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Diagnostic Accuracy of ^{68}Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection

A Multicenter Prospective Phase 3 Imaging Trial

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IMPORTANCE The presence of pelvic nodal metastases at radical prostatectomy is associated with biochemical recurrence after prostatectomy.

OBJECTIVE To assess the accuracy of prostate-specific membrane antigen (PSMA) ^{68}Ga-PSMA-11 positron emission tomographic (PET) imaging for the detection of pelvic nodal metastases compared with histopathology at time of radical prostatectomy and pelvic lymph node dissection.

DESIGN, SETTING, AND PARTICIPANTS This investigator-initiated prospective multicenter single-arm open-label phase 3 imaging trial of diagnostic efficacy enrolled 764 patients with intermediate- to high-risk prostate cancer considered for prostatectomy at University of California, San Francisco and University of California, Los Angeles from December 2015 to December 2019. Data analysis took place from October 2018 to July 2021.

INTERVENTIONS Imaging scan with 3 to 7 mCi of ^{68}Ga-PSMA-11 PET.

MAIN OUTCOMES AND MEASURES The primary end point was the sensitivity and specificity for the detection pelvic lymph nodes compared with histopathology on a per-patient basis using nodal region correlation. Each scan was read centrally by 3 blinded independent central readers, and a majority rule was used for analysis.

RESULTS A total of 764 men (median [interquartile range] age, 69 [63-73] years) underwent 1 ^{68}Ga-PSMA-11 PET imaging scan for primary staging, and 277 of 764 (36%) subsequently underwent prostatectomy with lymph node dissection (efficacy analysis cohort). Based on pathology reports, 75 of 277 patients (27%) had pelvic nodal metastasis. Results of ^{68}Ga-PSMA-11 PET were positive in 40 of 277 (14%), 2 of 277 (1%), and 7 of 277 (3%) of patients for pelvic nodal, extrapelvic nodal, and bone metastatic disease. Sensitivity, specificity, positive predictive value, and negative predictive value for pelvic nodal metastases were 0.40 (95% CI, 0.34-0.46), 0.95 (95% CI, 0.92-0.97), 0.75 (95% CI, 0.70-0.80), and 0.81 (95% CI, 0.76-0.85), respectively. Of the 764 patients, 487 (64%) did not undergo prostatectomy, of which 108 were lost to follow-up. Patients with follow-up instead underwent radiotherapy (262 of 379 [69%]), systemic therapy (82 of 379 [22%]), surveillance (16 of 379 [4%]), or other treatments (19 of 379 [5%]).

CONCLUSIONS AND RELEVANCE This phase 3 diagnostic efficacy trial found that in men with intermediate- to high-risk prostate cancer who underwent radical prostatectomy and lymph node dissection, the sensitivity and specificity of ^{68}Ga-PSMA-11 PET were 0.40 and 0.95, respectively. This academic collaboration is the largest known to date and formed the foundation of a New Drug Application for ^{68}Ga-PSMA-11.

TRIAL REGISTRATION ClinicalTrials.gov Identifiers: NCT03368547, NCT02611882, and NCT02919111

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Supplemental content

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Accurate staging in prostate cancer is key to planning initial treatments. In patients who undergo radical prostatectomy, the presence of pelvic lymph node metastases at time of surgery is correlated with biochemical failure.[1] However, conventional imaging used for staging, including computed tomography (CT), bone scan, and magnetic resonance imaging (MRI), is limited for the detection of metastatic disease, especially for nodal disease.[2] Therefore, improved detection of metastatic disease prior to definitive therapy is needed.

