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Detection and localisation of primary prostate cancer using ^{68}Ga-PSMA PET/CT compared with mpMRI and radical prostatectomy specimens

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Abstract

Objective:
To compare the accuracy of ^{68}Gallium prostate-specific membrane antigen positron emission tomography/computed tomography (^{68}Ga-PSMA PET/CT) with mpMRI in detecting and localising primary prostate cancer when compared with radical prostatectomy (RP) pathology.

Patients and methods:
Retrospective review of men who underwent ^{68}Ga-PSMA PET/CT and mpMRI for primary prostate cancer prior to RP across four centres between 2015 and 2018. Patients undergoing imaging for recurrent disease or prior to non-surgical treatment were excluded. We defined pathological index tumour as the lesion with highest ISUP Grade Group (GG) on RP. Our primary outcomes were rates of accurate detection and localisation of RP index tumour using ^{68}Ga-PSMA PET/CT or mpMRI. We defined tumour detection as imaging lesion corresponding with RP tumour on any imaging plane, and localisation as imaging lesion matching RP index tumour in all sagittal, axial and coronal planes. Secondary outcomes included localisation of clinically significant and transition zone index tumours. We defined clinically significant disease as GG 3-5. We used descriptive statistics and Mann-Whitney U

test to define and compare demographic and pathological characteristics between detected, missed and localised tumours using either imaging modality. We used the McNemar test to compare detection and localisation rates using 68Ga-PSMA PET/CT and mpMRI.

Results:

205 men were included in our analysis, including 133 with clinically significant disease. There was no significant difference between ^{68}Ga-PSMA PET/CT and mpMRI in the detection of any tumour (94% vs 95%, p>0.9). There was also no significant difference between localisation of all index tumours (91% vs 89%, p=0.47), clinically significant index tumours (96% vs 91%, p=0.15), or transition zone tumours (85% vs 80%, p>0.9) using ^{68}Ga-PSMA PET/CT and mpMRI. Limitations include retrospective study design and non-central review of imaging and pathology.

Conclusion:

We found no significant difference in the detection or localisation of primary prostate cancer between ^{68}Ga-PSMA PET/CT and mpMRI. Further prospective studies are required to evaluate a combined PET/MRI model in minimising tumours missed by either modality.

Introduction

Recent years have seen a significant shift in the diagnostic landscape of localised prostate cancer. Multiparametric MRI (mpMRI) is now a well-established tool in the assessment of primary tumours, and has demonstrated high sensitivity and excellent negative predictive values for clinically significant disease (1), leading to increasing uptake of pre-biopsy mpMRI and targeted prostate biopsy (2-4). Contemporary diagnostic biopsy, therefore, relies on precise identification of index tumour location on imaging. An index tumour is conventionally regarded as the focus of intra-prostatic cancer with highest grade, and carries important clinical implications from a prognostic standpoint (5). Moreover, knowing index tumour location adds value to diagnostic and therapeutic approaches, including target biopsy and treatment. Despite its accuracy, some concerns remain around underestimation of tumour size and identification of transition zone lesions using mpMRI (6,7).

^{68}Gallium labelled prostate-specific membrane antigen positron emission tomography (^{68}Ga-PSMA PET) has emerged as a viable staging tool alongside mpMRI (8,9). PSMA is a transmembrane protein found on prostatic cells and overexpressed in prostate cancer (10), and targeting this using ^{68}Ga-PSMA PET/CT has shown promise in accurately re-staging recurrent disease (11,12) and improving detection of lymph node metastases when compared with mpMRI (13-15). Still, beyond evidence for its utility in advanced disease, the added potential of PSMA PET/CT in detecting and characterising primary prostate cancer lesions remains to be fully explored (16,17), along with any clinical benefit it offers over mpMRI. We aimed to assess the accuracy of ^{68}Ga-PSMA PET/CT compared with mpMRI in detecting and localising primary prostate cancer lesions when compared with radical prostatectomy (RP) specimens.

Patients and methods

We performed a retrospective review of men who underwent ^{68}Ga-PSMA PET/CT and mpMRI for primary prostate cancer prior to radical prostatectomy across four Australian centres between 2015 and 2018. Patients undergoing re-staging for recurrent disease, or non-surgical treatment, including any focal therapy, were excluded. Ethical approval was obtained from Monash University and University of Melbourne (Melbourne, Australia). Clinical and demographic characteristics were collected, including age, PSA at diagnosis. PSA density was calculated using prostate volume on mpMRI.

