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Impact of Ga-68 PSMA-11 PET on Management in Patients with Biochemically Recurrent Prostate Cancer

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ABSTRACT

Purpose: The purpose of this prospective study was to estimate the effect of ^{68}Ga-prostate specific membrane antigen (PSMA)-11 PET on intended management of patients with biochemically recurrent prostate cancer.

Methods: Pre- and post-imaging surveys were filled out by referring providers in patients with biochemical recurrence who were imaged using ^{68}Ga-PSMA-11 PET. Inclusion criteria for this study required a PSA doubling time of less than 12 months after initial treatment (NCT02611882). Of the 150 consecutive patients imaged, 126 surveys were completed (84% response rate). Responses were categorized as major, minor, no change or unknown change.

Results: 103 (82%) of patients had disease detected on ^{68}Ga-PSMA-11 PET. Based on survey results, there were 67 (53.2%) patients with major changes, and 8 (6.4%) patients with minor changes in management. The proportion of cases resulting in a change in management did not significantly differ by baseline PSA level. In patients with PSA levels below 0.2 ng/dL, 7 of 12 patients had disease detected on PSMA PET scan, five of whom had a major change in management.

Conclusion: ^{68}Ga-PSMA-11 PET resulted in a major change in management in 53% of patients with biochemical recurrence. Further studies are warranted to investigate whether PSMA-based management strategies result in improved outcomes for patients.

INTRODUCTION

Up to 30% of prostate cancer (PCa) patients who are treated with definitive local therapy, such as radical prostatectomy (RP) or radiation therapy (RT), have evidence of recurrent or residual prostate cancer (*1-3*). Recurrence is generally manifested as an increase in prostate-specific antigen (PSA), termed biochemical recurrence (BCR). BCR frequently occurs months to years before there is evidence of disease on standard imaging, thereby limiting the selection of treatment options, since the site of recurrence is not evident. Conventional imaging for staging PCa includes computed tomography, magnetic resonance imaging and technetium-labeled phosphate bone scintigraphy ("bone scans"), all of which have a low sensitivity for recurrent disease, particularly at low PSA levels (*4,5*).

A number of molecular imaging radiotracers, most notably choline derivatives, have been used to increase detection rates in BCR patients, but they have limited sensitivity and specificity at PSA levels less than 1.0 ng/dL (*6,7*). Prostate Specific Membrane Antigen (PSMA) is overexpressed on prostate cancer cells and its expression appears to increase with aggressiveness as marked by higher Gleason score and higher rates of morbidity (*8,9*). Positron Emission Tomography (PET) targeting PSMA has demonstrated a much higher sensitivity compared to conventional imaging (*10,11*). In particular, the utility of ^{68}Ga-PSMA-11, also know as DKFZ-11 or HBED-CC PSMA, has been extensively reported over the past three years in PCa patients with localized disease or BCR (*11-14*).

One prospective and two retrospective studies have been performed evaluating the effect of ^{68}Ga-PSMA-11 PET on intended management (*15-17*). The

aim of this study was to determine the effect of ^{68}Ga-PSMA-11 PET on the intended management in PCa patients with BCR in a prospective clinical setting. Change in management is important in order to support eventual acceptance by referring clinicians and coverage by insurance companies.

MATERIALS AND METHODS

This study was approved by the local institution review board (IRB), and informed written consent was obtained from all subjects. An Investigational New Drug application was approved by the Food and Drug Administration (FDA) for this study. From December of 2015 to October of 2016, 225 patients were enrolled in a prospective study evaluating the use of ^{68}Ga-PSMA-11 PET in the staging of patients with prostate cancer (NCT02611882). The study included three cohorts: 1) patients prior to definitive therapy, 2) patients with BCR following definitive local therapy, and 3) patients with castrate resistant prostate cancer. This report focuses on the 150 patients evaluated for biochemical recurrence. Patient characteristics are provided in Table 1. Eligible patients had to have undergone definitive local therapy with curative intent, and subsequently found to have BCR. Inclusion criteria required a PSA doubling time less than 12 months. Patients were not required to have negative conventional imaging.

