BJR

https://doi.org/10.1259/bjr.20180667

Received: 30 July 2018 | Revised: 28 November 2018 | Accepted: 11 December 2018

Cite this article as:
Nandurkar R, van leeuwen P, Stricker P, Woo H, Kooner R, Yuen C, et al. ^{68}Ga-HBEDD PSMA-11 PET/CT staging prior to radical prostatectomy in prostate cancer patients: Diagnostic and predictive value for the biochemical response to surgery. *Br J Radiol* 2019; **92**: 20180667.

FULL PAPER

^{68}Ga-HBEDD PSMA-11 PET/CT staging prior to radical prostatectomy in prostate cancer patients: Diagnostic and predictive value for the biochemical response to surgery

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Objective: To determine the predictive and diagnostic value of ^{68}Ga-HBEDD PSMA-11 positron emission tomography (PET)/CT (prostate-specific membrane antigen, PSMA) for surgical response in males with prostate cancer prior to radical prostatectomy.

Methods: We analysed results of 142 males with staging PSMA prior to radical prostatectomy (RP). Data collected included PSMA PET/CT, bone scan (30/142), mpMRI (112/142), and pathological T stage (pT) stage, Gleason score, surgical margins and lymph node status at RP. Prostate-specific antigen (PSA) was documented at staging scan, and following surgery (median 45 days (interquartile range 38–59). A PSA of < 0.03 ng ml^{-1} was classified as surgical response (SR). Logistic regression was performed for association of pre-operative clinical variables and SR.

Results: 97.9% (139/142) of males had positive intraprostatic findings on PSMA. 14.1 % (20/142) of males had further sites of extra prostatic disease identified on PSMA PET. In males with disease confined to the prostate, 82.9 % (92/111) achieved an SR, compared to 28.6 % (4/14) in males with extraprostatic disease identified (lymph node positive and distant metastatic disease) (p < 0.001). On binary logistic regression PSMA had a superior predictive value for SR than Gleason score, PSA (at time of imaging) or pT stage. MRI was less sensitive and more specific for SVI, and less sensitive for nodal involvement.

Conclusion: Extraprostatic disease identified on staging pre-operative PSMA PET is independently predictive of a poor surgical response to RP, and may indicate a need for a multimodality approach to treatment.

Advances in knowledge: This is one of the first studies to correlate the PSMA PET's staging capacity to prostate cancer patient's outcomes to radical prostatectomy and indicates it's potential in predicting which patients will benefit from radical prostatectomy.

INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed cancer amongst males in Australia leading to considerable morbidity and mortality.[1] Radical prostatectomy (RP) is the most widely used treatment for localised PCa. However, up to 14–34% of males do not have a biochemical response to RP and a multimodality approach is required.[2–6] Lymph nodal (LN) involvement, pathological tumour (pT), and seminal vesicle involvement (SVI) are poor prognostic indicators of initial response to RP.[3,7,8] ^{68}Ga-prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging has emerged as a potential tool for staging

males prior to curative treatment. The aim of this study is to evaluate detection rates for extraprostatic disease in addition to the diagnostic value of PSMA as a staging tool for males undergoing RP. Furthermore, this study aims to evaluate ^{68}Ga-PSMA PET's usefulness in the pre-operative setting to guide clinical decision making as well as its predictive value in stratifying patients into those who will best respond to surgery as their primary curative treatment.

METHODS AND MATERIALS

Patient population

Between February 2015 and July 2016, PSMA PET/CT was performed in 657 consecutive patients at a single institution. Written informed consent was obtained from all patients using the Prostate Cancer Imaging Database (ProCan-I). The trial was approved by the St Vincent's Institutional Human Research and Ethics Committee (LNR/14/SVH/372). Data collected included the PSMA result and available results for bone scan and multiparametric MRI (mpMRI). PSMA result included site of anatomical lesion, number of lesions, a certainty score and the standard maximum uptake value (SUV_{max}). Histopathological information was obtained from patients' surgical pathology reports. Surgical information included: Gleason score, surgical margin status, extracapsular extension status, SVI and pT stage. For patients who underwent a lymph node (LN) dissection, the following information was recorded: number of LN removed, number of positive LN and size of largest node removed. Pelvic lymph node sampling was performed at the discretion of the surgeon. Serum prostate-specific antigen (PSA) was documented at time of staging scan and following RP (SR) [45 days (interquartile range, IQR 38–59)]. Surgical response (SR) was defined as a post-surgical PSA < 0.03 ng ml^{-1}. PSMA results were coded as either prostate-confined, pelvic lymph node disease, or distant disease (which included distant nodal disease, osseous lesions and other sites of metastatic disease). For the purpose of analysis, pelvic LN and distant disease were combined to define the extraprostatic PSMA cohort.