Patients underwent ^{68}Ga-PSMA PET/CT across four Australian institutions. PET/CT imaging was performed on Siemens Biograph mCT Excel and, Siemens Biograph mCT Flow and GE 710 Discovery PET/CT scanners. Imaging was reviewed and reported by nuclear medicine physicians (ZB, SR, MC, MSH). Index lesion on ^{68}Ga-PSMA PET/CT was defined as the focal lesion with highest avidity, quantified by maximum standardised uptake value (SUVmax), regardless of size. As such, when a small lesion with greater avidity and large lesion with lesser avidity were present, the smaller focus was considered the index lesion. All other lesions found on imaging were considered non-index. Scans with no focal lesion and mild, diffuse uptake only were considered negative.

^{68}Ga-PSMA PET/CT scanning protocols were similar across sites. Our first site used a Siemens Biograph mCT PET/CT scanner to acquire PET images from thighs to vertex at 60 minutes after administration of 2 MBq/kg body weight ± 5% of ^{68}Ga-PSMA. Our second site used a Siemens Biograph mCT 20 with extended FOV Biograph PET/CT scanner to acquire PET images from thighs to vertex at 45-60 minutes after administration of 2 MBq/kg ± 5% up to 300 MBq of ^{68}Ga-PSMA. Our third site used a GE 710 Discovery PET/CT scanner to acquire PET images from pelvis towards head at 45-75 minutes after administration of 1.8–2.2 MBq/kg body weight of ^{68}Ga-PSMA-11. Finally, our fourth site also used a GE 710 Discovery PET/CT scanner to acquire PET images from thighs to vertex at 55-60 minutes following administration of 2 MBq/kg ± 5% up to 200 MBq of ^{68}Ga-PSMA. At all sites, a low dose non-contrast CT was performed during tidal respiration for attenuation correction and anatomical correlation.

All multiparametric MRI images included were acquired using 3-Tesla MRI scanners, and imaging was reviewed and reported by specialised MRI radiologists, as per PIRADS v2 (18). Index lesion on mpMRI was defined as that with the highest PIRADS score. In the case of multiple lesions, those with lower PIRADS scores were considered non-index. If two lesions with identical PIRADS score were identified on MRI, the larger lesion was deemed the index tumour.

Findings on ^{68}Ga-PSMA PET/CT and mpMRI were compared with histopathology on formalin-fixed and paraffin-embedded RP specimens, as reported by specialised uro-pathologists. Index tumour on RP specimen was defined as the lesion with highest ISUP grade group (GG). In men with multiple foci with identical tumour grade, again, the larger lesion was deemed index tumour.

Our primary outcomes included rates of accurate detection and localisation of index tumour found on RP specimen, using ^{68}Ga-PSMA PET/CT or mpMRI. Detection of cancer was defined as identification of any corresponding lesion between imaging and histopathology, both index and non-index, in any imaging plane. Tumour localisation was considered accurate if location of index tumour on imaging correlated with that of index tumour on RP specimen in all three planes; sagittal (left, right), axial (apex, mid, base), and coronal (anterior, posterior). Index lesions on imaging which met all three criteria but only partially overlapped with pathological lesion were also considered accurate, as imaging-targeted biopsy of these lesions would still sample the histological index tumour. Clinically significant disease was defined as ISUP Grade Group 3-5. Secondary outcomes included the localisation of clinically significant index tumours, and localisation of index tumours in the transition/anterior and peripheral prostatic zones

Statistical analysis

Descriptive statistics were used for demographic and pathological characteristics of the overall cohort. Mann-Whitney U test was used to compare demographic and pathological characteristics of tumours detected, missed and localised using either imaging modality. McNemar test was used to compare detection and localisation accuracy of PET/CT and mpMRI within the cohort. All statistical analyses were performed using SPSS Statistics version 25 (IBM Corp., Armonk, NY).

Results

205 men who underwent both ^{68}Ga-PSMA PET/CT and mpMRI prior to RP were included in our analysis. Cohort characteristics are listed in Table 1. Median age was 67 years and patients had a median PSA of 7.18 ng/mL prior to imaging. Median PSA density (PSAD) was 0.204. All men had prostate cancer on final histopathology, including 133 (64.9%) with clinically significant disease (GG 3-5) and 127 (62.0%) with non-organ confined disease (Table 1). All 205 men had GG 2 or greater index tumour on final pathology.

