Impact of Staging ^{68}Ga-PSMA-11 PET Scans on Radiation Treatment Plans in Patients With Prostate Cancer

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OBJECTIVE To evaluate the impact of staging ^{68}Ga-PSMA-11 PET imaging on radiotherapy (RT) dose and volumes in patients with prostate cancer.

METHODS Forty-five patients (89% high or very high risk by NCCN criteria) who underwent ^{68}Ga-PSMA-11 PET imaging prior to definitive treatment for prostate cancer between December 2015 and December 2016 were included. Locations of ^{68}Ga-PSMA-11-avid lesions were compared to Radiation Therapy Oncology Group consensus pelvic nodal volumes (clinical target volume [CTV]); coverage of lesions outside the consensus CTV was considered a major change, while dose-escalation to lesions within the consensus CTV was considered a minor change.

RESULTS All patients had ^{68}Ga-PSMA-11 PET uptake in the prostate. Twenty-five patients (56%) had N1/M1a disease on ^{68}Ga-PSMA-11 PET scan, of whom 21 (47%) were previously N0. Six patients (13%) had bone metastases on ^{68}Ga-PSMA-11 PET scan, of whom 4 had prior negative bone scans. Eight patients (18%) had lymph node metastases outside the consensus CTV. Twelve patients (27%) received a RT boost to nodes within the consensus CTV. Six patients (13%) had limited bone metastases treated with focal RT. Overall PSMA PET imaging resulted in major and/or minor changes to RT plans in 24 patients (53%).

CONCLUSION ^{68}Ga-PSMA-11 PET imaging resulted in RT changes in 53% of patients. Prospective investigation is needed to evaluate the clinical benefit of RT changes based on staging ^{68}Ga-PSMA-11 PET imaging. UROLOGY 125: 154–162, 2019. Published by Elsevier Inc.

Radiation therapy (RT) is a standard of care treatment for prostate cancer.

Conventional imaging (CT, MRI, and bone scan) has limited sensitivity and specificity for nodal and osseous metastatic disease.[1,2] Accurate staging is essential for guiding treatment decisions, especially with regard to RT dose and volumes. The Radiation Therapy Oncology Group (RTOG) has published consensus guidelines for at-risk pelvic lymph node volumes.[3] While there is no level I evidence demonstrating a survival benefit with the addition of local RT to androgen deprivation therapy in patients with N1 disease, improvement in biochemical recurrence free survival and overall survival is supported by retrospective data[4] and is recommended as an initial therapy option by the NCCN.[5] Benefits of dose escalation for residual disease in the prostate bed has been demonstrated in the salvage setting,[6] which guides our institutional practice for boosting involved nodes. Long-term (2-3 years) androgen deprivation therapy (ADT) is recommended for patients with evidence of lymph node involvement.[7]

Prostate specific membrane antigen (PSMA) is a transmembrane protein that is overexpressed on prostate cancer cells, and increased expression is correlated with higher Gleason score and the development of metastatic

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disease.[8] Glu-NH-CO-NH-Lys-(Ahx)-[68-Ga(HBED-CC)] (^{68}Ga-PSMA-11) targets the extracellular domain of this transmembrane protein.

In treatment naïve patients, ^{68}Ga-PSMA-11 PET imaging has high specificity and moderate sensitivity for nodal staging, and high sensitivity and specificity for bone metastases.[9] ^{68}Ga-PSMA-11 PET imaging more accurately predicts lymph node involvement, with improved sensitivity and specificity, compared to MRI or CT in patients undergoing radical prostatectomy and pelvic lymph node dissection.[10]

To date, use of ^{68}Ga-PSMA-11 PET imaging to guide RT has been primarily in the setting of persistent PSA after radical prostatectomy or biochemical failure after surgery or radiation.[11,12] Literature evaluating the use of staging ^{68}Ga-PSMA PET imaging in RT planning has primarily been limited to small series, many of which also include patients with biochemical recurrence;[13-17] larger study of staging ^{68}Ga-PSMA PET and RT plans evaluates changes in treatment volumes but not dose escalation to involved nodes.[18] The purpose of this study is to further evaluate the impact of staging ^{68}Ga-PSMA-11 PET imaging on radiation treatment dose and volumes.

