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^{68}Ga-PSMA-PET/CT staging prior to definitive radiation treatment for prostate cancer

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Abstract

Aim: To explore the utility of prostate specific membrane antigen (PSMA)-positron emission tomography (PET)/computed tomography (CT) in addition to conventional imaging prior to definitive external beam radiation treatment (EBRT) for prostate cancer.

Methods: All men undergoing PSMA-PET/CT prior to definitive EBRT for intermediate and high-risk prostate cancer were included in our ethics approved prospective database. For each patient, clinical and pathological results, in addition to scan results including site of PSMA positive disease and number of lesions, were recorded. Results of conventional imaging (bone scan, CT and multiparametric magnetic resonance imaging [MRI]) were reviewed and included.

Results: One hundred nine men underwent staging PSMA-PET/CT between May 2015 and June 2017; all patients had national comprehensive cancer network (NCCN) intermediate or high-risk prostate cancer and 87% had Gleason score (GS) 4 + 3 or higher. There was positive uptake corresponding to the primary in 108, equivocal in one. All patients with image detected nodal or bony lesions had GS 4 + 3 or more disease. Compared to conventional imaging with bone scan, CT and multiparametric MRI, PSMA-PET/CT upstaged an additional 7 patients (6.4%) from M0 to M1, 16 from N0M0 to N1M0 (14.7%) and downstaged 3 (2.8%) from M1 to M0 disease.

Conclusion: PSMA-PET/CT identified the primary in 99% of patients, and altered staging in 21% of men with intermediate or high-risk prostate cancer referred for definitive EBRT compared to CT, bone scan and multiparametric MRI. Following this audit, we recommend the routine use of PSMA-PET/CT prior to EBRT in this patient group.

KEYWORDS
^{68}Ga-PSMA-PET/CT, prostate cancer, staging

1 | INTRODUCTION

The role of PSMA-PET/CT in the management of prostate cancer is evolving. Initial experience with PSMA-PET/CT was in patients with rising prostate specific antigen (PSA) post prostatectomy where this tracer detected disease even at very low absolute PSA values.[1,2] We have also demonstrated PSMA-PET/CT's ability to delineate sites of failure in those who have biochemical recurrence after definitive[3] or postprostatectomy[4] external beam radiation treatment (EBRT). A recent Australian multicenter collaboration which included 431 patients found that PSMA scanning, for both initial staging and relapsed disease, altered management in 51% of cases.[5] This study explores the impact of PSMA-PET/CT scanning in patients referred for definitive EBRT.

2 | METHODS AND MATERIALS

All men with prostate cancer referred to the Department of Radiation Oncology are entered on an ethics approved prospective database. PSMA-PET/CT has been routinely incorporated for all patients referred for definitive EBRT since 2015. For each patient, clinical and pathological results, conventional imaging results, in addition to PSMA scan results including site of PSMA positive disease and

number of lesions, were recorded. Conventional imaging included CT scan, bone scan and multiparametric MRI (mp-MRI) in all patients unless medically contraindicated.

The study assessed whether PSMA-PET/CT upstaged lymph nodal involvement compared to conventional imaging, including mp-MRI – this included from N0 to N1 and number of nodes. Second, the number of men upstaged from M0 to M1 or number of metastases. Finally, the number of men who were downstaged compared to conventional imaging was also documented.

2.1 | Imaging protocol

PSMA was produced on-site compliant to the Good Laboratory Practices procedure using a TRASIS automated radio-pharmacy cassette. Radio pharmacy quality control was undertaken using a high-pressure liquid chromatography method. Patients were injected with 2.0MBq/kg ^{68}Ga-PSMA (H-BED CC). For the PET/CT, a noncontrast-enhanced CT scan was performed a minimum of 45 min post tracer injection using the following CT parameters: slice thickness of 2 mm, 2 mm apart, soft tissue reconstruction kernel, 120 keV and 50 mAs, pitch of 0·828, 600 mm FOV and a 512 matrix. Immediately after CT scanning, a whole-body PET scan was acquired for 2 min per bed position.

2.2 | Image interpretation

All PSMA-PET/CT images were interpreted prospectively by credentialed nuclear medicine physicians or dual trained radiologists with experience in reporting prostate PET images. Data for all PSMA scans were analyzed both visually and quantitatively. For study purposes, each finding was coded as positive, negative or equivocal. Number of involved sites and lesions were recorded. Sites of disease were identified as nodal (pelvic, para aortic or other), bone or visceral on the database. All "equivocal" lesions were rereviewed by an independent imager to establish a consensus interpretation.