Detection of any prostate cancer

193 (94.1%) of 205 ^{68}Ga-PSMA PET/CT scans showed a focal lesion with PSMA avidity corresponding with any tumour on RP, and similarly a focal lesion was found in 194 (94.6%) MRI scans. There was no significant difference between the modalities for detection of any

tumour ($p > 0.9$). Examples of tumours detected and missed on 68Ga-PSMA PET/CT and mpMRI are shown in Figure 1.

In total, 127 (62.0%) of men had non-organ confined tumours, including 86 with pT3a and 41 with pT3b tumours. Of 127 men with pT3 disease, ^{68}Ga-PSMA PET/CT detected 120 (94.5%) index tumours, whilst mpMRI detected 123 (96.9%) (p=0.549). Similarly, ^{68}Ga-PSMA PET/CT localised 118 (92.9%) of these tumours, not significantly less than 120 (94.5%) by mpMRI (p=0.791).

Missed index tumours

Clinical and pathological characteristics of men with index tumours missed on 68Ga-PSMA PET/CT or mpMRI are listed in Table 2. 12 (5.9%) index tumours on RP were non-avid on ^{68}Ga-PSMA PET/CT, including 10 with no PSMA avidity and 2 men had PSMA uptake that did not correspond with any focus of tumour on histopathology (Figure 2). These men had a median PSA of 5.25 ng/mL (IQR, 3.63 – 8.43). Median PSAD was 0.114 (0.075 – 0.143), lower than 0.213 (0.155 – 0.311) for tumours detected on PET/CT ($p < 0.001$). Correspondingly, patients with non-PSMA PET avid lesions had a lower median index tumour volume on RP of 1.4 cc (0.8 – 2.2), compared with 3.0 cc (1.6 – 6.0) for all RPs (p=0.002). 3 of these 10 tumours were clinically significant, one each being GG 3, 4 and 5. The remaining 7 tumours were GG 2. Notably, 7 (58.3%) of 12 men had pT3a tumours.

Eleven (5.4%) index tumours were not detected on mpMRI, including 10 showing no focal lesion on imaging and 1 with a focal lesion that did not correspond with any intra-prostatic tumour. These men had a median PSA of 9.90 ng/mL (4.94 – 18.60). Median PSAD was 0.260 (0.159 – 0.380), not significantly different from 0.200 (0.144 – 0.297) for those lesions seen on mpMRI (p=0.254). However, median index tumour volume on RP was 1.2cc (0.6 – 2.8), significantly lower than 2.9cc (1.6 – 6.0) for mpMRI visible lesions (p=0.003). These 11 missed tumours consisted of six GG 2, four GG 3 and one GG 5 lesion. 4 men had non-organ confined disease, including 3 men with pT3a and 1 man with pT3b tumours.

Only 1 (0.5%) index lesion on RP was missed on both 68Ga-PSMA PET/CT and mpMRI. This patient had GG 2 disease on RP with a very small index tumour volume of 0.4cc. mpMRI identified 11 of the 12 lesions missed by 68Ga-PSMA PET/CT, and PET/CT identified 10 of the 11 tumours missed on MRI.

Index tumour localisation

^{68}Ga-PSMA PET/CT accurately localised index tumour on RP in 176 (85.9%) of 205 men. In a further 11 men (5.4%), index tumour on RP corresponded with non-index lesions with lower SUVmax values on ^{68}Ga-PSMA PET/CT. When adding these lesions, ^{68}Ga-PSMA PET/CT was able to accurately localise 187 (91.2%) index tumours seen on RP.

mpMRI accurately localised index tumour in 180 (87.8%) of 205 men. In a further 2 men (1.0%), index tumour on RP corresponded with non-index lesion location found on MRI with lower PIRADS score, giving a cumulative localisation rate of 88.8% using mpMRI. There was no significant difference between overall localisation of index tumour using ^{68}Ga-PSMA PET/CT (91.2%) and mpMRI (88.8%) (p=0.472). Localisation by RP segments in sagittal and coronal planes are shown in Table 3.