MATERIALS AND METHODS

Patient Selection

Patients with biopsy proven prostate cancer who received a ^{68}Ga-PSMA-11 PET/CT or PET/ MRI prior to definitive treatment on clinical trial NCT02611882 at our institution between December 2015 and December 2016 and were subsequently treated with RT were included in this analysis. Imaging findings for patients enrolled on NCT02611882 in the setting of biochemical recurrence have previously been reported.[19] This study was approved by the institutional review board and informed consent was obtained from all patients. Treatment naïve patients with (1) Gleason score ≥8, (2) Cancer of the Prostate Risk Assessment (CAPRA)[20] score ≥5, or (3) PSA ≥15 ng/mL were eligible. Exclusion criteria included Karnofsky performance status ≤50, inability to undergo PET scan, or prior treatment with chemotherapy, radiation, focal ablation (HiFu), or ADT. Lymph node involvement based on CT or MRI prior to ^{68}Ga-PSMA-11 PET scan was not an exclusion criteria; involved lymph nodes on CT or MRI were defined as abnormally rounded lymph nodes 8 mm or greater in diameter, or enlarged nodes 1 cm or greater regardless of morphology. Patients were prospectively enrolled, and details of radiation treatment plans and the recommended duration of ADT were abstracted from the medical record.

Investigational Drug, Dose, and Administration

^{68}Ga-PSMA-11 was produced using a ^{68}Ge/^{68}Ga generator and manual synthesis module (Isotope Technologies Garching, ITG; Munich, Germany) as has previously been reported.[21] ^{68}Ga-PSMA-11 was administered once intravenously 50-100 minutes prior to PET imaging. The radioactivity of the injected dose was estimated to be 111-259 MBq (3-7 miCu). A 20 mg dose of furosemide was administered in a subset of patients to decrease PET scatter artifact due to radiotracer accumulation in the kidney and urinary bladder.

Imaging Technique

Choice of PET/CT (Discovery VCT, GE Healthcare, Waukesha, WI) or PET/MRI (3.0T time-of-flight Signa PET/MRI, GE Healthcare, Waukesha, WI) was at the discretion of the ordering physician. Twenty-seven patients (60%) underwent PET/MRI while 18 patients (40%) underwent PET/CT. For PET/CT, patients were imaged from pelvis to vertex with 5-minute acquisitions up to the midabdomen (first 3 bed positions), followed by 3-minute acquisitions to the vertex. Postcontrast diagnostic CT scans were used for attenuation correction. PET data sets were reconstructed with a transaxial field of view of 620 mm and axial slices 5.0 mm thick.

For PET/MRI, patients underwent a 2-staged acquisition. The first stage was centered over the prostate with 15 minutes of PET data acquired, and the following sequences were obtained:

1. 3D small field of view T2 weighted image (CUBE): TR/eTE = 2400/137.3 milliseconds, matrix = 256 × 240, echo train length = 100, flip angle = 90°, slice thickness = 2 mm.
2. Reduced field of view diffusion (FOCUS):[22] TR/TE = 2000/96.1 milliseconds, matrix = 180 × 50, flip angle = 90°, slice thickness = 6 mm, b-values = 0 (NEX = 2) and 1350 (NEX = 1350).
3. Dynamic contrast enhanced imaging: acquired following the administration of gadobutrol (Gadavist, Bayer Healthcare, Berlin) using Differential Subsampling with Cartesian Ordering.[23] Seventeen phases were acquired using an 11-second temporal resolution with the following parameters: slice thickness = 2 mm, flip angle = 15°, matrix = 512 × 512, TE1/TE2/TR = 2.0/4.1/5.6 milliseconds, NEX = 0.7, parallel imaging acceleration factors of 2 (phase direction) × 2.5 (slice direction).

The second stage was a whole body acquisition that has been described previously,[23] with 3 minutes of PET data acquired at each bed position. PET data were reconstructed with transaxial and z-axis field of views measuring 600 and 250 mm respectively, with axial slices 2.8 mm thick.

Image Analysis

^{68}Ga-PSMA-11 PET/CT and PET/MRI images were interpreted by a nuclear medicine physician and a radiologist, both blinded to pre- and postimaging treatment recommendations. PET data were interpreted using an Advantage Workstation (version 5.0, GE Healthcare). Lesions were considered positive if they exhibited uptake above background, not attributable to physiological distribution.

