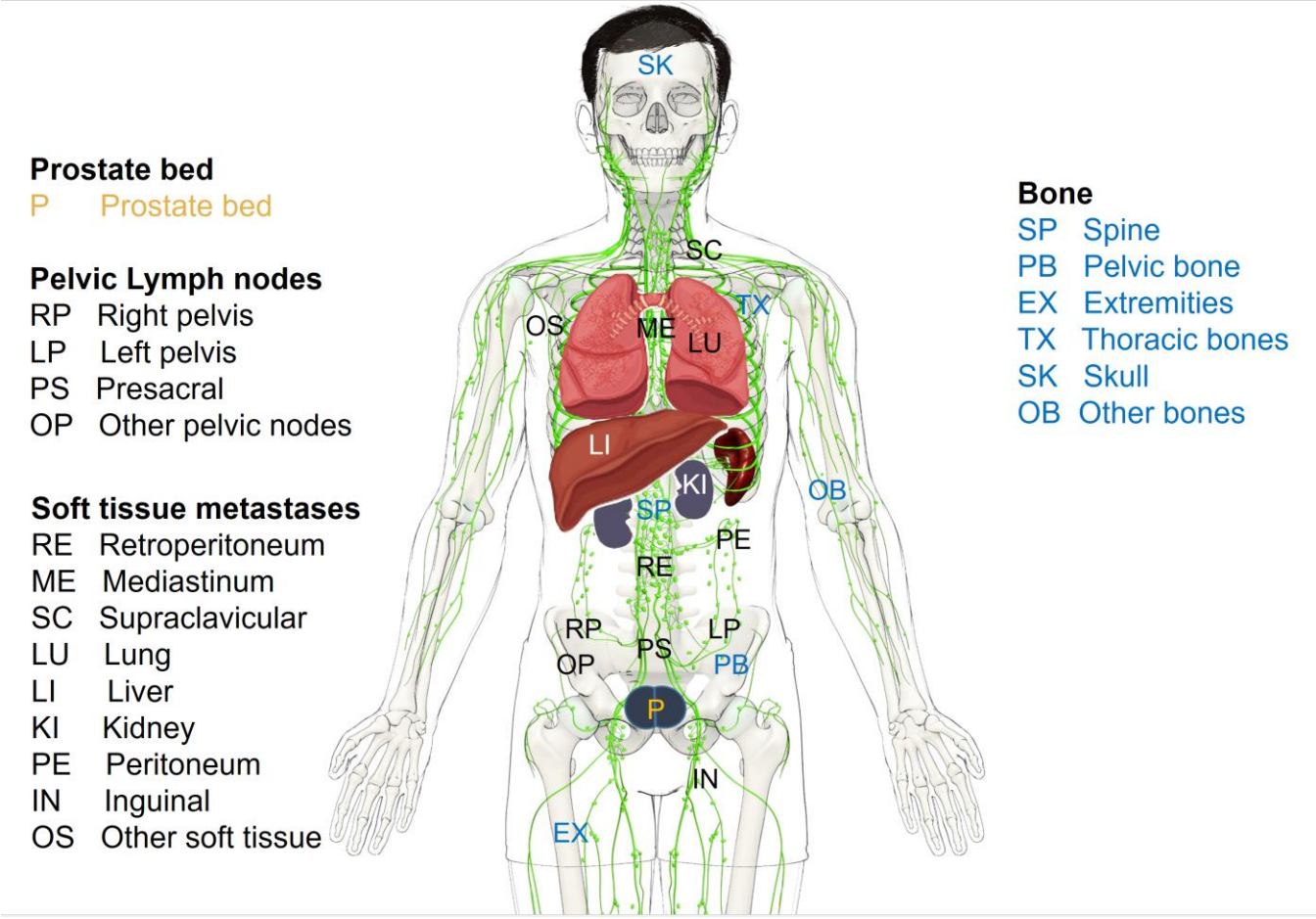
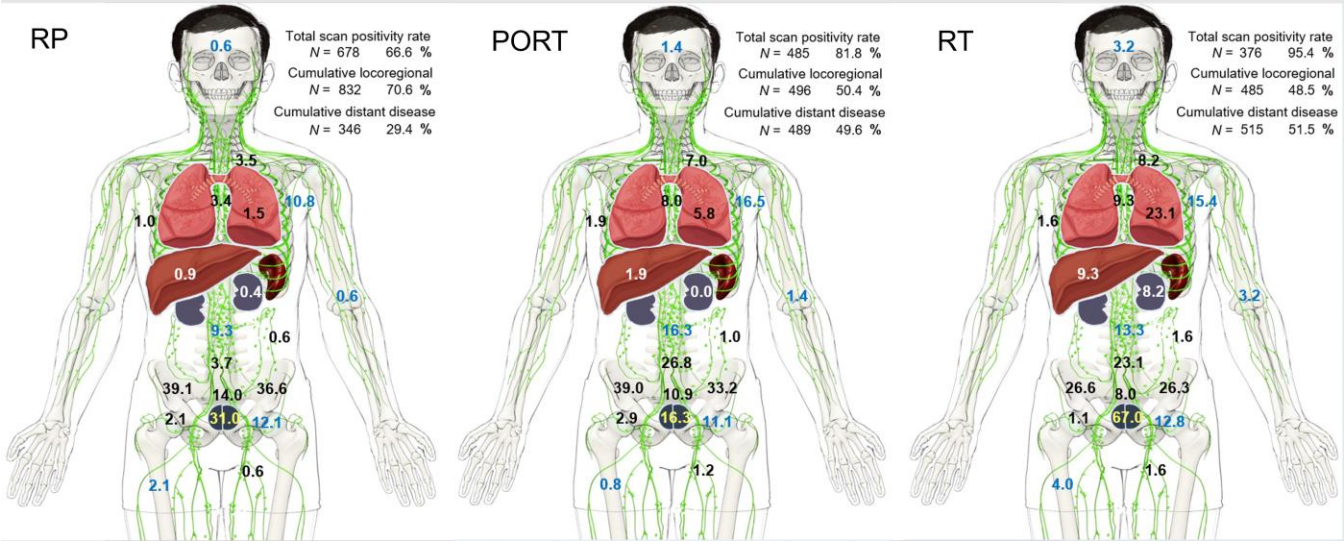
FIGURES