^{68}Ga-PSMA-11 synthesis and injection

^{68}Ga-PSMA-11 was synthesized as previously reported using a ^{68}Ge/^{68}Ga generator and a manual synthesis module supplied by Isotope Technologies

Garching (ITG, Germany) (*18*). Each synthesis was performed under good manufacturing practices and quality control was performed for purity, pyrogenicity and sterility. Patients were injected with 199.8±48.1 MBq (5.4±1.3 mCi) of ^{68}Ga-PSMA-11, and imaging occurred 63±10 minutes after injection. 20 mg of furosemide was administered to 110 of the patients, given 14±11 minutes prior to the injection of the radionuclide in order to minimized the halo artifact caused by scatter over correction associated with the high renal and urinary activity (*19*).

Imaging Protocol

Imaging was performed on a PET/CT (Discovery VCT, GE Healthcare, Waukesha, WI) or PET/MRI (3.0T time-of-flight Signa PET/MRI, GE Healthcare, Waukesha, WI), based on referring clinician preference. For PET/CT, we imaged from pelvis to vertex, using a 5 minute acquisition for the first three bed positions (up to the mid abdomen) and subsequent 3 minute acquisitions to the vertex. Iodinated contrast was administered to all patients and a post-contrast diagnostic CT was acquired and used for attenuation correction (mA = 240, kV = 120, slice thickness = 2 mm). PET data sets were reconstructed using iterative reconstruction using four iterations and 14 subsets, and a matrix size of 168 × 168. The PET transaxial field of view was 620 mm, and axial slices were reconstructed at 5.0 mm in thickness.

For PET/MRI, we imaged a pelvis and abdomen bed position using an 8-10 minute acquisition at both bed positions. PET data sets were reconstructed using time-of-flight, OSEM using two iterations and 28 subsets, and a matrix size of 256 ×

256. The PET transaxial and z-axis field of view was 600 and 250 mm, and axial slices were reconstructed at 2.8 mm in thickness. In the pelvis bed position we acquired a dynamic contrast enhanced sequence (DISCO) (*20*) after the administration of gadolinium contrast, a small field of view fast spin echo T2 weighted sequence (sFOV T2), diffusion weighted imaging (b=0 and b=500), and a post-gadolinium delayed axial T1 spoiled gradient echo (LAVA-FLEX). In the abdomen bed position the same sequences were acquired except for DISCO. For the whole body acquisition, PET data were acquired for three minutes at each bed position with axial LAVA-FLEX and variable refocusing flip angle single shot fast spin echo (vrfSSFSE) sequences in the coronal and axial plane (*21*). Attenuation correction was performed using a standard two-point Dixon acquisition converted into an attenuation map as previously described (*22*).

Image Analysis

All ^{68}Ga-PSMA-11 PET studies were interpreted and reported by a nuclear medicine physician and a radiologist blinded to the pre- and post-imaging treatment decision of treating clinician. All PET images and cross sectional images were available at time of review. PET data was interpreted using an Advantage Workstation (version 5.0; GE Healthcare). Lesions were characterized as positive if they demonstrated uptake above adjacent background, and the uptake could not be attributed to physiologic biodistribution (e.g. urinary activity). Lesion location was categorized based on imaging report by location as prostate bed, pelvic lymph

nodes, extra-pelvic retroperitoneal nodes, other lymph nodes, osseous lesions and visceral lesions.