3 | RESULTS

3.1 | Baseline characteristics

One hundred nine men underwent staging PSMA-PET/CT between May 2015 and June 2017; all patients had NCCN intermediate or high-risk prostate cancer. All men had had CT and bone scan, and 83 also had at least one mp-MRI scan.

Seventy-five men (69%) had gleason score (GS) 8–10 disease and 44 men (40%) had T3 or greater disease. Mean age at PSMA-PET/CT was 73 years (range 59–86 years). Median and mean PSA values at PSMA-PET/CT were 9.9 and 17.8, respectively (range 1.23–240). Eighty PSMA-PET/CT scans were performed at Royal North Shore Hospital (RNSH) with most of the remainder at St Vincent's Hospital, Sydney (SVHS). Baseline tumor characteristics are summarized in Table 1.

One hundred eight tumors within the prostate were classified as positive. One patient had an equivocal primary which, on review, was called positive; albeit with modest avidity (serial uptake value [SUV] 4). This man's tumor was GS 3 + 4, with less than 25% grade 4 component.

TABLE 1 Tumor details at the time of PSMA-PET/CT staging

Gleason score	*n*
6	1
3 + 4	13
4 + 3	20
8	28
9	45
10	2
T-stage	
1	26
2	39
3	42
4	2

3.2 | Lesion-based assessment: nodal staging

Twenty-five men had positive nodal only metastases reported on PSMA-PET/CT and five had nodal and bony disease. The likelihood of PSMA positive nodal disease appeared to increase with GS. None of those with GS 3 + 4 = 7 or less (n = 13) disease were positive in nodes compared with 4 of 20 (20%) and 26 of 75 (35%) of the GS 4 + 3 and GS 8–10 disease, respectively.

After accounting for those with "definite" or "suspicious" MRI and CT findings, 16 men were upstaged from N0 to N1, M0 disease. Two of these 16 men had "suspicious" pelvic bone metastases on MRI and/or bone scan where the bone lesions were not PSMA avid, but who had PSMA positive (and MRI negative) lymph nodes. These two men were "downstaged" from M1 to M0, but upstaged from N0 to N1.

Five men had 1–2 suspicious pelvic nodes on MRI which became multiple (three or more) pelvic nodes in three men and multiple pelvic + para-aortic nodes in two men. Two of these five men also had a single bone metastasis detected on PSMA-PET/CT.

In six cases, the PSMA-PET/CT confirmed the findings of one (five men) or two suspicious pelvic nodes (one patient) on MRI and was concordant with the number involved. Four men had "equivocal" nodes identified on PSMA-PET/CT. Three nodes had SUV values of 3 or less, one of whom had had a sclerotic bone lesion called on bone scan and CT (not avid on PSMA). The fourth equivocal node was immediately adjacent to the ureter in a patient who had "multiple" nodes regarded as suspicious on MRI. Following review, three were again reported as equivocal and one was reported as negative.

3.3 | Bone staging

Nine men had positive bony metastases reported on PSMA-PET/CT, and six were equivocal. The nine positive bone lesions by site included two solitary ribs, five solitary pelvic lesions, one patient with two pelvic lesions and one with two ribs and one pelvic metastasis. These nine included the five who were PSMA node positive as well.

TABLE 2 Per-patient-based change in stage with PSMA-PET/CT compared to conventional imaging

Upstaged from	to	*n* (%)
N0M0	N1M0	16 (15%)
N0M0	N1M1	3 (2.8%)
N1M0	N1M1	2 (1.8%)
N0M0	N0M1	2 (1.8%)
Downstaged from	**To**	***n* (%)**
N1M1	N1M0	2 (1.8%)
N0M1	N0M0	1 (0.9%)

The nine cases with reported bone metastases included 0 of 14 with GS 3 + 4 or less, 2 of 20 (10%) with GS 4 + 3 = 7 and 7 of 75 (9%) with GS 8–10 disease, respectively.