133 (64.9%) of 205 index tumours were clinically significant, with ISUP GG of 3-5. 127 (95.5%) of these clinically significant index tumours were localised by ^{68}Ga-PSMA PET/CT, and 121 (91.0%) were found on mpMRI (p=0.146). Three clinically significant index tumours were not completely localised on both imaging modalities, but all were detected by either ^{68}Ga-PSMA PET/CT or mpMRI. Localisation of index tumours stratified by ISUP Grade Group is shown in Figure 3. There was no significant difference between ^{68}Ga-PSMA PET/CT and mpMRI in the localisation of GG 2 (83% vs 85%, p>0.9), GG 3 (97% vs 92%, p=0.29), GG 4 (90% vs 80%, p>0.9) or GG 5 (94% vs 92%, p>0.9) tumours.

Twenty tumours were found exclusively in the transition or anterior zones on histopathology, of which ^{68}Ga-PSMA PET/CT localised 17 (85%) and mpMRI localised 16 (80%) (p>0.9). Similarly, there was no difference in localisation of 145 peripheral zone index tumours between PET/CT (130, 89.7%) and mpMRI (127, 87.6%) (p=0.690).

Discussion

The diagnosis and initial management of localised prostate cancer has grown increasingly reliant on imaging findings following the introduction of mpMRI and, more recently, ^{68}Ga-PSMA PET/CT. While mpMRI is now recommended prior to biopsy in men with a suspicion of localised prostate cancer (19), the emerging role of ^{68}Ga-PSMA PET/CT in primary staging is predominantly focussed on staging of regional and distant disease. Little is yet known of the value of ^{68}Ga-PSMA PET/CT in primary staging of lesions within the prostate itself. Despite the inherently heterogeneous and multifocal nature of prostate cancer, the highest tumour grade found on pathology remains a strong prognostic indicator for recurrence-free, metastasis-free and cancer-specific survival (5,20,21). Identification of these lesions on imaging, therefore, is pertinent to decision making surrounding diagnostic biopsy approach and local treatment options offered to patients. We assessed intra-prostatic index tumour detection and localisation using ^{68}Ga-PSMA PET/CT and mpMRI, and found equivalent rates between both. To our knowledge, our study is the largest in the literature comparing the accuracy of these modalities in localising primary prostate cancer lesions.

Detection

Both ^{68}Ga-PSMA PET/CT and mpMRI detected any tumour on RP in 94% of our cohort, and 96% and 91% of clinically significant index tumours were identified by ^{68}Ga-PSMA PET/CT and mpMRI, respectively. A recent Australian study found similar rates, but reported superior detection using ^{68}Ga-PSMA PET/CT over mpMRI, at 100% and 94% respectively (22). Discrepancy from our results may lie in varying definitions of index tumours; whilst defined as the lesion with highest tumour grade in our cohort, Berger et al assessed detection of the largest tumour found on RP. Larger lesions may be better detected using either modality, and accordingly smaller lesions with higher tumour grade may be more commonly missed. This was confirmed in a large, prospective cohort comparing mpMRI with RP pathology in which tumour size was found to be the strongest predictor of detection on imaging, and missed clinically significant lesions were smaller than those that were visualised (23). These results corroborate our finding of significantly smaller index tumour volumes in ^{68}Ga-PSMA PET/CT non-avid and MRI invisible tumours. A randomised multicentre study of 300 patients undergoing PET/CT and conventional imaging has recently completed accrual and will provide prospective data on the performance of ^{68}Ga-PSMA PET/CT in the primary staging setting (24).

Other cohorts have demonstrated sensitivity ranging between 49-68% and specificity between 92-95% for detection of any tumour on ^{68}Ga-PSMA PET/CT (25-27), regardless of index tumour status, demonstrating no significant difference between mpMRI and ^{68}Ga-PSMA PET/CT (25). The high sensitivity of ^{68}Ga-PSMA PET/CT suggests it may have a role in reducing uncertainty when excluding high risk disease prior to inclusion on active surveillance, or reassurance in men with rising PSA despite negative prostate biopsy. Nevertheless, consistent with existing reports suggesting 5% of tumours lack PSMA expression on immunostaining (28), 6% of index tumours in our cohort were non-avid on ^{68}Ga-PSMA PET/CT, potentially influencing detection rates. Again, these tumours were significantly smaller in volume than those visible on imaging, and one-third were clinically significant.