Molecular imaging using positron emission tomography (PET) improves the detection of metastatic disease, particularly in patients with biochemical recurrence after definitive therapy. Both carbon-11 choline and fluorine-18 fluciclovine are approved by the US Food and Drug Administration (FDA) for imaging of patients with biochemical recurrence and have shown higher detection rates compared with conventional imaging.[3,4] These agents have also been evaluated, but to a lesser extent, at time of initial staging.[5]

PET imaging targeting the prostate-specific membrane antigen (PSMA) was shown to outperform existing PET imaging agents in patients with biochemical recurrence.[6,7] For initial staging before definitive therapy, PSMA PET leads to increased diagnostic accuracy and a high management change rate.[8] Furthermore, PSMA PET has shown promise for detection of pelvic nodal metastasis at initial staging, with an initial retrospective analyses reporting a sensitivity of 66% when using histopathology reference.[9]

In this multicenter study, we set out to prospectively assess the diagnostic accuracy of ^{68}Ga-PSMA-11 PET for the detection of pelvic nodal metastases at initial staging in patients with intermediate- to high-risk prostate cancer using 3 blinded independent central readers and a histopathology reference standard. We hypothesized that ^{68}Ga-PSMA-11 PET increases the sensitivity for pelvic nodal metastases detection from 46% to 65%.

Key Points

Question What is the sensitivity and specificity of prostate-specific membrane antigen (PSMA) ^{68}Ga-PSMA-11 positron emission tomographic (PET) imaging for the detection of nodal metastases in men with intermediate- to high-risk prostate cancer?

Findings In this prospective single-arm diagnostic imaging trial that included 764 men with intermediate- to high-risk prostate cancer who underwent a ^{68}Ga-PSMA-11 PET scan, 277 of whom subsequently underwent radical prostatectomy, the sensitivity and specificity for pelvic nodal metastases were 0.40 and 0.95, respectively, compared with histopathology.

Meaning In men with intermediate- to high-risk prostate cancer, ^{68}Ga-PSMA-11 PET imaging may miss small pelvic nodal metastases, and therefore a PSMA PET scan negative for pelvic nodal metastasis does not indicate that a pelvic nodal dissection is not required; these data were the foundation of a New Drug Application for ^{68}Ga-PSMA-11.

Methods

Study Design and Participants

This was a prospective multicenter open-label single-arm phase 3 trial of diagnostic efficacy performed at 2 institutions: University of California, Los Angeles (UCLA) (NCT03368547; trial protocol in Supplement 1) and University of California, San Francisco (UCSF) (NCT02611882 and NCT02919111; trial protocol in Supplement 2). The study was conducted under separate but identical Investigational New Drug applications (IND Nos. 127621 and 130649) and was approved by local institutional review boards (IRBs) at UCSF (IRB No. 15-17570) and UCLA (IRB No. 16-001684). Patients were eligible if they had histopathology-proven prostate adenocarcinoma, were planning to undergo a radical prostatectomy, and had intermediate- to high-risk disease as determined by at least 1 of the following: elevated prostate-specific antigen (PSA) level (PSA >10 ng/mL; to convert to µg/L, multiply by 1.0), T-stage (T2b or greater), Gleason score (Gleason score >6), or other risk factors. Results of prior conventional imaging did not influence eligibility. Any prostate cancer therapy prior to prostatectomy was an exclusion criterion, including androgen deprivation therapy, neoadjuvant chemotherapy, radiotherapy, or any other focal ablation techniques. Written informed consent was obtained from all patients. Prescreening failure patients were not tracked prior to enrollment and imaging. Data were collected in a central REDCap database. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Procedures

^{68}Ga-PSMA-11 PET Imaging

All patients underwent a single ^{68}Ga-PSMA-11 PET study. The ^{68}Ga-PSMA-11 was synthesized based on harmonized release criteria, and imaging was performed following European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging guidelines.[10] Target injected activity was 185 MBq (5 mCi) (allowed range, 111-259 MBq [3-7 mCi]), and patients received a mean (SD) of 196 (35) MBq (5.3 [0.9] mCi). Target uptake period was 60 minutes (allowed range, 50-100 minutes), and image acquisition began a mean (SD) of 65 (12) minutes after injection. Patients were imaged using either a PET/CT or PET/MRI; 152 patients were imaged using PET/MRI (63 in the surgical cohort and 89 in the nonsurgical cohort). For PET/CT, a diagnostic CT scan (200-240 mAs, 120 kV) with 5-mm slice thickness was performed. For PET/MRI, an abbreviated pelvis PET/MRI was obtained followed by a whole-body MRI.[11] Whole-body PET images were acquired from pelvis to vertex. Depending on patient weight and bed position, emission time was 2 to 5 minutes per bed position. All PET images were corrected for attenuation, dead time, random events, and scatter. PET images were reconstructed with an iterative algorithm (ordered-subset expectation maximization). Intravenous contrast media (iodinated or gadolinium) was administered in 703 of 764 patients (94%).