Surveys and analysis

The ordering team was requested to fill out a pre-imaging intended treatment form and a post-imaging intended treatment form, using similar methodology reported in different tumor types (*23*). On both surveys, clinicians were asked to categorize their intended management as: surgery, radiation therapy, androgen deprivation therapy, second-generation androgen receptor targeted therapy (abiraterone/enzalutamide), active surveillance, biopsy, modify existing therapy, chemotherapy, radionuclide therapy (Ra-223), or other. Additionally they were asked to categorize the location of the patient's disease as: unknown, prostate bed, pelvic nodes, extrapelvic nodes, soft tissue, or bone. The pre-imaging survey also asked what test would be ordered if the ^{68}Ga-PSMA-11 PET was not available including: MRI, CT, FDG/Choline PET, bone scan, Prostascint, and image guided biopsy. On the post-imaging survey, the clinicians were asked if ordering a test was prevented, and to list which test was not ordered because of the ^{68}Ga-PSMA-11 PET.

Change in management was based upon survey results and categorized as major, minor, no change or unknown based on a predetermined categorization schema (see supplemental material). For patients where clinicians checked "other" without clarifying the intended management and therefor there was an unknown change in management, individual patient charts were reviewed by a genitourinary medical oncologist (R.A.) not involved in the care of the patient, and the patients

were recategorized if chart review made clear the change intended or implemented management. Biopsy was considered a form of active surveillance for our analysis. A chi-squared test was used to compare the rate of major changes in patients treated with RP versus RT or RT and RP.

RESULTS

A total of 150 patients with biochemical recurrence were enrolled in this study, and both pre-imaging and post-imaging intended treatment surveys were received for 126 patients (survey response rate of 84%) (Table 1). The average PSA at time of imaging was 5.9±10.3 ng/dL, with 49 patients having a PSA less than 2.0 at time of imaging. In patients who were previously treated with RP, the average PSA was 2.7±4.0 ng/dL; in those treated previously with RT, the average PSA was 9.9±14.6 ng/dL; in those treated previously with both RP and RT the average PSA was 3.9±6.9 ng/dL.

On the pre-imaging survey, the most common imaging study that would have been ordered in place of a PSMA-11 PET was a technetium-labeled phosphate bone scan in 70 (56%) of the patients (Table 2). On post-imaging surveys, it was reported that studies were prevented from being ordered in 48 (38%) patients. The most common prevented study was a bone scan in 21 (17%) patients.

Imaging results

103 (82%) of the patients had disease detected on ^{68}Ga-PSMA-11 PET at time of imaging. ^{68}Ga-PSMA-11 PET had a detection rate above 50% at all PSA levels,

including patients with a PSA less than 0.2 ng/dL (Fig. 1). There was an inflection point at PSA values of 1.5 ng/dL or higher, where the positive scan rate was 93% or higher. Broken down by PSAdt, detection rates were 83% (24/29), 90% (27/30), 97% (33/34) and 88% (21/24) for PSAdt from 0-3 months, 3-6 months, 6-12 months and greater than 12 months. The two most common sites of disease on ^{68}Ga-PSMA-11 PET were the prostate bed and pelvic lymph nodes seen in 36% and 42% of patients respectively (Fig. 2).

Based on the survey results, ^{68}Ga-PSMA-11 PET decreased the percent of patients with unknown sites of disease from 52% to 20% (Fig. 3). There was not perfect concordance between the reported sites of disease based on the clinical interpretation of the imaging study and the physician's description of where the disease was thought to be. For example, based on survey results, clinicians reported pelvic nodes in 30% of patients after ^{68}Ga-PSMA-11 PET, but the clinical reports described pelvic nodes in 42% of patients (Figs. 2 and 3).

Intended management results

Based on survey results, there were 67 patients (53.2%) with major changes and 8 patients (6.4%) with minor changes in intended treatments (Table 3). The most common treatment change was a conversion to focal (targeted) treatment from systemic therapy, including 40 (31.7%) patients who received radiation treatment when a systemic therapy or active surveillance was initially planned (Fig. 4). 15 patients initially had an unknown change in management ("other" was

selected on the survey form), which were converted to 1 major, 1 minor, 6 no changes and 7 unknowns after chart review.