Localisation

Accurate localisation of clinically significant tumours within the prostate carries wide diagnostic and treatment implications. mpMRI has been proposed as a triaging tool and sampling of MRI lesion-targeted cores has become paramount in contemporary biopsy practices, replacing systematic cores in some settings (29). Equivalent localisation using ^{68}Ga-PSMA PET/CT raises the possibility of its use as a primary diagnostic tool in this domain as well. In a North American cohort of MRI negative or MRI-naïve men with prior negative biopsy, ^{68}Ga-PSMA PET/TRUS fusion guided biopsy yielded 82% sensitivity and of 72% specificity for any cancer, and 100% sensitivity for clinically significant disease (30). Although only targeted biopsy cores were sampled in this study, potentially overestimating sensitivity, these results are somewhat promising, particularly for men who are ineligible for mpMRI. PSMA expression is also associated with tumour grade (28), and further investigation of the predictive ability of other parameters on ^{68}Ga-PSMA PET/CT, such as standardised uptake value (SUV), are required to identify whether PET/CT can function as a stand-alone test in this space.

Accordingly, this raises the potential of ^{68}Ga-PSMA PET/CT as a single test to assess both local and distant disease. ^{68}Ga-PSMA PET/CT has proven sensitivity in detecting metastases when compared with nodal histopathology in primary staging (31), and thus may have utility in detecting oligometastatic spread, thereby upstaging tumours that would otherwise be considered localised. Given anterior periprostatic tissue contains lymph nodes in 30% of men (32), detection of disease here using ^{68}Ga-PSMA PET/CT may also guide the adjustment of margins and surgical technique, including pelvic lymph node dissection, accordingly. From a treatment standpoint, confidence in tumour location can also guide decision making in nuances such as nerve sparing during radical prostatectomy and lesion-specific focal therapy.

Predominantly transition and anterior zone tumours have been traditionally more difficult to reach on biopsy, particularly from a transrectal approach, and thus need to be effectively localised using pre-biopsy imaging. Existing evidence for MRI in detecting impalpable anterior tumours missed by TRUS biopsy (33) is compounded by our finding of equivalent localisation rates using ^{68}Ga-PSMA PET/CT, suggesting molecular imaging may have a similar role in identifying these tumours.

Our finding of no significant difference in index tumour localisation rates between modalities is discrepant with some existing studies demonstrating inferior performance using mpMRI (22). Almost all mpMRI scans in our study were performed at a high volume centre and reported by specialised MRI radiologists with significant experience in mpMRI prostate, perhaps overestimating sensitivity in our cohort. Conversely, although PSMA avidity allows identification of focal lesions on PET/CT, assessment of true lesion size is difficult due to lack of sufficient detail on the CT component, and as apparent lesion size is dependent on the SUV threshold used at the time of reporting, which can be variable. The degree of anatomical detail offered by imaging is an important consideration in planning for focal therapy. Underestimation of tumour size on mpMRI remains a concern (6,34), and ^{68}Ga-PSMA PET/CT may suffer from a similar drawback, with attempts to estimate tumour volume using standardised uptake value thresholds to contour lesion borders revealing only moderate histopathological correlation (35). Consequently, a combination of mpMRI at the voxel level, co-registered with PSMA PET, is being explored as a machine learning framework to optimise planning for focal therapy (36).

Our study has a number of limitations. Firstly, as a result of its retrospective nature, radiologists and nuclear medicine physicians were not blinded to either mpMRI or ^{68}Ga-PSMA PET/CT results when reporting scans. Any cross examination of scans may have potentially overestimated the sensitivity of either test. Secondly, although required to precisely assess tumour location, evaluation of these imaging techniques in a RP cohort introduces selection bias, potentially overestimating imaging accuracy in a group of men with higher grade tumours. Men referred to undergo ^{68}Ga-PSMA PET/CT are inherently likely to be of intermediate-high clinical risk, compounding this potential bias. Our study was also limited to the characterisation of index tumours. Although we selected this outcome based on its prognostic significance, this meant only sensitivity and not specificity could be assessed. Finally, as mentioned earlier, more discrete evaluation of tumour volume and extent was not feasible on PET/CT, limiting classification of lesion location to sextant areas. Both of these issues may be addressed in future by way of large, per-segment or voxel-wise analyses (36).