Figure 1: Individual Sampled Disease Locations



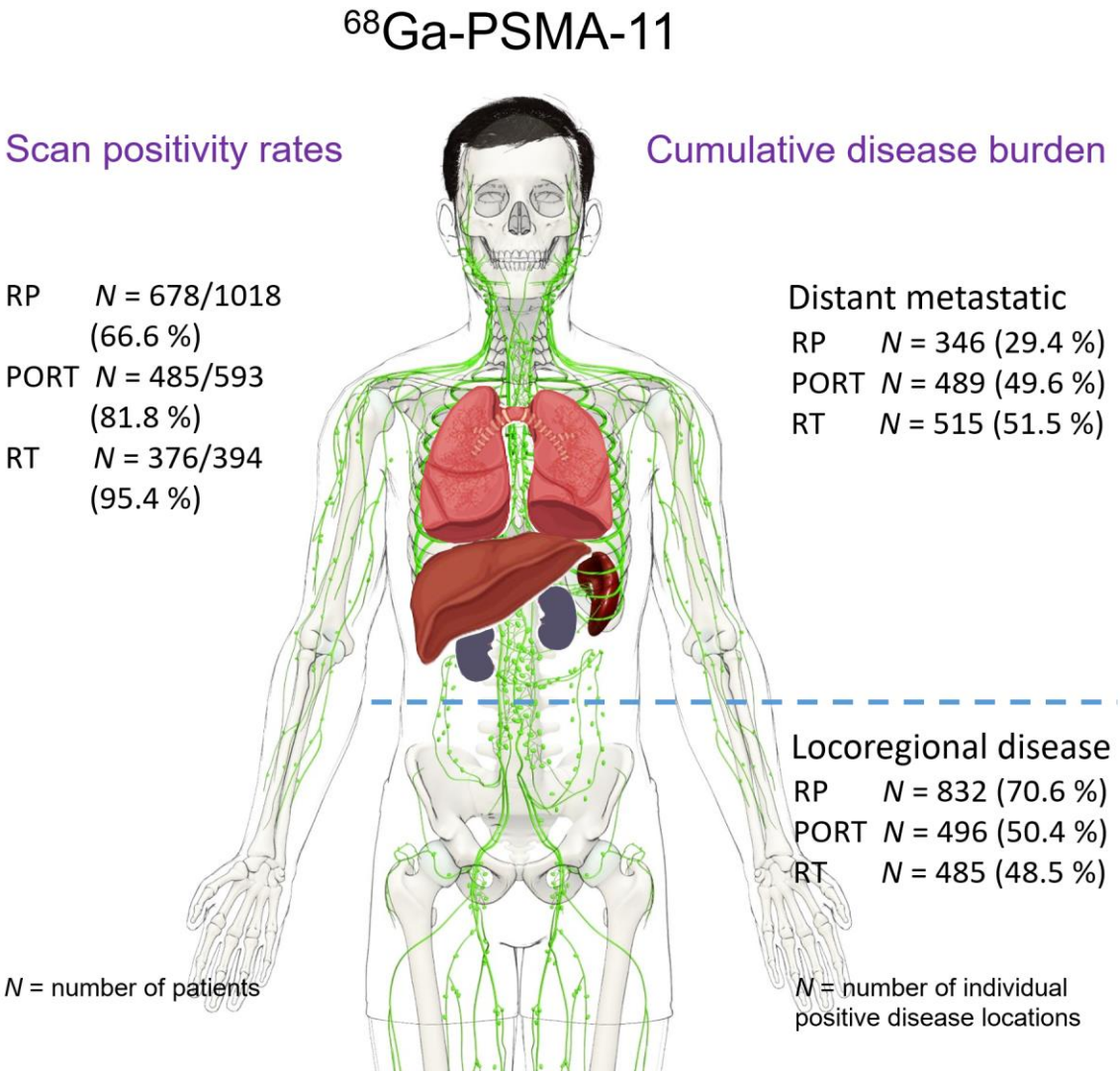
Schematics of identified PSMA-positive lesion locations (prostate/prostate bed (orange), bone lesions (blue), pelvic lymph nodes and soft tissue lesions (black)).

Figure 2: Cumulative Disease Burden and Disease Locations by Prior Treatment



The cumulative total scan positivity rate (relative to entire population in respective treatment groups prostatectomy (RP, n = 1018), prostatectomy and postoperative radiation therapy (PORT, n = 593), or definitive radiation therapy (RT, n = 394)) is given. Percent of individual PSMA-positive disease locations as listed in Figure 1 and cumulative locoregional and distant disease positivity rates are from PSMA scans rated positive (RP: n = 678, PORT: n = 485, RT: n = 376).