Imaging protocol

PSMA was produced on-site compliant to the Good Laboratory Practices procedure using a TRASIS® automated radiopharmacy cassette. Radiopharmacy quality control was undertaken using a high-pressure liquid chromatography method. Patients were injected with 2.0 MBq kg^{-1} ^{68}Ga-PSMA (HBED-CC). PET CT imaging was undertaken using a Phillips® Ingenuity TOF-PET/64 slice CT scanner. For PSMA PET/CT, a dose modulated contrast-enhanced CT scan was performed 60 min post-tracer injection. A diagnostic CT "window" was undertaken within the abdomen/pelvis with the remaining whole body CT acquired according to low dose parameters. Immediately after CT, a whole-body PET scan was acquired for 3 min per bed position. The emission data were corrected for randoms, scatter and decay using the Phillips® Body-dynamic.xml and Body.xml reconstruction protocol. All images were viewed and reported using the Phillips® Fusion Viewer.

Image interpretation

All PET images were interpreted prospectively by credentialed nuclear medicine physicians highly experienced in reporting prostate PET images. Data for all PSMA were analysed both visually and quantitatively. Visual analysis included a 4-point certainty scoring scale (definitely negative, equivocal probably negative, equivocal probably positive, definitely positive), as well as anatomical site and size of lesions. Visual criteria for either "probably positive" or "definitely positive" for lymph nodes and in bone included both the intensity of the PSMA avid focus including appearances on the embedded diagnostic CT scan. For lymph nodes, rounded lymph nodes that were hyperdense on diagnostic contrast CT and PSMA avid were classified as "definitely positive" while nodes with normal appearance on CT and only mild PSMA activity were classified as equivocal "probably positive". Symmetrical nodes with normal appearance on CT and mild PSMA activity in the distal external iliac node stations were also classified as equivocal "probably positive", rather than "definitely positive". Semi-quantitative analysis was undertaken using an automated standardized maximum uptake value (SUV max).

Statistical analysis

Comparison between groups and rates of surgical response were performed using the Mann–Whitney rank sum test for continuous variables and χ^2 or Fisher's exact for categorical variables. A binomial logistic regression was performed to evaluate the value of PSMA PET, Gleason score, PSA (at time of imaging) and pathological T-stage to predict SR and determine which clinical variables were more predictive of SR (Table 1). *p*-values < 0.05 were considered to indicate statistical significance. Statistical analysis was carried out with IBM SPSS Statistics v. 24.0 (SPSS INC., Chicago, IL).

RESULTS

Baseline characteristics

In total, 142 males underwent PSMA prior to RP and were included in the study. Baseline characteristics are summarized in Table 2. Median age was 66 years (IQR 61–70). 7.7% (11/142) of males commenced androgen deprivation therapy (ADT) prior to

Table 1. Binomial logistic regression analysis for the prediction of biochemical response to radical prostatectomy (SR)

	Significance (p-value)	Exponential B	95% CI for Exp B
PSMA PET result	0.024	3.598	1.19–10.92
Pathological T-stage	0.042	2.049	1.03–4.09
Gleason score	0.631	1.261	0.49–3.25
PSA (at time of imaging)	0.170	1.043	0.98–1.11

PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SR, surgical response.

