Journal of Nuclear Medicine, published on July 26, 2017 as doi:10.2967/jnumed.117.192625

^{68}Ga-PSMA PET/CT impact on prostate cancer management

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Financial support for Dr Afaq was received from the UCLH NIHR BRC, UCL Experimental Cancer Medicine Centre and London North West Healthcare Charitable Fund. Heather Payne's work was supported by the UCLH/UCL Comprehensive Biomedical Research Centre.

Word count: 2918

Short running title (max 40 characters)
Management change after ^{68}Ga-PSMA PET/CT

ABSTRACT

Aim

To assess the impact of ^{68}Ga-Prostate Specific Membrane Antigen (PSMA) Positron Emission Tomography/ Computed Tomography (PET/CT) on management of prostate cancer in patients with biochemical recurrence (BCR).

Methods

Documented management plans were retrospectively reviewed before and after ^{68}Ga-PSMA PET/CT in 100 patients with BCR and change in plans recorded.

Results

Management changed after ^{68}Ga-PSMA PET/CT in 39 patients (39%). These occurred in 23/68 (33.8%) of patients with radical prostatectomy (RP) and 16/32 (50%) of patients previously treated with radical radiotherapy. Positive scan ($p < 0.001$) and higher Prostate Specific Antigen (PSA) ($p=0.024$) were associated with management changes. No significant association with management change was found with Gleason grade, stage, presence of metastatic disease, PSA velocity or doubling time.

Conclusion

^{68}Ga-PSMA PET/CT altered management in 39% of patients with BCR, and occurred more often in patients with radical radiotherapy treatment, a positive ^{68}Ga-PSMA scan and higher PSA level.

Key words: PSMA, PET/CT, prostate cancer, biochemical recurrence, management change

INTRODUCTION

Management of biochemical recurrence depends on the location and extent of disease (*1*). Nomograms can be used to distinguish local and distant relapse with good sensitivity but cannot localize disease and have a limited role in patient-specific therapy planning (*2*). Early disease detection may allow curative treatment to be offered.

^{68}Ga-PSMA PET/CT has been rapidly adopted into clinical use. However, few studies have evaluated the influence of ^{68}Ga-PSMA on management of patients with prostate cancer. It is important to evaluate impact on management change for acceptance of this technology by referring physicians for clinical implementation and also health care providers for reimbursement.

The purpose of this study was to evaluate the observed changes in management of patients with BCR after ^{68}Ga-PSMA PET/CT.

MATERIALS AND METHODS

Summary of study design

This study was approved by the local institutional review board and the need for written informed consent was waived. Consecutive patients at a large tertiary referral center (University College London Hospital) with Prostate Cancer and BCR and a recordable management plan were retrospectively identified who had ^{68}Ga-PSMA PET/CT during the period June 2015–February 2017.

Radiopharmaceutical and imaging protocol

The conjugate of the PSMA-specific pharmacophore Glu-NH-CONH-Lys (^{68}Ga-PSMA-HBED-CC) was synthesized using a similar method to that described by Eder et al (*3*).

^{68}Ga-PSMA was administered intravenously by bolus injection. Mean injected dose was 159 ±42 MBq (range 77-295 MBq). Variation in injected dose was due to the short half-life of the tracer.

Studies were performed in line with published guidelines with 60 min tracer uptake time prior to PET imaging and, acquisition of non-contrast CT vertex to mid thighs (*4*).

Image analysis

PET/CT images were reviewed on Advantage Workstations 4.4, (General Electric, USA). A nuclear medicine physician with over 15 years' experience in PET imaging recorded disease status (positive, where areas of uptake were greater than background and did not correspond to physiological uptake).
Locations of disease were recorded as within the prostate or prostatectomy bed, within pelvic lymph nodes or metastatic disease.

Validation criteria

PET positive findings could only be validated in the setting of salvage prostatectomy or where targeted or template biopsy was subsequently performed. Pathological validation was available in 11 cases (3 prostatectomy and 8 biopsy). Ten of these cases were concordant with ^{68}Ga-PSMA findings. In one patient, template prostate biopsy did not reveal tumour, but the patient continued to have a rise in Prostate Specific Antigen (PSA) suggesting the biopsy may not have identified disease. Avid lesions were considered positive for disease even if these had not been positive on any recent bone scan or 18F Choline PET/CT study.