Changes in Radiation Treatment Plans and ADT

^{68}Ga-PSMA-11 PET images and radiation planning CT scans were imported into a treatment planning program (MIM 6.4.9, MIM Software Inc., Cleveland, OH). Treatment plans were designed based on ^{68}Ga-PSMA-11 PET findings and compared to RTOG consensus guidelines[3] with common iliac nodes contoured superiorly to the L4/L5 interspace. The pelvic nodal clinical target volume (CTV) included the common, internal, and external iliac nodes, obturator nodes, and presacral nodes inferiorly to the level of S3. Retroperitoneal nodes above the level of L4/L5 (paraaortic nodes), inguinal nodes, presacral nodes below S3, and perirectal nodes were considered outside the consensus CTV. Bone metastases were also considered outside the consensus CTV. Identification of ^{68}Ga-PSMA-11 avid lesions outside

the consensus CTV was considered a major RT change. Dose escalation (RT boost) to nodes identified within the consensus CTV was considered a minor RT change.

Statistical Analysis

Descriptive statistics were used to characterize variables of interest. The Shapiro-Wilk test was used to assess normality of all variables. Mann-Whitney U and chi-squared tests were used to assess the effect of clinical factors such as sites of ^{68}Ga-PSMA-11 uptake on changes to RT plans. All statistics were 2-sided and a *P* value less than 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics (Version 25, Armonk, NY).

RESULTS

Forty-five patients underwent ^{68}Ga-PSMA-11 PET scan prior to definitive treatment for prostate cancer. The median age was 70 years (interquartile range 66-74 years, Table 1). Eighty-nine percent of patients (40/45) had high risk or very high risk disease based on NCCN guidelines,[5] 80% (36/45) had high risk disease by CAPRA score,[20] and 47% (21/45) had clinical T3a/T3b disease. Median PSA for the cohort was 16 ng/mL (interquartile range 7.9-25 ng/mL). Eighty-seven percent (39/45) underwent staging with a combination of CT, MRI, and/or bone scan prior to ^{68}Ga-PSMA-11 PET.

Table 1. Patient characteristics

Characteristic	Value (% or IQR) (n = 45)
Median age (years)	70 (IQR 66-74)
Gleason score*	
6	1 (2%)
7	11 (24%)
8	10 (22%)
9	20 (44%)
10	2 (4%)
T-stage at diagnosis	
T1	6 (13%)
T2a	7 (16%)
T2b	5 (11%)
T2c	5 (11%)
T3a	13 (29%)
T3b	8 (18%)
T4	1 (2%)
CAPRA risk	
Low (0-2)	1 (2%)
Intermediate (3-5)	7 (16%)
High (6-10)	36 (80%)
Insufficient data	1 (2%)
Median PSA (ng/mL)	16 (IQR 7.9-25)
Median PSA doubling time (months)	14 (IQR 6.9-24)
Median PSA velocity (ng/ml/month)	0.45 (IQR 0.23-1.1)
RT intent	
Definitive	31 (69%)
Adjuvant	14 (31%)

* Sums to 44 patients as 1 patient had negative prostate biopsies in 9/2013 and 12/2015; diagnosis of prostate cancer was made on a subsequent biopsy of a pelvic lymph node.

Table 2. ^{68}Ga-PSMA-11 PET imaging findings

Imaging Characteristic	n	% (of 45)
Imaging modality		
^{68}Ga-PSMA-11 PET/MRI	27	60
^{68}Ga-PSMA-11 PET/CT	18	40
New nodal involvement (N1 or M1a) identified by ^{68}Ga-PSMA-11 PET scan	21	47
Node identified outside the consensus CTV	8	18
Pelvic/regional lymph node (N1)	2	4
Nonregional lymph node (M1a)	6	13
Bone metastases (M1b) identified by ^{68}Ga-PSMA-11 PET	6*	13
^{68}Ga-PSMA-11 PET identified new N1 and/or M1 disease	25	56

* Four patients with prior negative bone scan

All 45 patients had evidence of ^{68}Ga-PSMA-11 PET uptake in the prostate. Fifty-six percent of patients (25/45) had evidence of nodal involvement on ^{68}Ga-PSMA-11 PET scan (Table 2). Four of these patients (9%) had evidence of N1 disease prior to ^{68}Ga-PSMA-11 PET, detected by CT or MRI, thus 47% of patients (21/45) had new N1/M1a disease identified on ^{68}Ga-PSMA-11 PET scan (Figure 1 and Table 2). ^{68}Ga-PSMA-11 PET scan identified bone metastases in 13% of patients (6/45) (2 rib lesions, 3 lesions in the pelvis, and 1 patient with a lesion in the sternum and right humerus; Figure 1). Four of these 6 patients had negative bone scans prior to ^{68}Ga-PSMA-11 PET. Overall ^{68}Ga-PSMA-11 PET identified new N1 or M1 disease in 56% of patients (25/45).