Graphical Abstract



TABLES

Table 1: Patient Characteristics

		Prostatectomy (RP)	**PORT**	**Radiation Therapy (RT)**
		n = 1018 (51.2 %)	n = 593 (29.4 %)	n = 394 (19.4 %)
Sites (UM / UCSF / UCLA)	N (%)	372 (36.5 %) /109 (10.7 %) / 537 (52.8 %)	264 (44.5 %) / 82 (13.8 %) / 247 (41.7 %)	192 (48.7 %) / 81 (20.6 %) / 121 (30.7 %)
Age (years)	Median (IQR), [N missing]	68 (63 - 73), [0]	70 (65 - 74), [0]	72 (67 - 77), [0]
PSA (at scan) in ng/mL	Median (IQR), [N missing]	0.78 (0.4 - 2.3), [0]	1.58 (0.7 - 3.3), [0]	5.7 (3.4 - 10.9), [0]
PSA nadir in ng/mL	Median (IQR), [N missing]	0.2 (<0.1 - 0.3), [458]	<0.1 (<0.1 - 0.7), [212]	0.3 (0.1 - 0.8), [46]
Initial PSA (at diagnosis) in ng/mL	Median (IQR), [N missing]	7 (5.1 - 11.3), [651]	6.4 (4.7 - 10.2), [336]	7.6 (5.4 - 7.6), [209]
T-stage (prostatectomy)	Median (IQR), [N missing]	8 (6 - 10), [230]	7 (6 - 10), [433]	N/A
Clinical T-stage	Median (IQR), [N missing]	3 (3 - 4), [19]	3 (3 - 4), [433]	3 (3 - 6), [126]
Gleason grade group (prostatectomy)	Median (IQR), [N missing]	3 (2 - 5), [19]	3 (2 - 5), [5]	N/A
Gleason grade group (at biopsy)	Median (IQR), [N missing]	3 (2 - 4), [727]	3 (2 - 4), [403]	3 (2 - 4), [5]
PSMA inj. dose (mCi)	Median (IQR), [N missing]	5.4 (5 - 6.2), [4]	5.5 (5 - 6.2), [3]	5.8 (5.0 - 6.3), [1]
Time interval Tx to scan (months)	Median (IQR), [N missing]	40.2 (8.4 - 104.0), [23]	82.3 (48.4 - 130.6), [15]	75.4 (40.3 - 122.5), [24]

T-stage nomenclature: T1 = 1, T1a = 2, T1b = 3, T1c = 4, T2 = 5, T2a = 6, T2b = 7, T2c = 8, T3 = 9, T3a = 10, T3b = 11, T4 = 12

Table 2: ^{68}Ga-PSMA-11 Per-Patient Detection Rate Stratified by PSA Level and Prior Therapy.

PSA range	**Total**			**Prostatectomy (RP)**			**PORT**			**Radiation Therapy (RT)**		
	N Neg.	N Pos.	% Pos.	N Neg.	N Pos.	% Pos.	N Neg.	N Pos.	% Pos.	N Neg.	N Pos.	% Pos.
< 0.25 ng/mL	64	52	44.8	61	44	41.9	3	8	72.7			
0.25 - < 0.5 ng/mL	160	163	50.5	138	120	46.5	22	43	66.2			
0.5 - < 1.0 ng/mL	104	234	69.2	70	136	66.0	34	98	74.2			
1.0 - < 2.0 ng/mL	66	235	78.1	40	128	76.2	26	107	80.5			
2.0 - < 5.0 ng/mL	46	414	90.0	18	120	87.0	19	131	87.3	9	163	94.8
5.0 - < 10.0 ng/mL	18	238	93.0	10	74	88.1	3	55	94.8	5	109	95.6
≥10 ng/mL	8	203	96.2	3	56	94.9	1	43	97.7	4	104	96.3
Total	**466**	**1539**	**76.8**	**340**	**678**	**66.6**	**108**	**485**	**81.8**	**18**	**376**	**95.4**

(Neg. = Negative, Pos. = Positive)

Table 3: ^{68}Ga-PSMA-11 Accuracy Confirmed by Histopathology per Region.

	All Groups Combined				**RP**				**PORT**				**RT**			
	N	TP	FP	PPV	N	TP	FP	PPV	N	TP	FP	PPV	N	TP	FP	PPV
Prostate and prostate bed	77	64	13	0.83	10	8	2	0.80	7	6	1	0.86	60	50	10	0.83
Pelvic lymph nodes	47	34	13	0.72	25	16	9	0.64	19	16	3	0.84	3	2	1	0.67
Soft tissue	43	38	5	0.88	7	5	2	0.71	26	25	1	0.96	10	8	2	0.80
Bone	12	10	2	0.83	2	2	0	1.00	4	3	1	0.75	6	5	1	0.83
Total	**179**	**146**	**33**	**0.82**	**44**	**31**	**13**	**0.80**	**56**	**50**	**6**	**0.89**	**79**	**65**	**14**	**0.82**

(TP = true positive, FP = false positive, PPV = positive predictive value).

Supplemental Table 1: Gleason Grade Group Characteristics

Gleason Grade Groups (Prostatectomy Specimen)	All Patients		RP		PORT			
	N	%	N	%	N	%		
1	84	5.3	57	3.6	27	1.7		
2	423	26.7	275	17.3	148	9.3		
3	425	26.8	245	15.4	180	11.3		
4	212	13.4	140	8.8	72	4.5		
5	442	27.9	282	17.8	160	10.1		
Total	1586	100	999	63.0	587	37.0		
Gleason Grade Groups (Initial Prostate Biopsy)	All Patients		RP		PORT		RT	
	N	%	N	%	N	%	N	%
1	124	13.0	31	3.0	20	2.3	73	7.7
2	234	27.0	69	6.9	55	7.4	110	12.6
3	185	20.8	73	7.4	41	5.2	71	8.2
4	161	19.0	67	6.9	41	5.7	53	6.3
5	166	20.3	51	5.8	33	4.5	82	10.0
Total	870	100	291	30.1	190	25.2	389	44.8

Supplemental Table 2: ^{68}Ga-PSMA-11 Detection Rate in Prostate or Prostate Bed Stratified by PSA Level and Prior Therapy.