Image Interpretation

Each ^{68}Ga-PSMA-11 PET study was read locally by board-certified nuclear medicine physicians with access to all medical information to generate clinical reports. The ^{68}Ga-PSMA-11 PET images and report were sent to the referring physician, and treatment decisions were allowed to be based on the PET results. Patients who did not undergo prostatectomy were not included in the primary efficacy population and did not undergo central imaging review.

Each imaging study of the primary efficacy population (patients who underwent radical prostatectomy) was read by 3 blinded independent central readers, not involved in study design and data acquisition. In total, 6 blinded readers (F.B., F.C., A.F., S.M.S., M.U., and H.D.Z.) were used from outside institutions and were required to complete a training on 30 cases from a previously published data set.[12] Anonymized data sets for reader interpretation included attenuation-corrected PET images and contrast-enhanced CT or T1-weighted images postgadolinium and small field of view pelvic T2 images. Diffusion and dynamic contrast-enhanced images were not provided to readers for PET/MRI. Images were interpreted by visually using PROMISE (Prostate Cancer Molecular Imaging Standardized Evaluation) criteria: focal tracer uptake higher than surrounding background and not attributable to physiological uptake or known pitfall is considered suspicious for malignant neoplasm.[13] Readers assessed the presence of prostate cancer (positive vs negative) for 5 regions: prostate bed (T), pelvic lymph nodes (N), extrapelvic nodes (M1a), bone (M1b), or other organ (M1c). Pelvic lymph nodes were subdivided by side and location (left, right, other). Other included perivesical, perirectal, and presacral areas. Findings were entered by the readers directly into the central REDCap database. For analysis, a centralized per-region majority rule was generated by the local investigators.

Safety

Vital signs were recorded before and after radiotracer injection. Patients were monitored for self-reported adverse events up to 2 hours after injection. Finally, patients were contacted by phone 1 to 3 days to evaluate for delayed adverse events.

Follow-up and Histopathology Correlation

Patients were followed up after imaging by unblinded local investigators, who collected subsequent management. In patients who underwent prostatectomy after imaging, the surgical pathology report was obtained. The surgical approach was not standardized, and no resection template was required. The investigators coded the histopathology reference standard as negative or positive for pelvic lymph node metastasis. The size, number, and location (left, right, and other for perivesical, perirectal and presacral areas) of the pelvic lymph nodes were recorded.

Regions positive on imaging reads, based on majority rule, and positive on pathology were considered true positive (TP); regions positive on imaging without corresponding positive pathology finding were considered false positives (FPs); regions negative on imaging but positive on pathology were considered false negatives (FNs); and regions negative on imaging and pathology were considered true negatives (TNs). If a patient had a TP region, the patient was considered TP on the patient level. Patients were subsequently classified as FP, FN, and TN based on regional results.