The percent of major changes in management were relatively consistent across PSA levels at presentation. The percent of patients with major changes in intended management with PSA levels of 0 - 0.2, 0.2 - 1.0, 1.0 - 2.0, 2.0 - 5.0, and greater than 5.0 ng/dL were 42%, 40%, 65%, 57% and 56%, respectively. The percent of patients with major changes in management did depend on prior treatment with patients previously treated with RP having a lower rate than those treated with RT or RP and RT (Table 4: RP vs RT, p=0.018; RP versus RP and RT, p=0.001; Table 4). Additionally, the percent of patients with radiation therapy selected as the treatment on the pre-imaging survey was higher in patients previously treated with RP compared to patients previously treated with RT (Table 4).

DISCUSSION

^{68}Ga-PSMA-11 PET scanning resulted in a major change in management in 53% of PCa patients with BCR following definitive local therapy. A change from planned systemic therapy to focal targeted therapy such as radiation therapy was the most common change in management, occurring in 32% of patients. These results indicate that ^{68}Ga-PSMA-11 PET plays an important role in the appropriate staging and management of men with PCa who fail initial therapy. The results of this approach are currently being validated in a prospective multicenter trial.

Our results are consistent with prior reports on PSMA impact on clinical management. Albisinni et al retrospectively reviewed 131 patients who underwent PSMA PET and demonstrated a change in management in 75% of patients (*15*). Morigi et al prospectively compared fluorocholine and ^{68}Ga-PSMA-11, performed a retrospective survey of treating clinicians about how PSMA PET changed management, and demonstrated a change in management in 63% of cases (*17*). Sterzing et al retrospectively reviewed patients imaged prior to radiation treatment, evaluated the change on radiation treatment, and demonstrated a change in management in 51% of patients (*16*).

Our results showed that there was a lower level of change in management in patients post-RP compared to those treated with RT previously. This is likely because the standard therapy for RP patients is prostate-bed only RT, which is supported by the finding that 61% of post-RP patients had radiation selected as the pre-imaging treatment selection. As we did not evaluate changes in radiation field, in order to demonstrate a major change in management in the post-RP population, disease outside of the prostate bed that could not be targeted by radiation had to be demonstrated. This is consistent with the results of Sterzing, who showed a high change in management in patients undergoing radiation (51%), but only 7% of their patients were converted from radiation to a different treatment modality (*16*).

The detection rate as a function of PSA level in this study was in agreement with previously published data (*11,14*). However, of twelve patients imaged with a PSA less than 0.2 ng/dL, metastatic disease was detected in 7, which suggests that ^{68}Ga-PSMA-11 PET may play a role in patients with a PSA less than 0.2 ng/dL. As

confirmed in head-to-head comparisons, detection sensitivities in patients with ^{68}Ga-PSMA-11 are significantly higher than shown with fluorocholine (*17,24*).

One major concern with the use of ^{68}Ga-PSMA-11 currently is that there is no understanding of how to use the added information provided by scanning to inform clinical decisions. A large percentage of patients on this study had their therapy converted to targeted radiation treatment for oligometastatic disease seen on ^{68}Ga-PSMA-11. However, a major limitation of this study is that it was not designed to evaluate whether this change in management resulted in improved outcomes. The potential benefit derived from improved imaging will require prospective testing that evaluates overall survival or progression free survival as endpoints. Although randomized prospective trials will not be required for FDA approval, it will be critical in obtaining insurance coverage in the future.

A second limitation of this study is that it did not prospectively collect information regarding changes in the planned radiation field for patients already planning on undergoing radiation. A potential major benefit of PSMA PET is to inform radiation fields to include all sites of disease (*25*). Sterzing et al showed that 44% (25 of 57) of patients undergoing radiation treatment had a change in the radiation field that was used (*16*), suggesting that our results underestimated the change in management using PSMA PET.