PSA range		Total			RP			PORT			RT		
		Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total
< 0.25 ng/mL	N	98	18	116	89	16	105	9	2	11			
% of total N		4.89	0.9	5.79	8.74	1.57	10.31	1.52	0.34	1.85			
% per column		6.69	3.33		11.01	7.62		1.75	2.53				
% per row		84.48	15.52		84.76	15.24		81.82	18.18				
0.25 - < 0.5 ng/mL	N	287	36	323	229	29	258	58	7	65			
% of total N		14.31	1.8	16.11	22.5	2.85	25.34	9.78	1.18	10.96			
% per column		19.6	6.65		28.34	13.81		11.28	8.86				
% per row		88.85	11.15		88.76	11.24		89.23	10.77				
0.5 - < 1.0 ng/mL	N	289	49	338	166	40	206	123	9	132			
% of total N		14.41	2.44	16.86	16.31	3.93	20.24	20.74	1.52	22.26			
% per column		19.74	9.06		20.54	19.05		23.93	11.39				
% per row		85.5	14.5		80.58	19.42		93.18	6.82				
1.0 - < 2.0 ng/mL	N	240	61	301	127	41	168	113	20	133			
% of total N		11.97	3.04	15.01	12.48	4.03	16.5	19.06	3.37	22.43			
% per column		16.39	11.28		15.72	19.52		21.98	25.32				
% per row		79.73	20.27		75.6	24.4		84.96	15.04				
2.0 - < 5.0 ng/mL	N	291	169	460	97	41	138	134	16	150	60	112	172
% of total N		14.51	8.43	22.94	9.53	4.03	13.56	22.6	2.7	25.3	15.23	28.43	43.65
% per column		19.88	31.24		12	19.52		26.07	20.25		42.25	44.44	
% per row		63.26	36.74		70.29	29.71		89.33	10.67		34.88	65.12	
5.0 - < 10.0 ng/mL	N	138	118	256	57	27	84	44	14	58	37	77	114
% of total N		6.88	5.89	12.77	5.6	2.65	8.25	7.42	2.36	9.78	9.39	19.54	28.93
% per column		9.43	21.81		7.05	12.86		8.56	17.72		26.06	30.56	
% per row		53.91	46.09		67.86	32.14		75.86	24.14		32.46	67.54	
≥10 ng/mL	N	121	90	211	43	16	59	33	11	44	45	63	108
% of total N		6.03	4.49	10.52	4.22	1.57	5.8	5.56	1.85	7.42	11.42	15.99	27.41
% per column		8.27	16.64		5.32	7.62		6.42	13.92		31.69	25	
% per row		57.35	42.65		72.88	27.12		75	25		41.67	58.33	
Total	N	1464	541	2005	808	210	1018	514	79	593	142	252	394
% of total N		73.02	26.98		79.37	20.63		86.68	13.32		36.04	63.96	

Supplemental Table 3: ^{68}Ga-PSMA-11 Detection Rate in Pelvic Lymph Nodes Stratified by PSA Level and Prior Therapy.

PSA range		Total			RP			PORT			RT		
		Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total
< 0.25 ng/mL	N	86	30	116	78	27	105	8	3	11			
% of total N		4.29	1.5	5.79	7.66	2.65	10.31	1.35	0.51	1.85			
% per column		7.71	3.37		13.38	6.21		2.74	1				
% per row		74.14	25.86		74.29	25.71		72.73	27.27				
0.25 - < 0.5 ng/mL	N	219	104	323	180	78	258	39	26	65			
% of total N		10.92	5.19	16.11	17.68	7.66	25.34	6.58	4.38	10.96			
% per column		19.62	11.7		30.87	17.93		13.36	8.64				
% per row		67.8	32.2		69.77	30.23		60	40				
0.5 - < 1.0 ng/mL	N	198	140	338	123	83	206	75	57	132			
% of total N		9.88	6.98	16.86	12.08	8.15	20.24	12.65	9.61	22.26			
% per column		17.74	15.75		21.1	19.08		25.68	18.94				
% per row		58.58	41.42		59.71	40.29		56.82	43.18				
1.0 - < 2.0 ng/mL	N	149	152	301	82	86	168	67	66	133			
% of total N		7.43	7.58	15.01	8.06	8.45	16.5	11.3	11.13	22.43			
% per column		13.35	17.1		14.07	19.77		22.95	21.93				
% per row		49.5	50.5		48.81	51.19		50.38	49.62				
2.0 - < 5.0 ng/mL	N	246	214	460	66	72	138	65	85	150	115	57	172
% of total N		12.27	10.67	22.94	6.48	7.07	13.56	10.96	14.33	25.3	29.19	14.47	43.65
% per column		22.04	24.07		11.32	16.55		22.26	28.24		47.72	37.25	
% per row		53.48	46.52		47.83	52.17		43.33	56.67		66.86	33.14	
5.0 - < 10.0 ng/mL	N	140	116	256	42	42	84	23	35	58	75	39	114
% of total N		6.98	5.79	12.77	4.13	4.13	8.25	3.88	5.9	9.78	19.04	9.9	28.93
% per column		12.54	13.05		7.2	9.66		7.88	11.63		31.12	25.49	
% per row		54.69	45.31		50	50		39.66	60.34		65.79	34.21	
≥10 ng/mL	N	78	133	211	12	47	59	15	29	44	51	57	108
% of total N		3.89	6.63	10.52	1.18	4.62	5.8	2.53	4.89	7.42	12.94	14.47	27.41
% per column		6.99	14.96		2.06	10.8		5.14	9.63		21.16	37.25	
% per row		36.97	63.03		20.34	79.66		34.09	65.91		47.22	52.78	
Total	N	1116	889	2005	583	435	1018	292	301	593	241	153	394
% of total N		55.66	44.34		57.27	42.73		49.24	50.76		61.17	38.83	

Supplemental Table 4: ^{68}Ga-PSMA-11 Detection Rate in Soft Tissue Metastases Stratified by PSA Level and Prior Therapy.