Outcomes

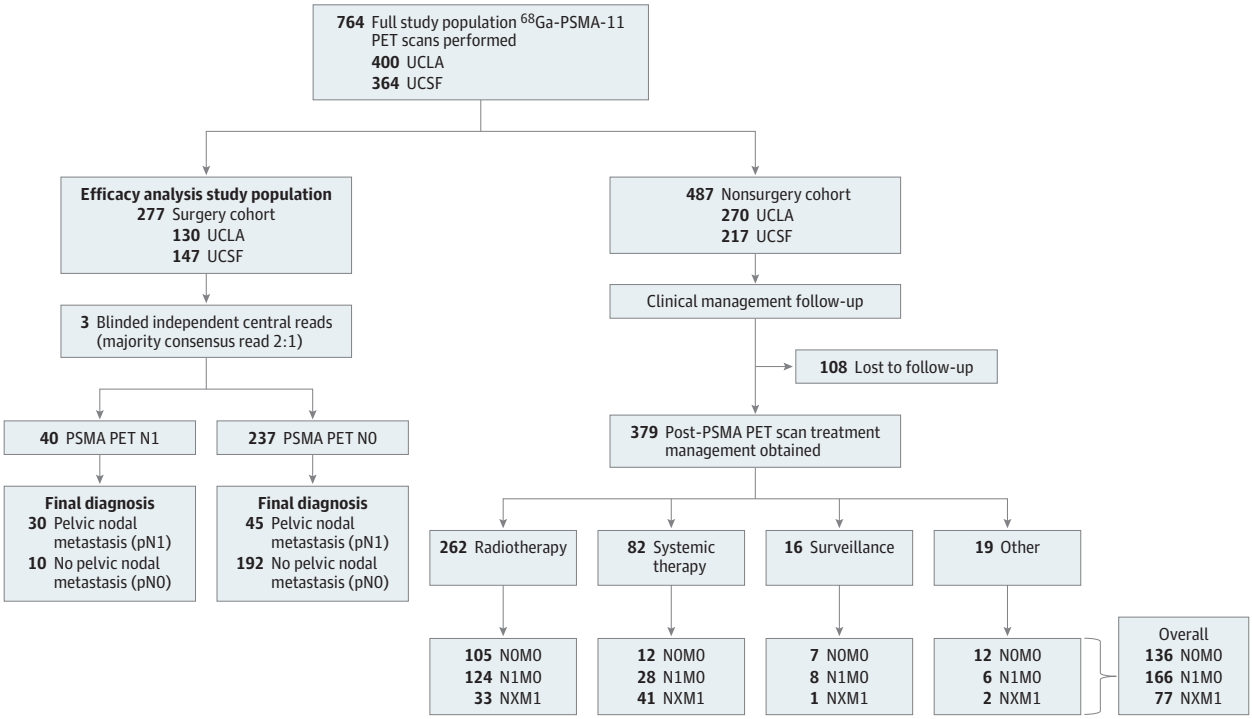
The primary end points of the study were the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ^{68}Ga-PSMA-11 PET for the detection of regional nodal metastases compared with pathology at radical prostatectomy on a per-patient basis using nodal regional correlation (left, right, other).

Statistical Analysis

Based on a retrospective analysis, the hypothesis was an increase in sensitivity for pelvic nodal metastasis detection from 46% to 65%.[9] A statistical power analysis established prospectively that a sample size of 68 patients with positive nodal metastases per histopathology provides at least 80% power and a significance level of .01. We required 226 patients to undergo prostatectomy with the assumption that 30% of patients with intermediate- to high-risk prostate cancer would have pelvic lymph nodes metastasis at prostatectomy (pN1). Initially we estimated that 25% of patients would not undergo prostatectomy, therefore requiring a total sample size of 302 patients. Based on an interim preliminary analysis, the sample size was increased because a lower percentage of patients underwent prostatectomy (123 of 325 [38%]). The interim analysis was unplanned and performed in 2018 for the purpose of a pre–New Drug Application meeting with the FDA. The data from the unplanned interim analysis included blinded reads and correlation with pathologic results. These results are available in the prescribing information for ^{68}Ga-PSMA-11.[14]

Descriptive statistics were used, including median and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. Confidence intervals were calculated using the Wilson score method. Wilcoxon sum rank test was used to compare the distributions of age and PSA between the 2 cohorts; and χ^2 test was used to assess if grade, low/high PSA level, and D'Amico risk were different between the 2 cohorts. A 2-sample *t* test was used to test the difference in average nodal sizes between positive and negative lesions. A χ^2 test was used to determine the association of Gleason score, PSA level, D'Amico risk, and node size with accuracy measurements. Specifically, to assess the outcome of PSA level on sensitivity, we compared the proportion of TP among the positive patients between low PSA level (<11 ng/mL) vs high PSA level (>11 ng/mL) by χ^2 test. We performed a similar analysis for node size, using a 1-cm cut point. Interreader agreement was determined by Fleiss' κ and interpreted by criteria of Landis and Koch by region.[15] A *P* value less than .05 was considered significant. Statistical analyses were performed with R, version 3.5.1 (R Foundation).