Radiation treatment intent was definitive in 69% of patients (31/45) and adjuvant in 31% of patients (14/45).[24] All patients had an estimated risk of lymph node involvement >15% based on the Roach formula[25] and would have received radiation to the prostate and pelvic lymph nodes at our institution. Compared to RTOG guidelines, 29% of patients (13/45) had a major change to their radiation treatment plan based on ^{68}Ga-PSMA-11 PET scan results, including 7 patients with nodal metastases outside the consensus CTV, 5 patients with osseous metastases, and 1 patient with both (Table 2 and Figure 1). Of the 8 patients with nodal metastases outside the consensus CTV, 4% (2/45) had extension of the nodal CTV within the pelvis while 13% (6/45) had extension of the nodal CTV outside the pelvis. Forty-four percent of patients (20/45) had minor changes to RT plans with RT boost to ^{68}Ga-PSMA-11 avid lymph nodes. Overall 53% of patients (24/45) had major and/or minor RT changes based on ^{68}Ga-PSMA-11 PET findings.

Two patients with new N1 or M1 disease identified on ^{68}Ga-PSMA-11 PET imaging did not have changes to their RT plans; 1 patient declined SBRT for an isolated pelvic bone metastasis, and 1 patient with a subcentimeter ^{68}Ga-PSMA-11-avid pelvic lymph node within the consensus CTV did not receive a RT boost.

Eighty-two percent of patients (37/45) initiated long-term ADT for at least 2 years for high-risk features, nodal involvement or bone metastases. Seven percent of patients (3/45) received long-term ADT rather than short-term ADT solely