PSA range		Total			RP			PORT			RT		
		Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total
< 0.25 ng/mL	N	107	9	116	98	7	105	9	2	11			
% of total N		5.34	0.45	5.79	9.63	0.69	10.31	1.52	0.34	1.85			
% per column		6.93	1.95		11.34	4.55		2.22	1.06				
% per row		92.24	7.76		93.33	6.67		81.82	18.18				
0.25 - < 0.5 ng/mL	N	289	34	323	239	19	258	50	15	65			
% of total N		14.41	1.7	16.11	23.48	1.87	25.34	8.43	2.53	10.96			
% per column		18.72	7.38		27.66	12.34		12.35	7.98				
% per row		89.47	10.53		92.64	7.36		76.92	23.08				
0.5 - < 1.0 ng/mL	N	297	41	338	191	15	206	106	26	132			
% of total N		14.81	2.04	16.86	18.76	1.47	20.24	17.88	4.38	22.26			
% per column		19.24	8.89		22.11	9.74		26.17	13.83				
% per row		87.87	12.13		92.72	7.28		80.3	19.7				
1.0 - < 2.0 ng/mL	N	243	58	301	143	25	168	100	33	133			
% of total N		12.12	2.89	15.01	14.05	2.46	16.5	16.86	5.56	22.43			
% per column		15.74	12.58		16.55	16.23		24.69	17.55				
% per row		80.73	19.27		85.12	14.88		75.19	24.81				
2.0 - < 5.0 ng/mL	N	340	120	460	110	28	138	96	54	150	134	38	172
% of total N		16.96	5.99	22.94	10.81	2.75	13.56	16.19	9.11	25.3	34.01	9.64	43.65
% per column		22.02	26.03		12.73	18.18		23.7	28.72		48.73	31.93	
% per row		73.91	26.09		79.71	20.29		64	36		77.91	22.09	
5.0 - < 10.0 ng/mL	N	168	88	256	58	26	84	28	30	58	82	32	114
% of total N		8.38	4.39	12.77	5.7	2.55	8.25	4.72	5.06	9.78	20.81	8.12	28.93
% per column		10.88	19.09		6.71	16.88		6.91	15.96		29.82	26.89	
% per row		65.63	34.38		69.05	30.95		48.28	51.72		71.93	28.07	
≥10 ng/mL	N	100	111	211	25	34	59	16	28	44	59	49	108
% of total N		4.99	5.54	10.52	2.46	3.34	5.8	2.7	4.72	7.42	14.97	12.44	27.41
% per column		6.48	24.08		2.89	22.08		3.95	14.89		21.45	41.18	
% per row		47.39	52.61		42.37	57.63		36.36	63.64		54.63	45.37	
Total	N	1544	461	2005	864	154	1018	405	188	593	275	119	394
% of total N		77.01	22.99		84.87	15.13		68.3	31.7		69.8	30.2	

Supplemental Table 5: ^{68}Ga-PSMA-11 Detection Rate in Bone Metastases Stratified by PSA Level and Prior Therapy.

PSA range		Total			RP			PORT			RT		
		Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total
< 0.25 ng/mL	N	104	12	116	96	9	105	8	3	11			
% of total N		5.19	0.6	5.79	9.43	0.88	10.31	1.35	0.51	1.85			
% per column		6.59	2.8		11.21	5.56		1.86	1.85				
% per row		89.66	10.34		91.43	8.57		72.73	27.27				
0.25 - < 0.5 ng/mL	N	284	39	323	230	28	258	54	11	65			
% of total N		14.16	1.95	16.11	22.59	2.75	25.34	9.11	1.85	10.96			
% per column		18.01	9.11		26.87	17.28		12.53	6.79				
% per row		87.93	12.07		89.15	10.85		83.08	16.92				
0.5 - < 1.0 ng/mL	N	289	49	338	184	22	206	105	27	132			
% of total N		14.41	2.44	16.86	18.07	2.16	20.24	17.71	4.55	22.26			
% per column		18.33	11.45		21.5	13.58		24.36	16.67				
% per row		85.5	14.5		89.32	10.68		79.55	20.45				
1.0 - < 2.0 ng/mL	N	244	57	301	147	21	168	97	36	133			
% of total N		12.17	2.84	15.01	14.44	2.06	16.5	16.36	6.07	22.43			
% per column		15.47	13.32		17.17	12.96		22.51	22.22				
% per row		81.06	18.94		87.5	12.5		72.93	27.07				
2.0 - < 5.0 ng/mL	N	339	121	460	102	36	138	103	47	150	134	38	172
% of total N		16.91	6.03	22.94	10.02	3.54	13.56	17.37	7.93	25.3	34.01	9.64	43.65
% per column		21.5	28.27		11.92	22.22		23.9	29.01		46.21	36.54	
% per row		73.7	26.3		73.91	26.09		68.67	31.33		77.91	22.09	
5.0 - < 10.0 ng/mL	N	179	77	256	60	24	84	39	19	58	80	34	114
% of total N		8.93	3.84	12.77	5.89	2.36	8.25	6.58	3.2	9.78	20.3	8.63	28.93
% per column		11.35	17.99		7.01	14.81		9.05	11.73		27.59	32.69	
% per row		69.92	30.08		71.43	28.57		67.24	32.76		70.18	29.82	
≥10 ng/mL	N	138	73	211	37	22	59	25	19	44	76	32	108
% of total N		6.88	3.64	10.52	3.63	2.16	5.8	4.22	3.2	7.42	19.29	8.12	27.41
% per column		8.75	17.06		4.32	13.58		5.8	11.73		26.21	30.77	
% per row		65.4	34.6		62.71	37.29		56.82	43.18		70.37	29.63	
Total	N	1577	428	2005	856	162	1018	431	162	593	290	104	394
% of total N		78.65	21.35		84.09	15.91		72.68	27.32		73.6	26.4	