Management changes

From electronic medical records, both the intended management plan prior to ^{68}Ga-PSMA PET/CT and the actual management following ^{68}Ga-PSMA PET/CT was recorded (Table 1 and 2). Management plans were reviewed with a Clinical Oncologist with >20 years of experience of management of prostate cancer.

PSA data and kinetics

Serum PSA data was recorded from the electronic medical notes for each patient, with the value and date of the sample taken closest to the scan as well as all values within a 12 month period prior to the scan. Any patient on hormone therapy at the time of the scan or in the 12 month period prior to scan was excluded from the PSA analysis. The PSA values were applied to the Memorial Sloan Kettering PSA Doubling Time tool (*5*).

Statistical analysis

For continuous variables, mean ± standard deviation was calculated. For categorical data, counts and percentage were calculated. Relationships between clinical parameters and management change were investigated by Fisher's exact test.

RESULTS

All patients

The study population comprised 100 patients, of whom 85 were not currently on hormone therapy or had been in the 12 months prior to scan. The median age of the patients was 67.95 ±7.38 years (range 4789 years). Original treatment was with RP in 68 (68%) and Radiotherapy in 32 (32%).

^{68}Ga-PSMA PET/CT was positive in 47 of the 100 patients (47%). In patients with positive scans, local disease (involving prostate/prostatectomy bed) was the most common (n=17). Pelvic nodal recurrence occurred in 9 patients and 21 patients had extra-pelvic metastatic disease.

Management change

Management changed after ^{68}Ga-PSMA PET/CT in 39 patients. Twenty-three of 68 (33.8%) patients in the RP group had a management change. Sixteen of 32 (50%) patients with Radiotherapy had a management change. Specific changes in management are shown in table 1 and those plans which remained unchanged in table 2.

Higher PSA was associated with management change (p=0.024). The highest proportion of cases where management changes occurred was when PSA was greater than 1ng/ml, as shown in Fig 1 . Although PSA kinetics did not show any significant association with management change, there was a trend of greater PSAv where a greater proportion of management changes occurred (p=0.086, Figure 2). Neither Gleason grade or tumour stage were associated with management change.

When a subgroup analysis was performed for RP and Radiotherapy, the significant relationship with higher PSA was not maintained. PSA kinetics, Gleason score, T stage or metastatic vs localised disease were all also not significantly associated with management change in the subgroups.

A positive ^{68}Ga-PSMA PET/CT study was associated with higher serum PSA (n<0.001), but no association was found with doubling time. However a higher velocity was observed in positive scans (p=0.03). The proportion of patients with a positive scan at different PSA, PSAdt and PSAv values is shown in figure 3.

Positive scans were associated with higher T stage (p=0.03), and although higher Gleason scores were found in patients with positive scans, this did not reach significance (p=0.13).

DISCUSSION

^{68}Ga-PSMA PET/CT led to a change in management plan in 39% of patients with BCR. Changes occurred more often with higher PSA values and in patients originally treated with radiotherapy compared to RP.

The proportion of changes in management is lower than some of the other few small published studies that have assessed management impact, but the proportion of positive studies in this cohort was also relatively lower.

In a retrospective study which included 42 patients with biochemical recurrence, scanned for radiotherapy planning, Sterzig et al reported a change in target volume or dose in 60.5% of patients, with 73.5% of scans being positive (*6*). Shakespeare found that an alteration in any aspect of management occurred in 53.7% of cases following ^{68}Ga-PSMA PET/CT, with a change to radiotherapy in 46.3% and a change to ADT in 33.3% (7).

Dewes et al observed that ^{68}Ga-PSMA PET/CT led to a change in staging classification in 53.3% of analyzed patients; revisions to the Radiotherapy concept occurred in 33.3% of patients, with relevant changes in the planning target volume (*8*).