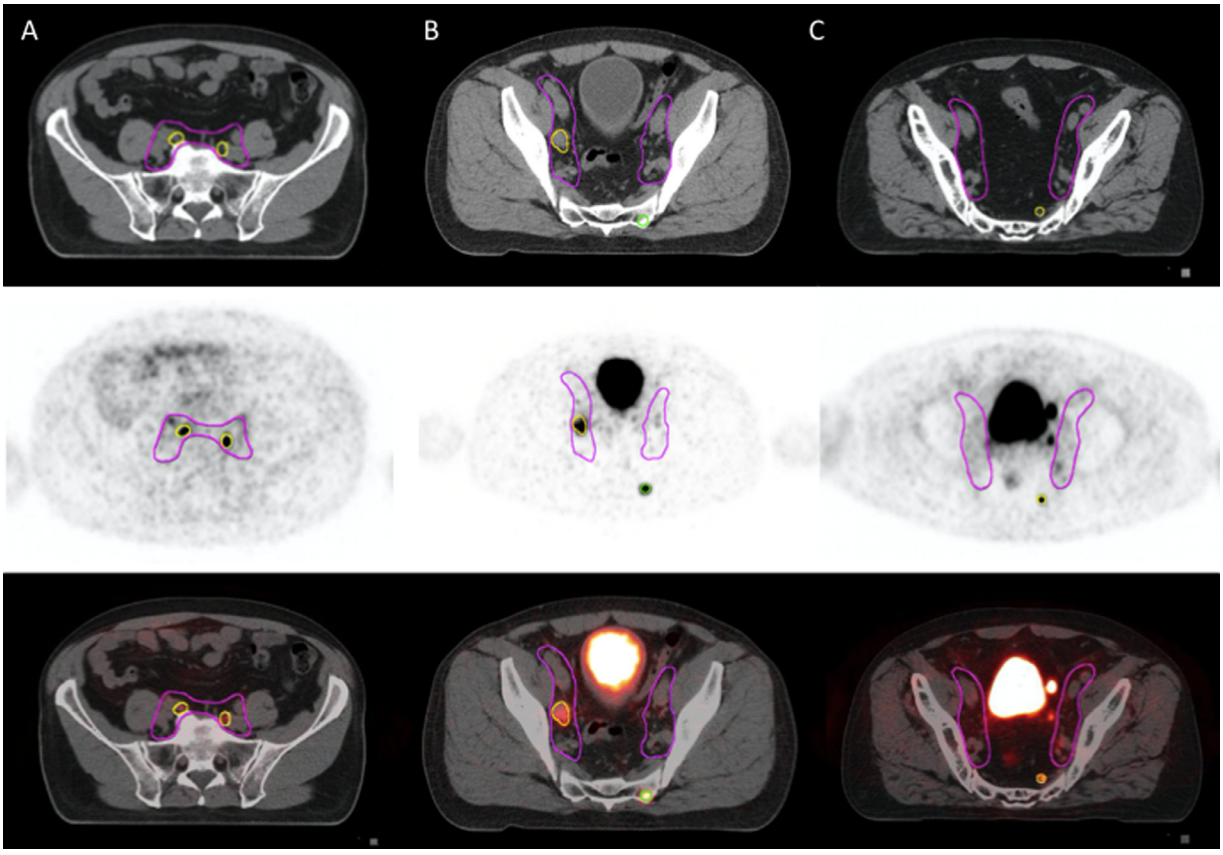

Figure 1. Radiotherapy planning based on ^{68}Ga-PSMA-11 PET imaging. Column A: 68-year-old man with Gleason 4+3 prostate cancer, T3bN1, PSA 17. ^{68}Ga-PSMA-11-avid lymph node identified in the consensus CTV and boosted to 66 Gy in 37 fractions (minor change). Column B: 55-year-old man with Gleason 4+5 prostate cancer, T3aN1M1b, PSA 30. ^{68}Ga-PSMA-11-avid lymph node identified within the consensus CTV and boosted to 64.8 Gy in 36 fractions (minor change). Additional ^{68}Ga-PSMA-11-avid bone metastasis (green) without CT correlate treated with focal radiation, 30 Gy in 5 fractions (major change). Column C) 71-year-old man with Gleason 4+3 prostate cancer, T3bN1, PSA 18. ^{68}Ga-PSMA-11-avid lymph node (yellow) was identified in the pelvis outside of the consensus CTV (pink); the pelvic nodal CTV was expanded to include this lymph node with a boost to 64.8 Gy in 36 fractions (major change). ^{68}Ga-PSMA-11-avid lymph nodes contoured in yellow, bone metastasis contoured in green. RTOG consensus nodal CTV contoured in pink. RT planning CT (upper panel), PET (middle panel), and fused PET/CT (lower panel). (Color version available online.)

Table 3. RT changes following ^{68}Ga-PSMA-11 PET imaging

Characteristics	N	% (of 45)
Major RT changes	**13***	**29**
Extension of nodal CTV within the pelvis (presacral, perirectal nodes)	2	4
Extension of nodal CTV outside of pelvis (inguinal, paraaortic nodes)	6	13
RT to bone mets	6	13
Minor RT changes	**20**	**44**
Boost avid node without extension of nodal CTV	11	24
Major and/or minor RT change based on ^{68}Ga-PSMA-11 imaging	**24**	**53**

* One patient with 2 types of major RT changes (extension of nodal CTV and RT to a bone metastasis).

based on identification of nodal involvement on ^{68}Ga-PSMA-11 PET scan. Patients with RT volume changes were more likely to be on long-term ADT (95% vs 70%, $P = .047$), primarily due to identification of nodal metastases.

COMMENT

The use of ^{68}Ga-PSMA-11 PET during initial staging resulted in major or minor RT changes in 53% of patients, primarily due to identification of new nodal metastases resulting in expansion of the at-risk nodal CTV or RT boost to PET-avid lymph nodes. Identification of limited metastatic disease by ^{68}Ga-PSMA PET scan also resulted in focal ablative treatment to bone metastases in 6 patients.

The majority of literature evaluating the role of ^{68}Ga-PSMA-11 PET imaging is in the setting of biochemical recurrence,[11,12,26] with relatively few studies specifically

evaluating the use of pre-RT ^{68}Ga-PSMA-11 PET scans.[17,27] Our data adds to limited literature demonstrating frequent changes to RT plans in response to staging ^{68}Ga-PSMA-11 PET scans. Five series have described the impact of staging ^{68}Ga-PSMA-11 PET imaging on radiation treatment plans.[13-16,18] The first 4 are limited in size, with 3 including 20 or fewer patients, and suggest general changes in a variable proportion of treatment plans (15%-46%), primarily due to identification of new nodal or distant metastatic disease. Calais et al.[18] is the only other study to evaluate specific changes to RT plans based on RTOG consensus nodal volumes; however this study does not address dose escalation to involved lymph nodes. Given the elective nodal volume is typically treated to 45-50.4 Gy, a dose sufficient for microscopic but not gross disease, dose escalation to involved lymph nodes is recommended[5] and may impact biochemical control based on evidence supporting dose escalation in the prostate.[28] The higher rate of RT changes in our study (53%) is likely attributable to eligibility criteria that selected for patients at higher risk for metastatic disease (Gleason score $\geq$ 8, CAPRA $\geq$ 5, or PSA $\geq$15 ng/mL).