Supplemental Table 6 Patient Characteristics of PSMA-positive Scans With or Without Histopathological Evaluation

	No Histology (PSMA-positive Scan)		Histology (PSMA-positive Scan)	
	N (%)	Median (IQR)	N	Median (IQR)
Prostatectomy (RP)	634 (46.7%)		44 (24.6%)	
PORT	429 (31.5%)		56 (31.3%)	
Radiation therapy (RT)	297 (21.8%)		79 (44.1%)	
Total	1360 (88.4%)		179 (11.6%)	
Age (years)	1360	70 (IQR 65 - 74)	179	70 (IQR 65 - 74)
PSA (ng/mL)	1360	2.2 (0.79 - 5.4)	179	3.11 (IQR 1.3 - 6.2)
PSA nadir (ng/mL)	889	0.08 (IQR < 0.1 - 0.4)	141	0.09 (IQR < 0.1 - 0.4)
T-stage (prostatectomy)	1343	7 (IQR 5 - 10)	157	6 (IQR 4 - 8)
Clinical T-stage	479	3 (IQR 3 - 5)	99	3 (IQR 3 - 4)
Gleason grade group (prostatectomy)	1043	3 (IQR 2 - 5)	99	3 (IQR 2 - 5)
Gleason grade group (biopsy)	757	3 (IQR 2 - 4)	113	2 (IQR 2 - 4)
PSMA inj. Dose (mCi)	1826	5.5 (IQR 5 - 6.2)	179	5.6 (IQR 5.1 - 6.3)
Locoregional disease present	1104 (81.2%)		151 (84.4%)	
Distant disease present	688 (50.6%)		70 (39.1%)	

T-stage nomenclature: T1 = 1, T1a = 2, T1b = 3, T1c = 4, T2 = 5, T2a = 6, T2b = 7, T2c = 8, T3 = 9, T3a = 10, T3b = 11, T4 = 12

Supplemental Table 7 Characteristics of Histologically False Positive Lesions.

Number	Group	Region	Sampling method	Histology
1	RPT	Prostate region	Biopsy	Urethral anastomosis, negative for malignancy
2	RT	Prostate region	Biopsy	Prostate needle biopsy, negative for malignancy with radiation effect
3	RPT	Soft tissue	Surgery	Right perineal tissue, negative for malignancy
4	RT	Prostate region	Biopsy	Prostate needle biopsy, negative for malignancy
5	PORT	Pelvic nodes	Surgery	Salvage pelvic lymph node dissection, negative for malignancy
6	RPT	Prostate region	Biopsy	Prostate needle biopsy, negative for malignancy
7	RT	Prostate region	Biopsy	Prostate needle biopsy, negative for malignancy
8	RPT	Prostate region	Surgery	Benign tissue
9	RPT	Pelvic nodes	Surgery	Presacral lymph node, negative for malignancy
10	RPT	Soft tissue	Biopsy	Benign inguinal lymph nodes
11	PORT	Prostate region	Biopsy	Periprostatic mass, negative for malignancy
12	RPT	Pelvic nodes	Surgery	External iliac lymph nodes, negative for malignancy
13	RPT	Pelvic nodes	Surgery	Salvage pelvic lymph node dissection, negative for malignancy
14	RT	Prostate region	Biopsy	Prostate needle biopsy, negative for malignancy
15	RPT	Pelvic nodes	Surgery	Presacral lymph node, negative for malignancy
16	RT	Prostate region	Biopsy	Prostate needle biopsy, negative for malignancy
17	RT	Soft tissue	Biopsy	Retroperitoneal nodes, negative for malignancy
18	RT	Pelvic nodes	Surgery	Pelvic mass, negative for malignancy
19	PORT	Soft tissue	Biopsy	Mediastinal lymph nodes, negative for malignancy
20	RT	Soft tissue	Biopsy	Mediastinal benign granulosa cell tumor

21	RPT	Soft tissue	Biopsy	Benign inguinal lymph nodes
22	RT	Prostate region	Biopsy	Prostate needle biopsy, negative for malignancy
23	RPT	Soft tissue	Biopsy	Benign inguinal lymph nodes
24	PORT	Soft tissue	Biopsy	Benign inguinal lymph nodes
25	RPT	Pelvic nodes	Surgery	Salvage pelvic lymph node dissection, negative for malignancy
26	RPT	Pelvic nodes	Surgery	Salvage pelvic lymph node dissection, negative for malignancy
27	RT	Prostate region	Biopsy	Prostate needle biopsy, negative for malignancy
28	PORT	Pelvic nodes	Surgery	Salvage pelvic lymph node dissection, negative for malignancy
29	RT	Prostate region	Biopsy	Prostate needle biopsy, negative for malignancy
30	RT	Prostate region	Biopsy	Prostate needle biopsy, negative for malignancy with radiation effect
31	RT	Prostate region	Biopsy	Targeted seminal vesicle biopsy, negative for malignancy
32	RT	Prostate region	Biopsy	Prostate needle biopsy, negative for malignancy
33	PORT	Bone	Biopsy	Sacrum negative for malignancy

Supplemental Table 8 Overall Disease Burden Listed as Number of Involved Regions by PSA.