Figure. CONSORT Flow Diagram



PET indicates positron emission tomography; PSMA, prostate-specific membrane antigen; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco.

Table 1. Baseline Characteristics

Characteristic	No. (%)			*P* value
	Total	Surgery cohort	Nonsurgery cohort	
No. (%)	764 (100)	277 (36)	487 (64)	NA
Age, median (IQR), y	69 (63-73)	67 (61-71)	70 (65-75)	<.001
PSA, median (IQR), ng/mL	11.4 (6.7-21.2)	11.1 (6.5-18.0)	11.9 (6.8-24.0)	.07
≥20	202 (26)	59 (21)	143 (29)	.73
ISUP grade group[a]				
1	30 (4)	8 (3)	22 (5)	.65
2	128 (17)	49 (18)	79 (22)	
3	151 (20)	59 (21)	92 (19)	
4	186 (25)	63 (23)	123 (26)	
5	264 (35)	98 (35)	166 (34)	
D'Amico risk[a]				
Intermediate	166 (22)	49 (18)	117 (24)	.12
High	590 (78)	225 (81)	365 (75)	

Abbreviations: IQR, interquartile range; ISUP, International Society of Uropathology; NA, not applicable; PSA, prostate-specific antigen.

SI conversion factor: To convert PSA to µg/L, multiply by 1.0.

[a] Numbers do not add up to 764 because of patients with missing data variables.

Results

From December 2015 to December 2019, a total of 764 patients (median [IQR] age, 69 [63-73] years) were enrolled at UCSF (n = 364) and UCLA (n = 400). Prescreen failure patients were not tracked prior to enrollment and imaging. The study CONSORT flowchart is shown in the **Figure**. Of the 764 patients, 277 (36%) underwent prostatectomy after imaging and were included in the primary analysis. The baseline characteristics for the surgery and nonsurgery cohorts are provided in **Table 1**. Of the 277 prostatectomies, 215 (78%) occurred at UCSF or UCLA.

Surgery Cohort: Efficacy Analysis Population

A total of 75 of 277 patients (27%) had regional pelvic node metastasis found on pathology (pN1). Pelvic nodal involvement was unilateral, bilateral, and in other in 45 of 75 (60%), 47 of 75 (63%), and 17 of 75 (23%), respectively (eTable 1 in Supplement 3). A total of 4683 nodes were removed, with a median

Table 2. ^{68}Ga-PSMA-11 Test Characteristics for the Composite 3 Blinded Reads and Overall Majority Rule Read

Test characteristic	Read 1	Read 2	Read 3	Majority read
True positive	30	33	29	30
False positive	13	16	15	10
True negative	189	186	187	192
False negative	45	42	46	45
Sensitivity[a]	0.40 (0.30-0.51)	0.44 (0.33-0.55)	0.39 (0.28-0.50)	0.40 (0.30-0.51)
Specificity[a]	0.94 (0.89-0.96)	0.92 (0.88-0.95)	0.93 (0.88-0.95)	0.95 (0.91-0.97)
PPV[a]	0.70 (0.55-0.81)	0.67 (0.53-0.79)	0.66 (0.51-0.78)	0.75 (0.60-0.86)
NPV[a]	0.81 (0.75-0.85)	0.82 (0.76-0.86)	0.80 (0.75-0.85)	0.81 (0.76-0.85)

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; PSMA, prostate-specific membrane antigen.

[a] 95% CIs in parentheses.

(IQR) of 17 (10-22) nodes per patient. In 15 of 277 patients (5.5%), no lymph nodes were reported in the pathology report. The median (IQR) size of the largest positive lymph node on pathology per patient was 6 (3-10) mm.