It remains to be seen if RT changes based on staging ^{68}Ga-PSMA-11 PET scans improve meaningful outcomes such as time to biochemical failure, rate of distant metastatic disease, or overall survival. While our institutional practice has been to include pelvic nodal radiation in patients with >15% risk of nodal involvement by the Roach formula, this is not standard practice. RTOG 0924 (NCT01368588) seeks to address the lack of consensus for prophylactic treatment of lymph nodes in intermediate and high-risk patients, however it is still accruing at this time. While we await the results of RTOG 0924, our finding that 56% of patients had evidence of nodal involvement on ^{68}Ga-PSMA-11 imaging suggests that the risk of occult nodal disease may be higher than estimated based on the Roach formula or other nomograms.

We must also emphasize that while ^{68}Ga-PSMA-11 PET-avid lymph nodes were interpreted as pathologically involved for the purposes of RT planning in this study, the sensitivity, specificity, positive, and negative predictive value of ^{68}Ga-PSMA-11 PET for nodal staging is still being investigated. The literature on ^{68}Ga-PSMA-11 PET imaging prior to radical prostatectomy and lymph node dissection suggests reasonable sensitivity (80%-90%), high specificity (up to 100%, though likely influenced by patient selection, with greater specificity in higher risk patients), high positive predictive value of 84%-100%, and negative predictive value of 80%-90%.[29-31] However, it must be noted that these studies are limited in the number of patients included (23-34) and the patient populations themselves are quite heterogeneous.

While there is no level 1 evidence for treating oligometastatic prostate cancer, prospective data suggests focal ablative RT without ADT is associated with high rates of local control and a meaningful median biochemical disease-free interval of almost 1 year, with very little toxicity.[32] When used in carefully selected patients, this approach may substantially delay initiation of ADT,[33] with improvement in quality of life over that period.

Changes to RT treatment plans as mentioned above are dependent on imaging modalities that enable identification of bone metastases as well as involved lymph nodes, which are often normal by size criteria. In recent years there has been significant interest in using choline-based PET,[34] ^{18}F-fluciclovine PET (anti-3[^{18}F]FACBC),[35] and now ^{68}Ga-PSMA-11 PET-based imaging to improve localization of prostate cancer metastases.

While this study characterizes changes to RT plans based on ^{68}Ga-PSMA-11 PET imaging and is prospectively monitoring treatment outcomes, follow-up at this time is insufficient to evaluate clinically relevant endpoints such as PSA nadir or freedom from biochemical recurrence, much less prostate cancer specific survival. Additionally, we did not generate blinded pre- ^{68}Ga-PSMA-11 PET RT plans for comparison, but rather compared post-^{68}Ga-PSMA-11 PET RT plans to the RTOG consensus guidelines. Another limitation is that patients had variable staging workup prior to ^{68}Ga-PSMA-11 PET scan, with 87% undergoing a CT/MRI and/or bone scan prior to PET imaging. Finally, despite high specificity in lymph nodes, the sensitivity of ^{68}Ga-PSMA-11 PET is often reported in the range of 60%-70%,[9] necessitating caution when interpreting negative ^{68}Ga-PSMA-11 PET scans; detection of small lymph node metastases is still limited due to radiotracer accumulation and spatial resolution.

CONCLUSION

This study adds to literature evaluating changes to RT plans based on staging ^{68}Ga-PSMA-11 PET scans, demonstrating major or minor changes to RT plans in over half of patients through identification of new nodal or osseous metastatic disease. Further prospective investigation is needed to assess the impact of RT changes on patient outcomes, as well as acute and late toxicity related to intensified treatment.