Albissini et al (*9*) evaluated 131 patients, found positive scans in 75% of cases and an impact on management in 76%. Although PSA values were studied in relation to scan positivity, the authors did not differentiate cases into the key groups of prostatectomy and radiotherapy, as has been done in our study. Explanation of the differences may include the proportion of patients treated with radical prostatectomy in this study is greater and this may account for differences as patients with prostatectomy had a lower rate of management change. Also, the number of positive studies in our patient population was also lower which would influence the proportion of management changes. However, in a prospective study with predominant radical prostatectomy patients, Morigi et al found an impact on management after ^{68}Ga-PSMA PET/CT in 24/38 patients (63%) and 68% of scans were positive (*10*).

The proportion of positive PET/CT scans in our study (47%) is significantly lower than the rates described by Afshar-Oromieh [82.8%], (*11*) and by Ceci et al [74.2%] in recurrent PCa (*12*). Our population had a high number of patients with a very low PSA, in view of the large proportion of patients treated with prostatectomy (where PSA relapse will be at significantly lower PSA values), and the large numbers of patients referred with a low PSA level at our centre, which may account for differences.

A positive study was associated with a higher PSA, PSAvelocity and higher T stage. No significant association was demonstrated with PSAdt . There was a trend of higher Gleason score in patients with positive scans, but this did not reach significance. It is possible that the smaller proportion of the cohort in whom data were available to calculate kinetics may have led to a masking of the association with PSAdt. In a recent meta analysis, PSMA positivity was 64% for PSAdt > 6 mo and 92% for PSAdt <6 mo. High heterogeneity between subgroups was noted and in the long PSAdt subgroup, there was evidence of a small-study effect (*13*).

The relationship between PSA and a positive scan has also been investigated by others(*11, 14, 15*). The proportion of positive scans at each PSA threshold was lower in our study than in previous reports. For example, 15.8% of studies were positive at PSA 0.2- <=0.5, compared with 57.89% in the study by Eiber et al (*15*), and 50% in the study by Afshar-Oromeih et al (*11*), and 20% positive at PSA 1-2, compared with 93.06% (*15*) and 71.8% (*11*). Possible explanations may have been due to the exclusion of patients on ADT in our study, which would have reduced the PSA level at the time of a positive scan in other studies where this was not within the exclusion criteria. Patients may also

have been referred at earlier time points within the biochemical recurrence pathway, as ^{68}Ga-PSMA had become more routine practice for early investigation compared with older studies.

Limitations of our study include a retrospective design, which prevented the collection of data on how ^{68}Ga-PSMA PET/CT may have impacted on confidence in management decisions. Only a small number of patients had pathology as validation, in common with other studies on BCR. However, good sensitivity and specificity of ^{68}Ga-PSMA PET/CT in disease detection have already been described in multiple reports, and this is part of the rationale for its accelerated acceptance into clinical practice.

CONCLUSION

^{68}Ga-PSMA PET/CT altered management in 39% patients with BCR. Changes occurred more often in patients with radical radiotherapy treatment, a positive scan and higher PSA level. Gleason score, T stage, PSA kinetics and disease distribution were not associated with management change after ^{68}Ga-PSMA PET/CT.

ACKNOWLEDGEMENTS

Asim Afaq's work is part funded by the UCLH NIHR BRC, the UCL Experimental Cancer Medicine Centre, and the London North West Healthcare Charitable Fund. Heather Payne's work was supported by the UCLH/UCL Comprehensive Biomedical Research Centre.

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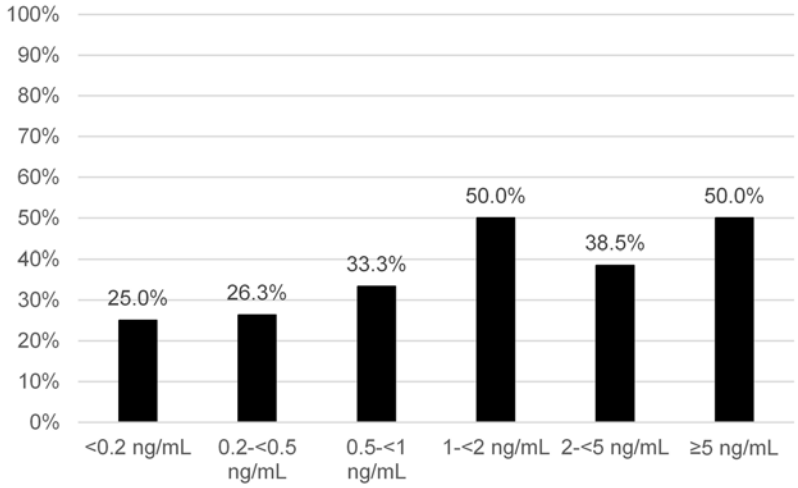