A third limitation is that not all patients received furosemide, and therefore there may be a limited detection rate for local recurrence in the 40 patients imaged without furosemide. A fourth limitation is that the definition of biochemical recurrence was based on PSA doubling time, and not more well accepted criteria; a

follow-up study is being performed using standard definitions of biochemical recurrence. Finally, patients included in this study had varying conventional imaging studies performed and therefore may effect what the pre-imaging intended management was. In addition to varying pre-imaging studies, patients also received either PET/MRI or PET/CTs, which provide different cross sectional imaging correlates that may have affected the individual reads.

Finally, one of the inherent limitations of an analysis of change in intended management is the subjectivity in interpretation of scan results by different providers and the bias that clinicians may have towards one particular treatment modality. Nevertheless, the current study does capture the full spectrum of clinical specialties that order PSMA PET scans, namely urologists, radiation oncologists, and medical oncologists, and accurately reflects real-world clinical practice.

CONCLUSION

Existing treatment recommendations are based on staging using conventional imaging. ^{68}Ga-PSMA-11 PET has a high detection rate that resulted in a major change in management in 53% of patients with biochemical recurrence in our study. Further work should be performed to determine if these changes in management result in improved outcome for patients.

DISCLOSURE

TA Hope receives grant support from GE Healthcare. The authors have no other relevant affiliations or financial involvement with any organization or entity with a

financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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FIGURES

Figure 1: Percent of patients with disease detected on ^{68}Ga-PSMA-11 PET broken down by prostate-specific antigen (PSA) level at time of imaging. Numbers in brackets are patients with positive disease in each group. The percentage is the percent of patients in each group with positive disease.

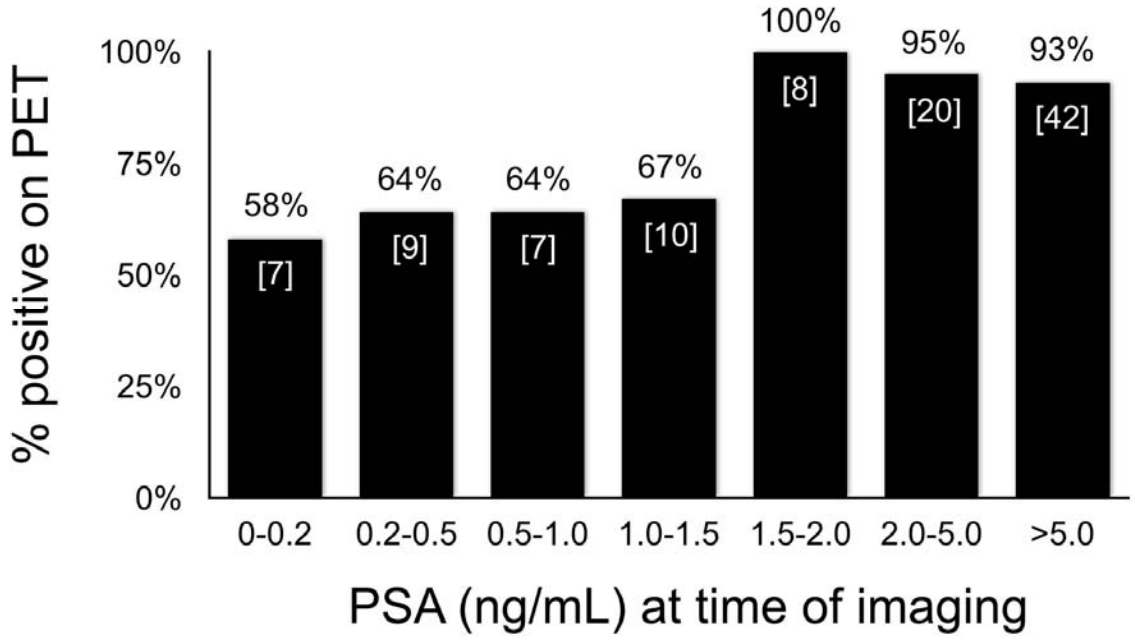


Figure 2: Distribution of sites of disease seen on ^{68}Ga-PSMA-11 PET as a percentage of total patients. The most common sites of disease were the prostate bed and pelvic lymph nodes (LN). RP = extra-pelvic retroperitoneal.