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EDITORIAL COMMENT

Hope et al.[1] report on the impact of pretreatment ^{68}Ga-PSMA-PET/CT or PET/MRI in the management of 45 patients with high-risk prostate cancer (PCA). Results of PSMA-PET/CTs were compared to the findings of CT scans and skeletal scintigraphy. Based on their data, PSMA-PET imaging resulted in changes of radiation therapy (RT) dose and volumes in 47% of the patients due to newly diagnosed N1/M1a disease. RT changes resulted in the extension of clinical target volume (CTV) covering the small pelvis and even the retroperitoneum or a RT boost to avid lymph nodes. Noteworthy, 82% of the patients received long-term androgen deprivation therapy (ADT). No data for oncological or functional outcome are given and no data with regard to the treatment associated toxicity of extended RT protocols are reported.

The data transported by the paper are important for several reasons. Firstly, we know from previous studies that whole body MRI detects systemic or extrapelvic metastases in 20%-30% high-risk PCA.[2] Secondly, previous prospective evaluations did not show any benefit of diffusion weighted MRI or ^{11}C-choline-PET/CT to improve the preoperative identification of lymph node metastases.[3] Although Hope et al[1] add some more data to the literature with regard to the clinical usefulness of ^{68}Ga-PSMA-PET/CT in staging and subsequent therapy of men with high-risk PCA, a variety of issues have to be considered carefully prior to the implementation of new imaging modalities in clinical routine.

Although not described in detail, the patient cohort included in this report is quite heterogenous: 31 (69%) patients underwent RT for curative intent whereas 14 (31%) patients underwent radical prostatectomy (RP) followed by adjuvant RT. It needs to be emphasized that all patients underwent PSMA-PET/CT prior to RT or RP but not prior to adjuvant RT. Those patients treated in an adjuvant approach need to be analyzed separately: Based on the data given, we even do not know if the lymph nodes depicted on the preoperative PSMA-PET/CT scans have been dissected at time of RP. In this scenario, preoperative PSMA-PET/CT would not have given clinically useful additional information with regard to the presence of locoregional lymph nodes metastases (LNM) as compared to a properly performed extended pelvic lymphadenectomy.[4,5] It would have been quite interesting to receive some more information about those patients such as the number of retrieved lymph nodes, number of positive lymph nodes, PSA at time of adjuvant RT. In addition, the level of evidence with regard to adjuvant RT of the whole pelvis is rather low and current guidelines do recommend this approach only in a highly selected group of patients[4] reflecting that the natural history of pN+ patients with 1-2 positive lymph nodes results in a 5- and 10-year CSS rate of 94% and 72%.[6]

When it comes to the identification of pelvic lymph node or systemic metastases, additional metastatic foci were identified in 21 (47%) men indicating a clinically important diagnostic benefit of ^{68}Ga-PSMA-PET/CT.

The authors used the Roach formula to predict lymph node involvement and to include pelvic lymph nodes in the CTV. It has to be remembered that the Roach formula was calculated based on the Partin nomograms which rely on a limited pelvic lymphadenectomy only.[7] The Roach formula will overpredict the risk of lymph involvement in clinically organ confined disease and it might underpredict the risk of LNM in high risk disease.[8] There are numerous nomograms which have been proven to result in a higher reliability[9] and which should be used in daily routine.

The diagnostic accuracy of pretherapeutic PSMA-PET/CTs is still discussed controversially even in the studies cited by Hope et al[1] Cantiello et al[10] used ^{64}copper which is not the standard radiotracer of choice. Herlemann et al[11] comprised only 34 patients of whom only 20 did undergo primary RP and, Gorin et al[12] used ^{18}fluoride so that already these 3 studies are heterogenous. In a recent systematic meta-analysis of 298 patients pretherapeutic PSMA-PET/CT demonstrated a modest sensitivity and specificity to identify LNM.[13]

Furthermore, therapeutic implications of ^{68}Ga-PSMA-PET/CT are unclear when it comes to RT since the standard of care in high-risk PCA would be RT plus ADT.[4] If there is any oncological benefit when pelvic or even extrapelvic lesions are included in the CTV is completely unknown. Even the subgroup analysis of 173 pN1 patients treated in the RTOG 85-31 study reported on a significantly improved outcome in terms of 5 year (54% vs 33%, $P < .0001$) and 9 year (10% vs 4%, $P < .0001$) if RT was combined with ADT as compared to RT alone.[14] The extension of RT to oligometastatic foci in the retroperitoneum or skeletal system represents an experimental and individual therapy.