Figure 1. Management changes occuring at different PSA levels. A greater proportion of changes occurred with higher PSA levels and this was significant (p=0.024).

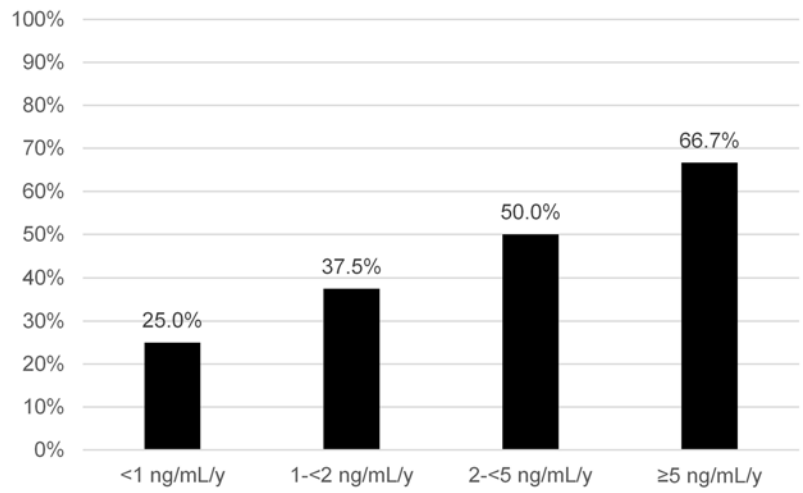

Figure 2. A higher PSA velocity was seen when a greater proportion of management changes occured but this did not reach statistical significance (p=0.086).

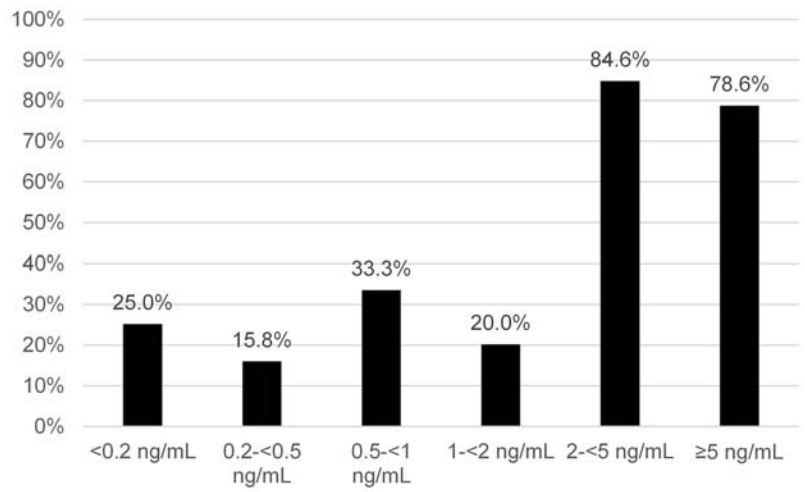

Figure 3a The proportion of positive 68Ga-PSMA PET/CT at different PSA levels. A significantly higher rate of positive scans was seen at high PSA levels ($p<0.001$).