Table 2. Baseline characteristics

Total number of patients	n = 142
Pathological tumor stage	
T_2c or less	29.4% (42/142)
T_3a	44.0% (62/142)
T_3b or more	26.6% (38/142)
Positive surgical margins	23.1% (33/142)
Extracapsular extension	70.6% (101/142)
Seminal vesicle involvement	25.9% (37/142)
Gleason score	
6–7	62.7% (89/142)
8–10	37.3% (53/142)
PSMA PET result	
Negative	1.4% (2/142)
Prostate only	84.5% (120/42)
Lymph node positive	10.6% (15/142)
Distant disease	3.5% (5/142)
Lymph node dissection status	
Nodes removed	71.1% (101/142)
Positive histological nodes removed	26.7% (27/101)

PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

RP. These males were included in the assessment of PSMA PET results; but excluded from analysis of surgical response results as true response rates to surgery would not be ascertainable in this group of patients.

PSMA PET results

97.9% (139/142) of males had intraprostatic disease identified on PSMA. 14.1% (20/142) of males had further sites of disease identified beyond the prostate on PSMA. Of these 10.6% (15/142) had PSMA positive findings in pelvic LN and 3.5% (5/142) of males had distant disease (3/5 skeletal sites and 2/5 distant lymph nodes). Two males had definitely negative PSMA results, both of whom had acinar adenocarcinoma, large volume pT3b disease. Patients with prostate confined disease on PSMA had a median PSA of 7.5 (IQR 5.5–10.25) while those with extraprostatic findings had a median PSA of 9.8 (IQR 6.1–13.4) (p = 0.051).

Surgical findings

Patient specific pathology parameters are summarized in Table 2. The SR rate for extraprostatic disease (lymph node and distant disease) was 28.6%, compared to 82.9% SR rate for patients with prostate-confined disease on PSMA PET ($p < 0.001$). Of the five patients who had distant disease, only two were not on pre-operative ADT. One of these patients achieved SR and the other did not. On binomial logistic regression, PSMA PET positive for extraprostatic disease was more independently predictive (greater significance value) for SR to RP than other pre-operative parameters including Gleason score, PSA (at time of imaging) and pT stage (Table 1). Comparison of predictive value of clinical variables for treatment response to RP is summarised in Table 3.

Table 3. Comparison of predictive value of clinical variables for treatment response to RP[a]

	SR	p value
PSMA PET result (excluding two males with negative scans)		
Disease confined to prostate	82.9% (92/111)	
Extraprostatic disease	28.6% (4/14)	0.0001
Pathological T-stage		
pT2	90% (36/40)	
PT3a	77.6% (45/58)	
pT3b≤	55.2% (16/29)	0.006
Gleason score		
6–7	78.6% (66/84)	
8–10	72.1% (31/43)	ns
Surgical margins		
Negative	80.6% (83/103)	
Positive	58.3% (14/24)	0.037
Extracapsular extension		
Absent	90.2% (36/40)	
Present	70.1% (61/87)	0.014
Seminal vesicle involvement		
Absent	83% (83/100)	
Present	51.9% (14/27)	0.002

PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy.
[a]excluding 15/142 men on pre-operative ADT.

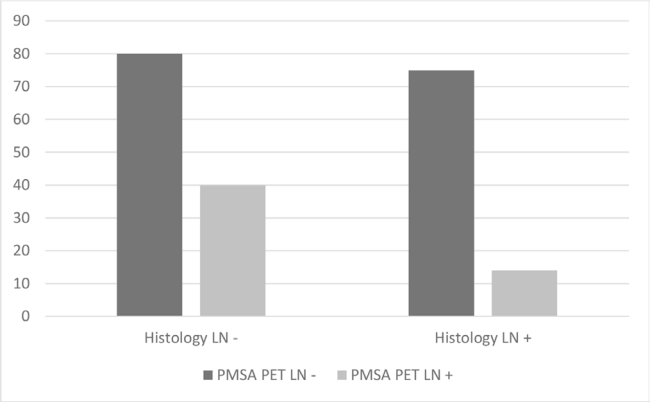
71.1% (101/142) males underwent a LN dissection, with a mean 13 nodes (±1.3) removed. Of those males who underwent LN resection, 26.7% (27/101) males had positive nodes histologically. A total 1358 LN were removed, of which 5% (70/1358) were positive at histopathology. Of the patients who had intermediate-risk disease according to D'Amico risk classification, 56% of patients underwent a lymph node dissection, of whom none had positive nodes removed. Of those with D'Amico high-risk disease, 73% of patients underwent a lymph

Table 4. Comparison of D'Amico risk classification with PSMA PET result and surgical lymph node status

D'Amico risk	Intermediate	High
PSMA lymph node negative	100% (18/18)	84% (104/124)
PSMA lymph node positive	0%	16% (20/124)
LN dissection completed	56% (10/18)	73% (91/124)
Histological lymph node positive	0%	31% (28/91)
Surgical response rate[a]	89% (16/18)	74% (81/109)

LN, lymph nodal; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.
[a]Excluded 15/142 patients on pre-operative ADT.