	Total						RP						PORT						RT					
PSA Range	Nega-tive	One Region	Two Regions	Three Regions	Four Regions	Total	Nega-tive	One Region	Two Regions	Three Regions	Four Regions	Total	Nega-tive	One Region	Two Regions	Three Regions	Four Regions	Total	Nega-tive	One Region	Two Regions	Three Regions	Four Regions	Total
< 0.25 ng/mL N	64	37	13	2	0	116	61	31	11	2	0	105	3	6	2	0	0	11						
% of total N	3.2	1.9	0.7	0.1		5.8	6.0	3.1	1.1	0.2		10.3	0.5	1.0	0.3			1.9						
% neg./pos.	13.6	4.0	2.9	1.5			18.0	6.8	6.2	6.1			2.7	2.1	1.3									
% in PSA range	55.2	31.9	11.2	1.7			58.1	29.5	10.5	1.9			27.3	54.6	18.2									
0.25 - < 0.5 ng/mL N	159	122	36	5	1	323	137	93	24	3	1	258	22	29	12	2	0	65						
% of total N	7.9	6.1	1.8	0.3	0.1	16.1	13.5	9.1	2.4	0.3	0.1	25.3	3.7	4.9	2.0	0.3		11.0						
% neg./pos.	33.8	13.1	8.1	3.8	4.0		40.4	20.4	13.6	9.1	7.7		20.0	10.1	8.1	4.4								
% in PSA range	49.2	37.8	11.2	1.6	0.3		53.1	36.1	9.3	1.2	0.4		33.9	44.6	18.5	3.1								
0.5 - < 1.0 ng/mL N	104	192	40	1	1	338	70	114	21	0	1	206	34	78	19	1	0	132						
% of total N	5.2	9.6	2.0	0.1	0.1	16.9	6.9	11.2	2.1		0.1	20.2	5.7	13.2	3.2	0.2		22.3						
% neg./pos.	22.1	20.6	9.0	0.8	4.0		20.7	25.0	11.9		7.7		30.9	27.3	12.8	2.2								
% in PSA range	30.8	56.8	11.8	0.3	0.3		34.0	55.3	10.2		0.5		25.8	59.1	14.4	0.8								
1.0 - < 2.0 ng/mL N	66	160	60	12	3	301	40	92	29	5	2	168	26	68	31	7	1	133						
% of total N	3.3	8.0	3.0	0.6	0.2	15.0	3.9	9.0	2.9	0.5	0.2	16.5	4.4	11.5	5.2	1.2	0.2	22.4						
% neg./pos.	14.0	17.2	13.5	9.1	12.0		11.8	20.2	16.4	15.2	15.4		23.6	23.8	20.8	15.2	50.0							
% in PSA range	21.9	53.2	19.9	4.0	1.0		23.8	54.8	17.3	3.0	1.2		19.6	51.1	23.3	5.3	0.8							
2.0 - < 5.0 ng/mL N	49	244	125	38	4	460	19	75	32	10	2	138	19	76	40	14	1	150	11	93	53	14	1	172
% of total N	2.4	12.2	6.2	1.9	0.2	22.9	1.9	7.4	3.1	1.0	0.2	13.6	3.2	12.8	6.8	2.4	0.2	25.3	2.8	23.6	13.5	3.6	0.3	43.7
% neg./pos.	10.4	26.2	28.0	28.8	16.0		5.6	16.5	18.1	30.3	15.4		17.3	26.6	26.9	30.4	50.0		50.0	49.2	44.2	26.4	10.0	
% in PSA range	10.7	53.0	27.2	8.3	0.9		13.8	54.4	23.2	7.3	1.5		12.7	50.7	26.7	9.3	0.7		6.4	54.1	30.8	8.1	0.6	
5.0 - < 10.0 ng/mL N	20	114	87	29	6	256	10	37	31	4	2	84	5	17	27	9	0	58	5	60	29	16	4	114
% of total N	1.0	5.7	4.3	1.5	0.3	12.8	1.0	3.6	3.1	0.4	0.2	8.3	0.8	2.9	4.6	1.5		9.8	1.3	15.2	7.4	4.1	1.0	28.9
% neg./pos.	4.3	12.2	19.5	22.0	24.0		3.0	8.1	17.5	12.1	15.4		4.6	5.9	18.1	19.6			22.7	31.8	24.2	30.2	40.0	
% in PSA range	7.8	44.5	34.0	11.3	2.3		11.9	44.1	36.9	4.8	2.4		8.6	29.3	46.6	15.5			4.4	52.6	25.4	14.0	3.5	
≥10 ng/mL N	9	62	85	45	10	211	2	14	29	9	5	59	1	12	18	13	0	44	6	36	38	23	5	108
% of total N	0.5	3.1	4.2	2.2	0.5	10.5	0.2	1.4	2.9	0.9	0.5	5.8	0.2	2.0	3.0	2.2		7.4	1.5	9.1	9.6	5.8	1.3	27.4
% neg./pos.	1.9	6.7	19.1	34.1	40.0		0.6	3.1	16.4	27.3	38.5		0.9	4.2	12.1	28.3			27.3	19.1	31.7	43.4	50.0	
% in PSA range	4.3	29.4	40.3	21.3	4.7		3.4	23.7	49.2	15.3	8.5		2.3	27.3	40.9	29.6			5.6	33.3	35.2	21.3	4.6	
Total N	471	931	446	132	25	2005	339	456	177	33	13	1018	110	286	149	46	2	593	22	189	120	53	10	394
% of total N	23.5	46.4	22.2	6.6	1.3		33.3	44.8	17.4	3.2	1.3		18.6	48.2	25.1	7.8	0.3		5.6	48.0	30.5	13.5	2.5	

Regions may represent either prostate/bed, pelvic lymph nodes, soft tissue metastases and/or bone metastases.

Supplemental Table 9 Locoregional Disease Burden (Prostate/Prostate Bed and/or Pelvic Lymph Nodes) by PSA.