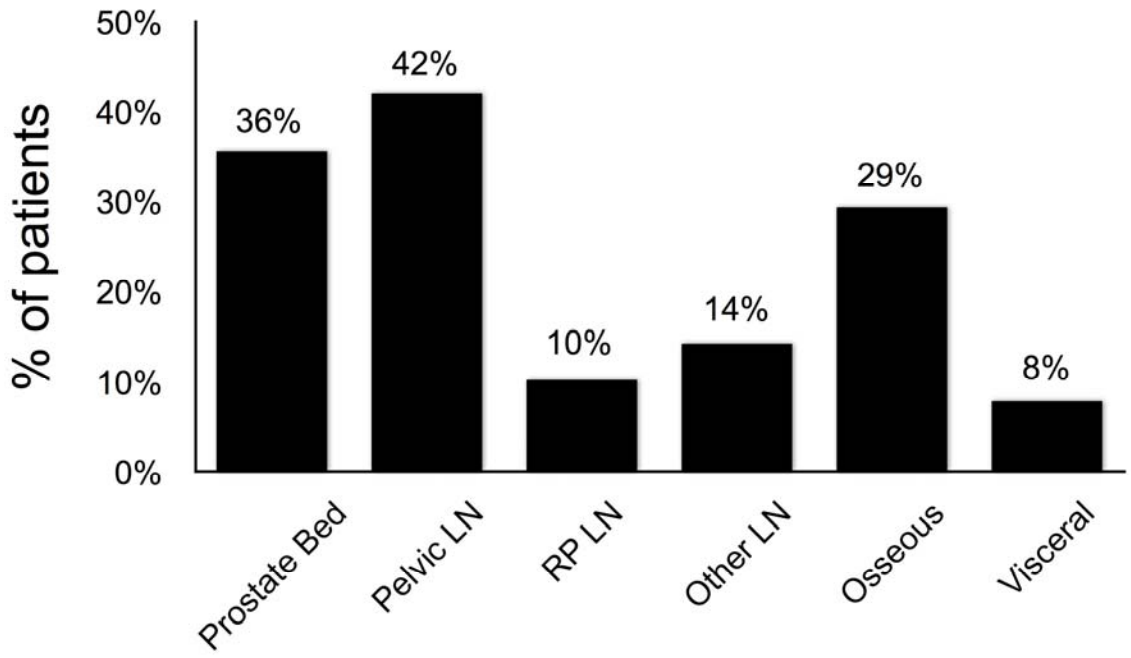


Figure 3: Change in clinician's description of where patient's disease is before and after imaging. There was a reduction in the percent of patients where the clinicians did not know where the disease was from 52% to 20%. ST = soft tissues.