Figure 1. Comparison of PSMA PET positivity and histology positivity for pelvic lymph nodes and associated SR rates. LN,lymph nodal; PET,positron emission tomography; PSMA, prostate-specificmembrane antigen.



node dissection, of whom 31% had positive nodes removed (Table 4). Of patients who underwent a lymph node dissection, 19.8% of patients with prostate-confined disease on PSMA PET had positive histological node removed. Conversely, 57.9% of patients with extraprostatic disease on PSMA PET had positive nodes removed ($p < 0.05$). 30 males did not achieve a surgical response (excluding males on pre-operative ADT), of whom 11 patients were both negative for extraprostatic disease on PSMA and had no positive lymph nodes found on dissection. 91% of these patients had high-risk disease according to D'Amico risk classification.

A comparison of PSMA PET positivity and histology positivity for pelvic lymph nodes was performed in males who underwent a lymph node dissection, with results correlated with SR rates (Figure 1). 84% (61/73) of males who were node negative on PSMA were true-negative at surgery, while 16% (12/73) males who were PSMA negative for pelvic LN had involved nodes confirmed on histology.

The presence of PSMA positive pelvic LN was a strong predictor of SR. Males with no pelvic nodes on PSMA had an SR of 79% compared to 25% in males with positive pelvic nodes on PSMA ($p < 0.001$). In males with nodes identified as PSMA node negative, but with histologically positive nodes identified (PSMA false-negative), 75% (9/12) still achieved an SR. Predictably, males who were negative for pelvic LN on PSMA and histology performed best at SR (80%), whilst those positive on PSMA and histology had the lowest SR (14%).

Impact of reporter certainty on surgical outcome

All extraprostatic findings were assigned a certainty score on PSMA. For analysis, only extraprostatic disease scored as "definitely positive" were included. An additional 11% (16/142) males had LN reported as "equivocal probably positive", of whom 75% achieved SR. By contrast, 25% (3/12) of males whose pelvic LN were reported as "definitely positive" achieved SR.

Correlative imaging results

79% (112/142) males underwent staging MRI. 8% (9/112) males had extraprostatic disease on MRI of whom 78% (7/9) were within pelvic LN, and 22% (2/9) had osseous sites identified as consistent with prostate cancer metastases. 71% (5/7) LN positive and 100% (2/2) osseous positive males (78% (7/9)) on MRI achieved SR. Both males with osseous disease identified on MRI were negative for osseous disease on PSMA. 26% (37/142) males had confirmed SVI on histopathology. For detection of SVI, PSMA PET had 47% sensitivity and 87% specificity. MRI demonstrated lower sensitivity (30%) but a higher specificity (99%).

21% (30/142) males underwent a staging bone scan (BS), of which 97% (29/30) were negative. 3% (1/30) had metastatic disease reported on BS, with no extraprostatic disease detected on the corresponding PSMA. This patient achieved a SR following RP.

DISCUSSION

PSMA PET is increasingly utilized for the diagnosis of prostate cancer, particularly in the biochemical failure setting.[9–13] However, there is growing evidence to support its use as a staging tool for PCa, with evidence from histopathology trials that it has moderate sensitivity and high specificity for LN involvement in the primary disease setting.[14,15] Maurer et al[14] reported that ^{68}Ga-PSMA PET had a superior sensitivity and specificity (65.9 and 98.9%, respectively) than CT and MRI for primary LN staging.[16] It has also demonstrated superior sensitivity and specificity to BS for the detection of osseous metastases.[17]