Following review of CT, bone scan and MRI, seven of nine were upstaged from M0 to M1 (6% of total). In two cases, the PSMA-PET/CT confirmed the bone scan and MRI reports. However, in one of these two cases, the patient had multiple pelvic lesions reported on both MRI and bone scan, but on PSMA-PET/CT only two were avid. These two lesions were incorporated into our definitive EBRT fields and boosted with simultaneous integrated boost following PSMA-PET/CT fusion into the planning CT.

Seven bone lesions were reported as equivocal on PSMA-PET/CT, in all cases these involved either the ribs (five men) or the pelvis (four men), and in close proximity to the sacro-iliac joints in three of these four. All equivocal cases had SUV < 4. In all cases, the patients proceeded to definitive EBRT. On review, all these lesions remained equivocal.

3.4 | Per-patient staging

In total, 19 men (17%) were upstaged from N0 to N1 disease including 3 men with single bone metastases on PSMA-PET/CT (not present on conventional imaging). An additional four men (3.7%) were upstaged from M0 to M1 disease. Three men (2.8%) were downstaged from M1 to M0; two with definite nodal involvement and one with an equivocal node on PSMA-PET/CT.

Therefore, on per-patient analysis, PSMA-PET/CT upstaged an additional 7 patients (6.4%) from any N, M0 to M1; 16 from N0M0 to N1M0 (14.7%) and downstaged 3 (2.8%) from M1 to M0 disease. The change in individual patient staging on account of PSMA-PET/CT, compared to conventional imaging, is presented in Table 2.

4 | DISCUSSION

This is, we believe, the first audit specifically examining the role of PSMA-PET/CT for staging men with intermediate or high-risk prostate cancer referred for consideration of EBRT.

Our results demonstrate that on lesion-based assessment, there was additional positive PSMA nodal and bone disease in 19 and 7 cases, 17% and 6%, respectively. These lesions were not detected on CT, bone scan or mp-MRI. In total, 21% of patients were upstaged; and perhaps more importantly, 3% were downstaged.

Second, all bone and nodal lesions reported on imaging occurred in men with at least GS 4 + 3 (ISUP 3) disease. This audit supports our continued use of PSMA-PET/CT staging in those with high-tier intermediate and high-risk disease. However, as only 13 patients had GS 3 + 4 = 7 disease and one had GS 3 + 3 disease, this study cannot quantify the impact of PSMA scanning in this subgroup of patients.

In a recently published prospective multicenter study,[5] 431 men from four centers had PSMA scans performed for staging of primary (25%) or recurrent disease including biochemical failure (75%). Although PSMA-PET/CT altered intended management in 51% of cases, the impact was greater for those men who had biochemical failure (62% change in planned management) than in those being staged for primary disease (21% change). Of the latter group (n = 108), only 47 were staged prior to definitive radiotherapy (RT) with the majority being assessed prior to surgical management. In these 108 men, PSMA-PET/CT detected additional nodal disease in 39%, and metastatic disease in 16% compared to clinical findings and conventional imaging. In the RT cohort (n = 47), there was no change in the number of men in whom RT was intended; but higher doses and larger volumes were planned for 15% following the PSMA-PET/CT result.

These results are broadly similar to ours, although the additional nodal and metastatic disease detected with PSMA-PET/CT is much higher than in our report – 39% versus 17% and 16% versus 6%, respectively. These figures are surprisingly similar to the rates of PSMA-PET/CT positivity in our series *before* we reviewed the results of the conventional imaging (28% and 8%). Some of this may be explained by selection bias, as in our series, most of the patients had had at least one mp-MRI performed in addition to bone scan and CT imaging (see Limitations). If we exclude mp-MRI from our analysis, the rates of upstaging would be similar to the rates reported in the report by Roach et al., which did not specify the imaging modalities included in their definition of conventional imaging, nor was their imaging reviewed. However, the change in management intent reported by Roach et al. (15–21%) very closely reflects the additional findings due to PSMA-PET/CT in this report.

We intend to keep using PSMA-PET/CT for staging this patient group. Furthermore, we believe that bone scan and CT are redundant in those patients who will undergo mp-MRI and PSMA-PET/CT imaging. Omitting staging CT and bone scan would largely offset the financial cost of the PSMA-PET/CT.

4.1 | Limitations

There are several limitations to this study which is a retrospective audit subject to a number of biases. However, it reflects contemporary clinical practice in a tertiary setting and provides insight into the effect of PSMA-PET/CT on the staging of these patients.