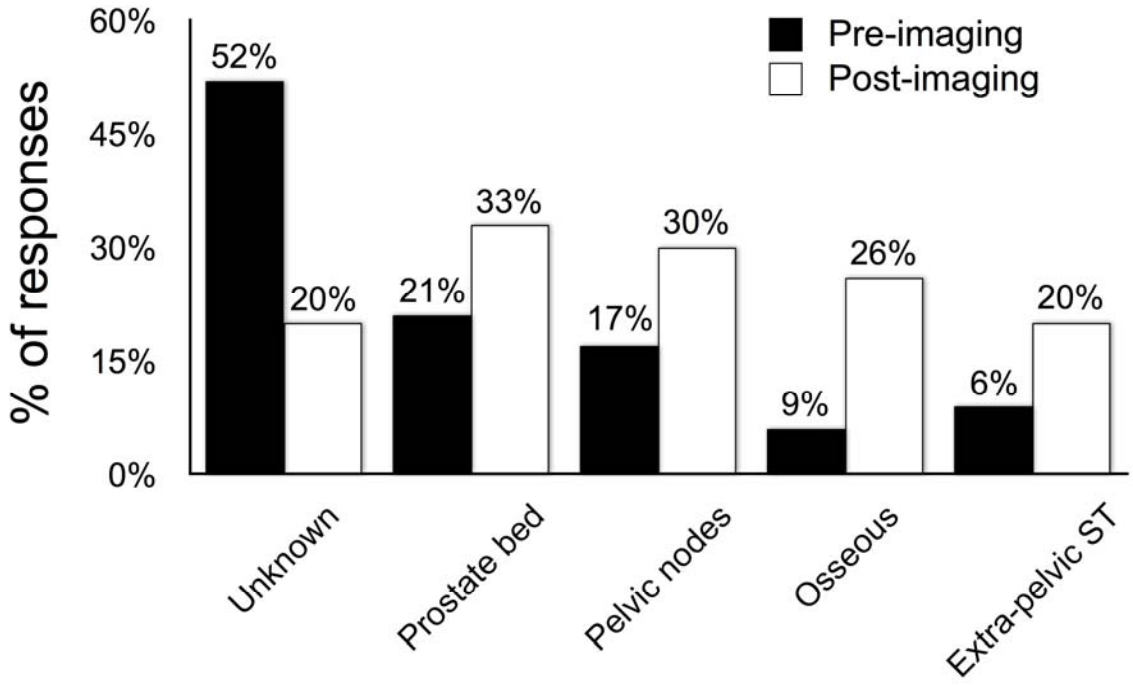
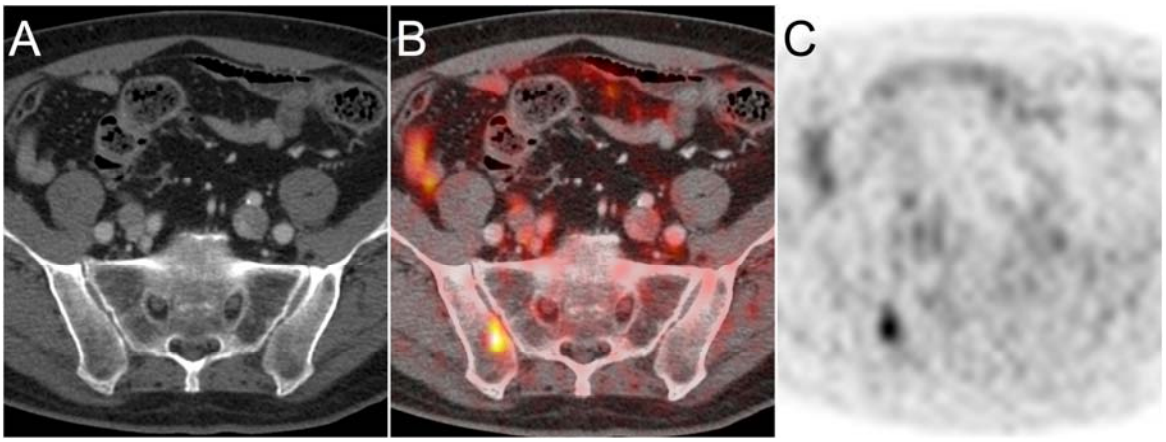


Figure 4: Example of a major change in management. 69-year-old man with biochemically recurrent prostate cancer, who was originally treated with a radical prostatectomy in 2014, then with salvage radiation therapy in 2015. He presented for ^{68}Ga-PSMA-11 PET with a PSA of 0.059. Imaging demonstrated a single PSMA positive lesion in the right iliac bone (C) with no correlate seen on CT (A, fused image B). The patient was converted from active surveillance to radiation combined with ADT therapy.



TABLES

Table 1: Patient characteristics. * Five patients did not have Gleason score at initial biopsy available. ADT = androgen deprivation therapy. PSA = prostate-specific antigen.