RP is the most common treatment choice for patients with disease confined to the prostate, and often includes LN dissection in males with high risk of LN spread.[18–20] However, many patients fail to achieve an undetectable PSA (<0.03 ng ml^{-1}) following RP, with 14–34% of patients failing to respond at the first post-operative PSA reading.[2–6]Information that predicts how well a patient responds to surgery is beneficial when weighing up the pros of curative treatment against the cons of unwanted side-effects. Patients who fail to respond following RP are likely to experience continuously rising PSA levels requiring additional treatments with their attendant morbidities in addition to those of the primary treatment.[4] This occurs in 50% of patients with pT3 stage tumors and increases to 75% when patients have positive surgical margins.[21,22]

This study demonstrates that in the cohort of males who are being considered for RP, PSMA PET identified 14% of males with disease beyond the prostate. Furthermore, the finding of extraprostatic disease on pre-operative PSMA effectively stratifies males into those with a high versus incomplete biochemical response to RP. In fact, PSMA result proved to be more predictive of initial treatment response to RP than established clinical predictors such as PSA level at time of imaging, Gleason score and pT stage.

Positive pelvic LN's on staging PSMA was a strong predictor for poor SR to RP. We found that only 25% of males with PSMA positive LN experienced a treatment response to RP, despite extended LN dissection. By contrast, 79% of males without LN detected on

PSMA PET, had an SR. This has important implications for the future management of males with PCa suggesting that consideration should be given to multimodality treatment or to alternative treatments in males with LN positive PSMA PET.

MRI and PSMA scans were both undertaken in the majority of males enrolled in this study. MRI was less sensitive for the identification of LN involvement, and was not predictive of SR. It did, however, demonstrate superiority over PSMA in accurately identifying SVI. This finding points to the complementary roles for these modalities in accurately risk stratifying males prior to RP. A smaller number of patients underwent a bone scan. Given the incidence of metastatic, osseous disease was low in this cohort, comparison between PSMA and BS was less meaningful.

The identification of lymph nodes on PSMA can be difficult with a significant number of LN in this study reported as "equivocal probably positive", rather than "definitely positive" by the experienced PSMA PET imagers involved in the study. There was clearly a concordant increase in risk of incomplete SR as certainty of the reporter regarding LN involvement increased. PSMA with LN reported as definitely positive had only a 25% complete SR to surgery. By contrast, PSMA LN reported as "equivocal, probably positive" had a 75% SR to RP, suggesting many equivocal lymph nodes on PSMA were false-positive. The difference in response rates between "definitely positive" nodes and "equivocal probably positive" nodes likely reflect the difference between lymph nodes with PSMA activity related to prostate cancer, and normal nodes showing PSMA activity related to inflammatory changes from other causes. In this study, "definitely positive" lymph nodes were not those that were larger. They were lymph nodes that demonstrated a minimum mild-to-moderate PSMA activity on PET and must also have been hyperdense or rounded on the corresponding diagnostic contrast CT image.

There is a paucity of literature evaluating the outcome of males with PSMA informed RP. This study demonstrated that PSMA offers valuable, prognostic information in the staging setting prior to RP. Based on this study, males with PSMA positive nodal or distant disease will have a poor SR to RP alone, and a high risk of requiring adjuvant therapy.

There are several significant limitations to this study. This study was a retrospective analysis of a prospective database. As males included were only those who underwent RP, those males being considered for RP, but as a result of staging had their treatment changed, were not captured in the analysis. This means the study may have underestimated the number of males identified as having metastatic disease on PSMA.

Not all males underwent an extended LN dissection, meaning a comprehensive comparison of PSMA PET positivity and histological positivity was not possible. A number of males with PSMA positive LN did not have histological confirmation of LN positivity, but had an incomplete SR to surgery. This suggests not all involved LN were removed at surgery. However, this study did not attempt to accurately determine sensitivity and specificity of PSMA PET for LN involvement, which has previously been undertaken. Instead, it aims to evaluate the predictive value of PSMA for early post-surgical outcomes.

CONCLUSION

Extraprostatic disease identified on staging pre-operative PSMA PET is independently predictive of a poor surgical response to RP, and may indicate a need for a multimodality approach to treatment. Larger prospective trials are needed to further evaluate this.

ACKNOWLEDGMENT

The study would like to thank those who participated in the study, the staff at St Vincent's Hospital and the Garvan Institute of Medical Research. We would also like to thank the Australian Commonwealth Department of Health for their support for the Australian Prostate Cancer Research Centre – NSW.

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