In summary, the data presented by Hope et al[1] add clinically important data to the literature concerning the role of modern imaging techniques to detect locoregional or systemic metastases in newly diagnosed high-risk PCA. A high percentage of patients will undergo treatment changes based on a PSMA-PET/CT. However, due to the lack of large patient cohorts and prospective clinical trials as well as the known pitfalls of PSMA-PET/CT it still does not represent a routine imaging study and we still need to do our homework to initiating cooperative research projects which shed some light on the pros and cons of modern, likely sensitive but also expensive and restrictive imaging studies.

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AUTHOR REPLY

We greatly appreciate the thoughtful comments in regards to our manuscript, which highlight a number of important issues about the use of PSMA-PET. It should be noted at the outset that PSMA-PET should not be considered a standard imaging modality. In the United States, PSMA-PET is investigational and is not FDA approved. Although PSMA-PET may be considered standard of care in a few countries, its use in the United States is limited to clinical trials. Nonetheless, the prevalence of PSMA-PET is likely to increase in the next few years, as we should be close to approval of this agent in the coming year. Our hope is that the preliminary data presented in our manuscript may help guide the use of PSMA-PET imaging.

PSMA-PET scans were available to patients meeting certain high-risk criteria prior to definitive treatment (as outlined in the manuscript) or in the setting of biochemical recurrence. We do not routinely obtain repeat PSMA-PET scans following radical prostatectomy (RP) prior to adjuvant radiation; unfortunately we are not able to verify if all PSMA-avid lymph nodes were removed at the time of lymph node dissection (LND) in our cohort. However, from our data we can tell that patients with PSMA-avid lymph nodes had more extensive LNDs (median 31 vs 17 lymph nodes removed, $p = 0.009$).

Table 1 demonstrates the cohort of patients who underwent prostatectomy prior to salvage RT. Four of the patients had negative PSMA-PET scans and negative nodes at surgery. In our cohort, median PSA after RP was 0.14 ng/mL (interquartile range 0.09-0.43). The estimated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in this cohort was 63%, 83%, 80%, and 56% respectively. Other institutional series with histopathologic correlates have estimated higher sensitivity and NPV[1-3], though lower sensitivity has also been reported.[4] One reason for the difference between our small cohort and the literature is that there is a bias in our study, as patients with PSMA-avid nodes that were not removed at time of

Table 1. Nodal status on PSMA-PET, postop PSA, and pathologic characteristics of the 14 patients who underwent radical prostatectomy after PSMA-PET scan

Patient Number	Nodal Status Based on PSMA-PET (Number of Nodes Identified)	Pathologic Nodal Status	Number of Pathologically Involved Lymph Nodes	Number of Lymph Nodes Removed	Max Dimension of Pathologically Involved Nodes (NA if pN0)	Postop PSA
1	–	+	3	21	9 mm	0.15
2	–	–	0	18	NA	0.04
3	–	+	1	27	4 mm	0.09
4	+ (2)	+	2	39	10 mm	0.16
5	–	–	0	11	NA	0.77
6	+ (4)	+	5	28	7 mm	0.50
7	–	–	0	14	NA	0.08
8	–	–	0	10	NA	0.04
9	–	+	5	29	6 mm	0.13
10	–	–	0	6	NA	0.11
11	–	+	2	17	6 mm	0.09
12	+ (2)	+	3	31	18 mm	0.41
13	+ (4)	–	0	34	NA	1.84
14	+ (2)	+	2	22	3 mm	0.40

RP were referred for RT, thereby increasing the number of false negative lesions in our cohort.

It is important to note that in the 3 patients with pathologic lymph node involvement not identified on PSMA-PET, involved lymph nodes measured 7 mm or less (Table 1). This suggests, there is a limit to the resolution of PSMA-PET imaging, which may be technique dependent; prior data has suggested that the average size of missed lymph nodes on PSMA-PET may be smaller than what was seen in our cohort at <3 mm.[1] Further pathologic findings are in Table 1.

We also acknowledge that the Roach formula has limitations, and was validated at a time when surgical and diagnostic techniques were very different.[5,6] We include this method of estimating lymph node involvement solely to help readers understand what guides the decision to treat pelvic lymph nodes at our institution; this is not universal practice, and remains the topic of great debate in the field of radiation oncology as we await the results of RTOG 0924.

We agree that further outcomes-driven data is required to evaluate the impact of PSMA-PET imaging. Subsequent research should be prospective, and in the context of multi-institutional cooperative groups, with adequate power and follow-up to detect clinically meaningful outcomes. These randomized trials will be imperative to perform, but difficult to accrue to once PSMA-based radiotracers become widely available.

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