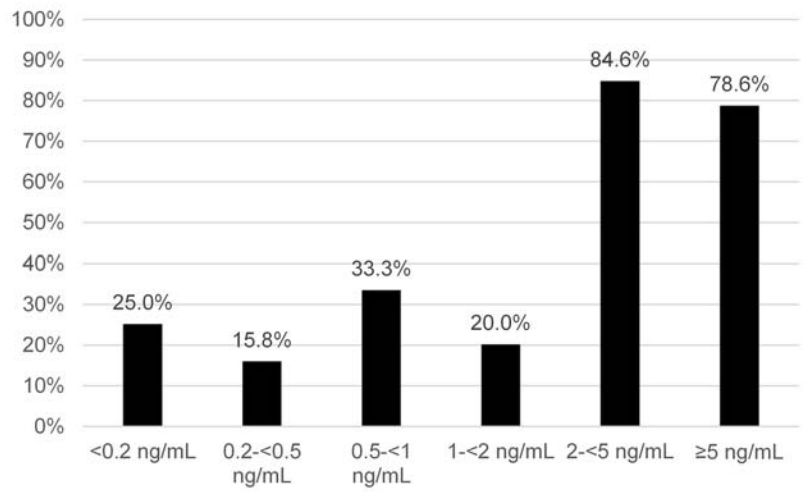

Figure 3b The proportion of positive 68Ga-PSMA PET/CT at different PSAdt. No significant association was shown (p=0.946)

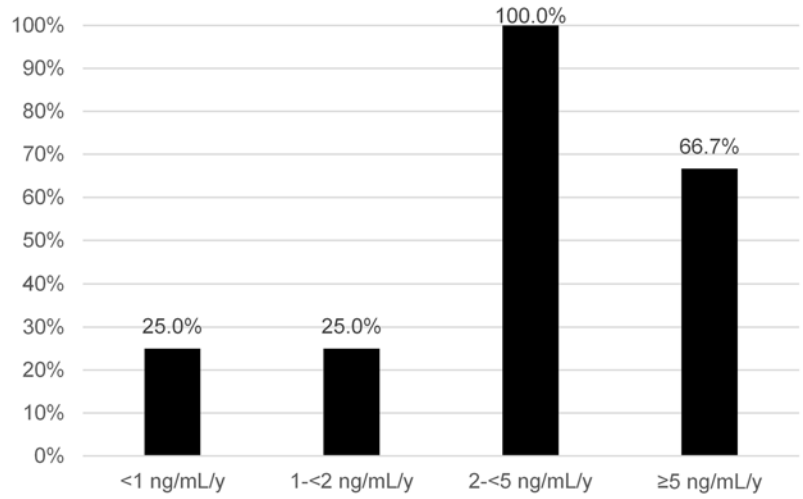

Figure 3c. The proportion of positive 68Ga-PSMA PET/CT at different PSAv. A significantly higher rate of positive scans was seen at high PSAv (p=0.033).

Table 1. Management plans before and after 68Ga-PSMA PET/CT where management was altered. Original categories of management plans are shown in the left hand column.

Initial management plan	Revised management plan (n=39)
PSA surveillance	Prostate/ bed radiotherapy (1)
	Prostate/ bed and pelvic lymph node radiotherapy (1)
	Hormone therapy (3)
	Focal therapy (1)
	Cyberknife (2)
	Follow up of avid site (7)
	Follow up of non avid site (2)
	Radical prostatectomy and extended lymph node dissection (1)
Prostatectomy	Hormone therapy (1)
Prostate/bed radiotherapy	PSA surveillance (1)
	Prostate/ bed and pelvic lymph node radiotherapy (2)
	Radiotherapy to oligometastatic disease (1)
	Hormone therapy (1)
	Follow up of non avid site (1)
	Chemotherapy (1)
HIFU	Prostatectomy (2)
Hormone therapy	Prostate bed radiotherapy (2)
	Prostate/ bed and pelvic lymph node radiotherapy (1)
	Radiotherapy to oligometastatic disease (2)
	Focal therapy (2)
	Targeted biopsy (1)
	Radical prostatectomy and extended lymph node dissection (1)
	Alteration to hormone therapy regimen or introduction of enzalutamide(2)

Table 2. The management plans which were not altered after ^{68}Ga-PSMA PET/CT.

Initial management where no change occurred after ^{68}Ga-PSMA PET/CT	n=
PSA surveillance	32
Prostatectomy	1
Prostate/bed radiotherapy	14
Hormone therapy	10
Focal therapy	2
Targeted biopsy	2