Based on the majority reads, ^{68}Ga-PSMA-11 PET was positive in 40 of 277 (14%), 2 of 277 (1%), and 7 of 277 (3%) patients for pelvic nodal, extrapelvic nodal, and bone disease. On a per-patient level, the sensitivity, specificity, PPV, and NPV of ^{68}Ga-PSMA-11 PET based on the majority reads were 0.40 (95% CI, 0.34-0.46), 0.95 (95% CI, 0.92-0.97), 0.75 (95% CI, 0.70-0.80), and 0.81 (95% CI, 0.76-0.85). Results for individual readers are provided in **Table 2**. In a post hoc analysis that excluded the 15 patients with no nodes on pathology, the sensitivity, specificity, PPV, and NPV were 0.41 (95% CI, 0.36-0.47), 0.95 (95% CI, 0.91-0.97), 0.74 (95% CI, 0.69-0.79), and 0.82 (95% CI, 0.76-0.86).

We retrospectively reviewed patients characterized as having FPs and obtained their postsurgery follow-up; 5 of 10 (50%) patients had PSA persistence after surgery, and a postsurgery ^{68}Ga-PSMA-11 PET scan showed the same PET-positive lymph nodes as the presurgery scan. Consequently, it is highly likely that these nodes were not removed, and therefore the histopathology reference standard might have been inaccurate. If one were to consider these nodes as TP lesions, the sensitivity, specificity, and PPV would be 0.44 (95% CI, 0.33-0.55), 0.97 (95% CI, 0.94-0.99), and 0.88 (95% CI, 0.74-0.95).

Additionally, we performed a post hoc retrospective analysis to determine if PSA level, Gleason score, D'Amico risk, and node size were associated with the sensitivity, specificity, PPV, and NPV of ^{68}Ga-PSMA-11 PET (eTable 2 in Supplement 3). Larger pelvic lymph node metastasis size (>10 mm) was associated with higher sensitivity of ^{68}Ga-PSMA-11 PET for the detection of pelvic nodal metastases. True-positive and FN pelvic lymph node metastasis measured an average of 1.1 cm and 0.6 cm, respectively (P = .01). There was insufficient evidence to conclude that Gleason score, PSA level (categorized) and D'Amico risk were associated with sensitivity.

Interreader Variability

On a per-region level, interreader agreement was substantial for right-sided nodes (κ = 0.61; 95% CI, 0.55-0.67) and left-sided nodes (κ = 0.66; 95% CI, 0.60-0.71). For other nodes, there was moderate interreader agreement (κ = 0.52; 95% CI, 0.46-0.58).

Nonsurgery Cohort

Of the 764 patients, 487 (64%) did not undergo prostatectomy, of which 108 patients had no follow-up data. In the nonsurgery cohort, the unblinded local reads were positive for pelvic lymph node disease (N1), extrapelvic lymph node disease (M1a), and bone metastatic disease (M1b) in 252 of 487 (52%), 47 of 487 (10%), and 62 of 487 (13%), respectively. In the subset of patients with follow-up, the majority of nonsurgery patients underwent radiotherapy (262 of 379 [69%]), followed by systemic therapy (82 of 379 [22%]), surveillance (16 of 379 [4%]), or other treatments (19 of 379 [5%]). If we break down the nonsurgery cohort into N0M0, N1M0, and NXM1 based on local reads, the rate of radiotherapy was higher with N0M0 and N1M0 vs NXM1 (77% [105 of 136] and 75% [124 of 166] vs 43% [33 of 77]), and the rate of systemic therapy was higher with NXM1 vs N0M0 and N1M0 (53% [41 of 77] vs 9% [12 of 136] and 16% [28 of 166]) (Figure).

Safety Evaluation

There was no grade 2 or higher adverse event. Grade 1 events were reported in 44 of 764 patients (6%), and none required intervention. The most common adverse events were diarrhea (n = 16 of 764 [2%]) and fatigue (n = 6 of 764 [1%]). Rash and nausea were reported by 4 patients apiece. These events were not considered to be related to the study drug and possibly were related to contrast administration.