PSA range		Total			RP			PORT			RT		
		Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total
< 0.25 ng/mL	N	73	43	116	67	38	105	6	5	11			
% of total N		3.6	2.1	5.8	6.6	3.7	10.3	1.0	0.8	1.9			
% per column		9.8	3.4		15.5	6.5		2.5	1.4				
% per row		62.9	37.1		63.8	36.2		54.6	45.5				
0.25 - < 0.5 ng/mL	N	191	132	323	158	100	258	33	32	65			
% of total N		9.5	6.6	16.1	15.5	9.8	25.3	5.6	5.4	11.0			
% per column		25.6	10.5		36.6	17.1		13.8	9.1				
% per row		59.1	40.9		61.2	38.8		50.8	49.2				
0.5 - < 1.0 ng/mL	N	154	184	338	87	119	206	67	65	132			
% of total N		7.7	9.2	16.9	8.6	11.7	20.2	11.3	11.0	22.3			
% per column		20.6	14.6		20.1	20.3		27.9	18.4				
% per row		45.6	54.4		42.2	57.8		50.8	49.2				
1.0 - < 2.0 ng/mL	N	107	194	301	52	116	168	55	78	133			
% of total N		5.3	9.7	15.0	5.1	11.4	16.5	9.3	13.2	22.4			
% per column		14.3	15.4		12.0	19.8		22.9	22.1				
% per row		35.6	64.5		31.0	69.1		41.4	58.7				
2.0 - < 5.0 ng/mL	N	127	333	460	38	100	138	52	98	150	37	135	172
% of total N		6.3	16.6	22.9	3.7	9.8	13.6	8.8	16.5	25.3	9.4	34.3	43.7
% per column		17.0	26.5		8.8	17.1		21.7	27.8		50.0	42.2	
% per row		27.6	72.4		27.5	72.5		34.7	65.3		21.5	78.5	
5.0 - < 10.0 ng/mL	N	59	197	256	23	61	84	15	43	58	21	93	114
% of total N		2.9	9.8	12.8	2.3	6.0	8.3	2.5	7.3	9.8	5.3	23.6	28.9
% per column		7.9	15.7		5.3	10.4		6.3	12.2		28.4	29.1	
% per row		23.1	77.0		27.4	72.6		25.9	74.1		18.4	81.6	
≥10 ng/mL	N	35	176	211	7	52	59	12	32	44	16	92	108
% of total N		1.8	8.8	10.5	0.7	5.1	5.8	2.0	5.4	7.4	4.1	23.4	27.4
% per column		4.7	14.0		1.6	8.9		5.0	9.1		21.6	28.8	
% per row		16.6	83.4		11.9	88.1		27.3	72.7		14.8	85.2	
Total	N	746	1259	2005	432	586	1018	240	353	593	74	320	394
% of total N		37.2	62.8		42.4	57.6		40.5	59.5		18.8	81.2	

Supplemental Table 10 Distant Disease Burden (Soft Tissue and/or Bone Metastases) by PSA.

PSA range		Total			RP			PORT			RT		
		Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total	Negative	Positive	Total
< 0.25 ng/mL	N	100	16	116	93	12	105	7	4	11			
% of total N		5.0	0.8	5.8	9.1	1.2	10.3	1.2	0.7	1.9			
% per column		8.0	2.1		12.5	4.4		2.3	1.4				
% per row		86.2	13.8		88.6	11.4		63.6	36.4				
0.25 - < 0.5 ng/mL	N	256	67	323	214	44	258	42	23	65			
% of total N		12.8	3.3	16.1	21.0	4.3	25.3	7.1	3.9	11.0			
% per column		20.6	8.8		28.8	16.0		14.1	7.8				
% per row		79.3	20.7		83.0	17.1		64.6	35.4				
0.5 - < 1.0 ng/mL	N	252	86	338	170	36	206	82	50	132			
% of total N		12.6	4.3	16.9	16.7	3.5	20.2	13.8	8.4	22.3			
% per column		20.2	11.3		22.9	13.1		27.4	17.0				
% per row		74.6	25.4		82.5	17.5		62.1	37.9				
1.0 - < 2.0 ng/mL	N	201	100	301	127	41	168	74	59	133			
% of total N		10.0	5.0	15.0	12.5	4.0	16.5	12.5	10.0	22.4			
% per column		16.1	13.2		17.1	14.9		24.8	20.1				
% per row		66.8	33.2		75.6	24.4		55.6	44.4				
2.0 - < 5.0 ng/mL	N	255	205	460	82	56	138	68	82	150	105	67	172
% of total N		12.7	10.2	22.9	8.1	5.5	13.6	11.5	13.8	25.3	26.7	17.0	43.7
% per column		20.5	27.0		11.0	20.4		22.7	27.9		51.5	35.3	
% per row		55.4	44.6		59.4	40.6		45.3	54.7		61.1	39.0	
5.0 - < 10.0 ng/mL	N	118	138	256	43	41	84	18	40	58	57	57	114
% of total N		5.9	6.9	12.8	4.2	4.0	8.3	3.0	6.8	9.8	14.5	14.5	28.9
% per column		9.5	18.2		5.8	14.9		6.0	13.6		27.9	30.0	
% per row		46.1	53.9		51.2	48.8		31.0	69.0		50.0	50.0	
≥10 ng/mL	N	64	147	211	14	45	59	8	36	44	42	66	108
% of total N		3.2	7.3	10.5	1.4	4.4	5.8	1.4	6.1	7.4	10.7	16.8	27.4
% per column		5.1	19.4		1.9	16.4		2.7	12.2		20.6	34.7	
% per row		30.3	69.7		23.7	76.3		18.2	81.8		38.9	61.1	
Total	N	1246	759	2005	743	275	1018	299	294	593	204	190	394
% of total N		62.1	37.9		73.0	27.0		50.4	49.6		51.8	48.2	