First, there was no gold standard in that we did not perform biopsies to validate or refute the PSMA-PET/CT results. PSMA-PET/CT avid nodes were generally less than 1 cm in diameter so attempts to obtain adequate tissue may have been futile. Evidence from van Leeuwen et al.[6] suggests that although PSMA-PET/CT staging of pelvic nodes

prior to radical prostatectomy and extended lymph node dissection has moderate sensitivity (54%) for detecting nodal micrometastases, it is extremely specific (99%). As such, PSMA-PET/CT *underestimates* rather than overestimates the extent of nodal micrometastatic disease as a proportion of nodal deposits < 5 mm in diameter; and all deposits < 2 mm in diameter will be missed with the current generation of PET camera technology. The sensitivity of over 50% is superior to the 39–42% that meta-analysis suggests for CT and MRI imaging.[7] As we have excluded equivocal lesions (generally SUV < 4) from those patients being upstaged with PSMA scanning, our results are likely to be a conservative underestimate of the potential impact of PSMA scanning in this patient group.

Our imaging specialists were not blinded to the results of the other imaging modalities. Many of our patients had had two mp-MRI scans – the first performed prior to biopsy and the second performed for RT planning (standard for all prostate planning at RNSH). This bias may have favored the MRI reports in that the MRI radiologists had access to the staging PSMA-PET/CT results performed in house ($n = 80$) when reporting the RT planning MRI.

Finally, the nuclear medicine physicians at RNSH and SVHS are all dedicated PSMA-PET/CT reporters, so these results may not be generalizable to a community nuclear medicine practice nor even a tertiary institution at the beginning of its learning curve. There are efforts underway to harmonize the reading of PSMA-PET/CT scans, in fact, one of our nuclear medicine experts (LE) was involved in a recent multinational effort to standardize PSMA/PET-CT reporting.[8] In our experience, a synoptic report with a minimum documentation set, including site and number of metastases, SUV of each lesion and corresponding anatomical location – with bony or vascular landmarks, greatly improves the quality of reporting and its clinical application. The synoptic report, in addition to dedicated imaging meetings with MRI radiologists and nuclear medicine physicians, is a crucial part of our team approach.

5 | CONCLUSION

Compared to conventional imaging with bone scan, CT and mp-MRI, PSMA-PET/CT upstaged an additional 7 patients (6.4%) from M0 to M1, 16 from N0M0 to N1M0 (14.7%) and downstaged 3 (2.8%) from M1 to M0 disease. This supports our continued use of PSMA-PET/CT for staging intermediate and high-risk prostate cancer prior to consideration of radiation treatment.

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CONFLICT OF INTEREST

The authors do not have any conflict of interest.

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REFERENCES

1. van Leeuwen PJ, Stricker P, Hruby G, et al. (68) Ga-PSMA has a high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment. *BJU Int*. 2016;117:732–739.
2. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid (6)(8)Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med*. 2015;56:668–674.
3. Hruby G, Eade T, Kneebone A, et al. Delineating biochemical failure with 68Ga-PSMA-PET following definitive external beam radiation treatment for prostate cancer. *Radiother Oncol*. 2017;122:99–102.
4. Byrne K, Eade T, Kneebone A, et al. Delineating sites of failure following post-prostatectomy radiation treatment using ^{68}Ga-PSMA-PET. *Radiother Oncol*. 2017. https://doi.org/10.1016/j.radonc.2017.10.022.
5. Roach P, Francis R, Emmett L, McCarthy M, Scott A. Clinical management intent of Ga68 PSMA PET/CT imaging in prostate cancer: an Australian multicentre study. *J Nucl Med*. 2017;58(Suppl 1):706.
6. van Leeuwen PJ, Emmett L, Ho B, et al. Prospective evaluation of 68Gallium-PSMA positron emission tomography/computerized tomography for preoperative lymph node staging in prostate cancer. *BJU Int*. 2017;119:209–215.
7. Hovels AM, Heesakkers RA, Adang EM, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. *Clin Radiol*. 2008;63:387–395.
8. Fanti S, Minozzi S, Morigi J, et al. Development of standardized image interpretation for 68Ga-PSMA PET/CT to detect prostate cancer recurrent lesions. *Eur J Nucl Med Mol Imaging*. 2017;44:1622–1635.

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