Discussion

In this multicenter prospective phase 3 imaging trial using 3 blinded independent central readers, the sensitivity and specificity of ^{68}Ga-PSMA-11 PET for the detection of pelvic nodal metastases compared with histopathology were 0.40 and 0.95, respectively. To our knowledge, this study is the largest prospective study using PSMA PET at time of initial staging and was conducted in a cohort of 277 patients with intermediate- to high-risk prostate cancer. The results of this study were used to support the FDA approval of ^{68}Ga-PSMA-11 PET at initial staging.[16]

Recent studies comparing ^{68}Ga-PSMA-11 with pelvic nodal dissection reported similar sensitivities of 0.42 (n = 97), 0.41 (n = 117), and 0.38 (n = 208).[17-19] Additionally, the multicenter OSPREY trial of ^{18}F-DCFPyL, which was per-

formed in 252 patients, reported a sensitivity ranging from 0.31 to 0.42 across the 3 blinded independent central readers.[20] These recent reports using blinded reads are in line with our results.

It should be noted that the sensitivity of 85% reported in the ProPSMA study[8] is not comparable to our results: the reported sensitivity was for any metastasis and based on a composite end point with multiple criteria other than histopathology, including the presence and number of metastasis, other imaging modalities, symptoms, or changes in lesion size and PSA level. In ProPSMA, 83 of 126 men (66%) who underwent prostatectomy had pelvic node sampling, and only 14 of 295 patients (4.7%) had pelvic nodes confirmed by histology. The sensitivity and specificity in patients with histologic verification was not provided but would be much lower than 85%.

The study did not meet the predefined threshold sensitivity of 0.65.[9] Early promising results of ^{68}Ga-PSMA-11 were not reproducible as summarized by a recent meta-analysis reporting a weighted sensitivity of 59%, but with a wide range of 23% to 100%.[21] Most of these early studies were small single-center retrospective studies and did not use blinded independent central readers. It has been documented that wide disease spectrum, nonconsecutive recruitment, open-label reading of tests, and retrospective data collection are associated with higher estimates of diagnostic accuracy.[22] We used a centralized majority rule, which decreases the sensitivity compared with consensus reads, which can introduce a non-independent, nonmasked major bias. Additionally, unblinded local reads are guided by clinical need and tend to be more sensitive.[23]

Although our study had a lower sensitivity than our predefined threshold, it did demonstrate a high specificity (0.95). It is clear that if the ^{68}Ga-PSMA-11 PET is positive, then disease is present. On the other hand, the NPV was 0.81, indicating that 20% of patients who underwent prostatectomy with a negative PET will have nodes on pathology. For this reason, it is important that surgeons do not use a negative PET to forgo a pelvic nodal dissection. Prospective trials based on PSMA PET findings are warranted. Additionally, the sensitivity estimates of the blinded independent readers were similar, and the interreader agreement was substantial (>0.6), confirming the high reproducibility of PSMA PET imaging.[12,23]

Limitations

One limitation of our study is the high proportion (64%) of patients who did not undergo prostatectomy, which introduced a bias that likely lowered the reported sensitivity because patients with larger size and number of nodes were treated with nonsurgical approaches. The cause of this is that our study was open label, and the PSMA PET results were used for treatment decision. As such, patients with more extensive disease on PET underwent treatments other than prostatectomy. In the nonsurgery cohort, 52% were PSMA PET N1, while in the surgery cohort, only 14% were PSMA PET N1. This removed patients with pelvic nodes metastasis that were more easily detected by PSMA PET from the surgery cohort. This illustrates the rapid clinical acceptance of PSMA PET by uro-oncologists. Even when PSMA PET was a nonapproved research procedure, the referring urologists changed their management from surgery because of disease upstaging. However, this limitation is also a strength of our study, as our sensitivity and specificity rates likely reflect the performance of PSMA PET imaging in the context of guiding urologists in their radical prostatectomies; these metrics reflect real-world practice.