Characteristic	
Age (years, mean)	69.0±6.9
Imaging modality	*Number (percent)*
PET/CT	63 (50)
PET/MRI	63 (50)
Prior treatment	*Number (percent)*
Radical prostatectomy	43 (34)
Radiation therapy	41 (33)
Both prostatectomy and radiation	33 (26)
Other treatments	9 (7)
Prior ADT	41 (32)
Currently on ADT	8 (6)
Time since last treatment (years)	5.3±5.4
Prior conventional imaging	*Number (percent)*
CT abdomen/pelvis	57 (45)
Bone scan or NaF PET	55 (44)
MRI pelvis	22 (17)
Any prior imaging	80 (73)
Laboratory values	*Average (standard deviation)*
PSA (ng/dL)	5.9±10.3
PSA doubling time (months)	8.7±11.0
Gleason score at diagnosis*	*Number (percent)*
3+3	19 (16)
3+4	27 (22)
4+3	34 (28)
4+4	17 (14)
4+5	17 (14)
5+4	4 (3)
5+5	3 (2)

Table 2: Imaging studies that would have been ordered in place of ^{68}Ga-PSMA-11 PET on pre-imaging surveys, and studies that were prevented from being ordered on post-imaging surveys.

Imaging study	Study that would have been ordered (pre)	Study prevented from being performed (post)
Bone scan	70 (56%)	21 (17%)
CT	44 (35)	17 (13)
MRI	36 (29)	3 (2)
PET (FDG/choline)	16 (13)	13 (10)
Image guided biopsy	5 (4)	8 (6)
Prostascint	1 (1)	0 (0)

Table 3: Changes in intended management after ^{68}Ga-PSMA-11 PET. RT = radiation therapy. AS = active surveillance, ADT = androgen deprivation therapy, RLT = radioligand therapy

Treatment change	n	%
Major changes	67	53.2%
Conversion to targeted treatment	*40*	*31.7*
ADT > RT	12	9.5
AS > RT	10	7.9
ADT > RT+ADT	6	4.8
AS > RT+ADT	5	4.0
Biopsy > RT	2	1.6
Biopsy > RT+ADT	2	1.6
Biopsy > cryoablation	1	0.8
RT+ADT > surgery	1	0.8
Sipuleucel-T > RT	1	0.8
Conversion to systemic treatment	*12*	*9.5*
AS > ADT	5	4.0
RT+ADT > ADT monotherapy	2	1.6
RT > ADT	2	1.6
AS > abiraterone	1	0.8
Surgery > ADT	1	0.8
Biopsy > ADT	1	0.8
Conversion to AS	*10*	*7.9*
RT+ADT > AS	4	3.2
ADT > AS	4	3.2
RT > AS	2	1.6
Miscellaneous	*5*	*4.0*
Surgery > RT+ADT	2	1.6
RT+ADT > cryoablation	1	0.8
RT+ADT > RT+ADT+chemotherapy	1	0.8
ADT > PSMA RLT	1	0.8
Minor changes	8	6.4%
RT > RT+ADT	5	4.0
RT+ADT > RT	3	2.4

Table 4: Breakdown of patients with major changes in management by prior treatment and broken down by PSA level. Patients with prior radical prostatectomy (RP) had a lower rate of major change in management compared to those previously treated with RT (radiation therapy) or RT and RP. PSA = prostate specific antigen.

	Prior treatment		
	RP	RT	RP and RT
Patients (n)	43	41	33
PSA (ng/dL, SD)	2.7±4.0	9.9±14.6	3.9±6.9
Major change (n, %)	14 (33)	24 (59)	23 (70)
Number with RT as treatment option on pre-imaging survey (n, %)	26 (61)	10 (24)	5 (15)
PSA < 2 ng/dL			
Patients (n)	29	9	20
Major change (n, %)	9 (31)	6 (67)	14 (70)
PSA > 2 ng/dL			
Patients (n)	14	32	13
Major change (n, %)	5 (36)	18 (56)	9 (69)