Finally, the histopathology reference standard was not accurate because in 5 patients, PSMA PET–positive lymph nodes were not removed and were considered as FPs. Additionally, 5% of the surgery cohort had no nodes reported in the pathology report, potentially missing additional sites of disease.

Conclusions

In this multicenter prospective phase 3 diagnostic imaging trial in 277 patients with intermediate- to high-risk prostate cancer prior to prostatectomy, the sensitivity and specificity of ^{68}Ga-PSMA-11 PET for the detection of pelvic nodal metastases compared with histopathology on a patient level were 0.40 and 0.95, respectively. This academic collaboration is the largest to date and formed the foundation of a New Drug Application for ^{68}Ga-PSMA-11.

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Invited Commentary

Prostate-Specific Membrane Antigen Positron Emission Tomography and the New Algorithm for Patients With Prostate Cancer Prior to Prostatectomy

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After several decades of development of prostate-specific membrane antigen (PSMA) as a biomarker for prostate cancer, a recent series of studies have defined its diagnostic clinical significance in patients with prostate cancer, including prior to radical prostatectomy, as in the diagnostic imaging study by Hope et al[1] in this issue of *JAMA Oncology*. Importantly, these data comport with a similarly designed prospective trial evaluating PSMA positron emission tomography (PET) diagnostic performance of a similar agent (^{18}F-DCFPyL) in cohort A of the OSPREY trial.[2] There is a clear message from both trials: clinicians taking care of patients with high-risk prostate cancer being assessed for prostatectomy can use a positive PET scan as a true positive (0.95 [95% CI, 0.92-0.97][1] vs 0.98 [95% CI, 0.94-0.99] in the OSPREY trial[2]), whereas a negative scan cannot be used to exclude disease or inform nodal dissection (both studies had a diagnostic sensitivity near 40%). One methodologic issue to mention is that clinicians were not blinded to PSMA PET results, and patients with evidence of extraprostatic disease may not have gone on to surgery. Post hoc analysis of these "negative" PET studies in both investigations also have a common message. Both demonstrate that many of the false-negative studies are found in patients who have pathologically PSMA-positive lymph nodes that are smaller than 1.0 cm or 0.5 cm, below the resolution of this technology. These truly micrometastatic lesions may have a better prognosis than those identified by imaging and lead to the hypothesis that these are likely the patients with long-term benefit from surgical resection.

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In addition, false-positive scans have been described, but not all false-positive scans are actually correctly categorized as such. Hope et al[1] describe a subset of patients with positive ^{68}Ga-PSMA-11 imaging results with negative pathology of dissected lymph nodes. These patients then had persistent detectable postoperative prostate-specific antigen as well as positive postoperative PSMA imaging results. These cases might be better characterized as false-negative lymph node dissections. An additional area of ongoing research is PSMA-radioguided surgery using intraoperative probes to assist with identification of areas to resect beyond typical lymph node dissection templates.[3]

The study by Hope et al[1] provided the context for US Food and Drug Administration approval of ^{68}Ga-PSMA-11 PET and has provided a road map for how preintervention PSMA PET imaging will guide the appropriateness of radical prostatectomy for the referring urologists. As such, these results are practice changing for the nuclear medicine physicians, urologists, and medical oncologists who will manage this cohort of patients. While there are radiochemical and practical differences between ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL, in the clinic, both present notable improvements over previously standard imaging modalities. The similar positive and negative predictive values across studies suggest that ^{68}Ga-PSMA will not be inferior to ^{18}F-PSMA for this and probably any other diagnostic task. It is likely that a large number of patients would need to be assessed in a head-to-head study to see meaningful differences. It is possible that novel tracers or imaging techniques might lead to advances in the future.

There were many published studies and meta-analyses that hinted at the qualities and value of a variety of PSMA PET agents in these patients,[4,5] but to our knowledge, this is the first for ^{68}Ga-PSMA-11 with a real-world prospective design that simulated a viable practice pattern. The prior designed prospective clinical trial (proPSMA)[6] was an important step, but it included composite end points and a small number of patients who underwent prostatectomy with pathologically positive lymph nodes, which likely affected the reported sensitivity of