It is possible that, ultimately, a combined ^{68}Ga-PSMA PET/MRI approach may be the ideal tool in characterising primary disease on imaging. PSMA PET adds high sensitivity and staging accuracy to the anatomical detail afforded by mpMRI, and early studies have shown promising results in using PET/MRI to improve the localisation of tumours when compared with either modality alone (16). However, PET/MRI is an expensive platform and is predominantly restricted to the research setting. Fusion of mpMRI and PET/CT acquired independently may be a more practical approach.

Conclusion

We found no significant difference in the overall detection or localisation of primary prostate cancer between ^{68}Ga-PSMA PET/CT and mpMRI. Both modalities were also comparable in the detection of clinically significant cancer and transition zone tumours. Tumours that were missed using either ^{68}Ga-PSMA PET/CT or mpMRI were smaller and associated with a lower PSA density. Further studies are required to compare the localisation accuracy of ^{68}Ga-PSMA PET/CT and mpMRI per-segment, and also evaluate the added utility of a combined PET/MRI model.

Conflict of Interest

None declared

References

1. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017 Feb 25;389(10071):815–22.

2. Nzenza T, Murphy DG. PRECISION delivers on the PROMIS of mpMRI in early detection. Nat Rev Urol. 2018 Sep;15(9):529–30.

3. Hansen NL, Barrett T, Kesch C, et al. Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naïve men with suspicion of prostate cancer. BJU Int. 2017 Oct 11;313:390.

4. Barnett CL, Davenport MS, Montgomery JS, Wei JT, Montie JE, Denton BT. Cost-effectiveness of magnetic resonance imaging and targeted fusion biopsy for early detection of prostate cancer. BJU Int. 2018 Feb 1;157:120.

5. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. Eur Urol. 2016 Mar;69(3):428–35.

6. Priester A, Natarajan S, Khoshnoodi P, et al. Magnetic Resonance Imaging Underestimation of Prostate Cancer Geometry: Use of Patient Specific Molds to Correlate Images with Whole Mount Pathology. J Urol. 2017 Feb;197(2):320–6.

7. Hoeks CMA, Hambrock T, Yakar D, et al. Transition zone prostate cancer: detection and localization with 3-T multiparametric MR imaging. Radiology. 2013 Jan;266(1):207–17.

8. Murphy DG, Azad AA, Sandhu S, Violet J, Hofman MS. Prostate-specific Membrane Antigen Across the Spectrum of Prostate Cancer: Detection, Surgery, and Theranostics. Eur Urol. 2019 Jan 4.

9. Murphy DG, Hofman M, Lawrentschuk N, Maurer T. Bringing clarity or confusion? The role of prostate-specific membrane antigen positron-

emission/computed tomography for primary staging in prostate cancer. BJU Int. 2017 Feb;119(2):194–5.

10. Maurer T, Eiber M, Schwaiger M, Gschwend JE. Current use of PSMA-PET in prostate cancer management. Nat Rev Urol. 2016 Apr;13(4):226–35.

11. Perera M, Papa N, Roberts M, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol. 2019 Feb 14.

12. 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 May;117(5):732–9.

13. Chaloupka M, Herlemann A, D'Anastasi M, et al. 68Gallium-Prostate-Specific Membrane Antigen PET/Computed Tomography for Primary and Secondary Staging in Prostate Cancer. Urol Clin North Am. 2017 Nov;44(4):557–63.

14. van Leeuwen PJ, Emmett L, Ho B, et al. Prospective evaluation of 68Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer. BJU Int. 2017 Feb;119(2):209–15.

15. van Leeuwen PJ, Donswijk M, Nandurkar R, et al. Gallium-68-prostate-specific membrane antigen (68 Ga-PSMA) positron emission tomography (PET)/computed tomography (CT) predicts complete biochemical response from radical prostatectomy and lymph node dissection in intermediate- and high-risk prostate cancer. BJU Int. 2018 Aug 3.

16. Eiber M, Weirich G, Holzapfel K, et al. Simultaneous 68Ga-PSMA HBED-CC PET/MRI Improves the Localization of Primary Prostate Cancer. Eur Urol. 2016 Nov;70(5):829–36.

17. Hofman MS, Eu P, Jackson P, et al. Cold Kit for Prostate-Specific Membrane Antigen (PSMA) PET Imaging: Phase 1 Study of 68Ga-Tris(Hydroxypyridinone)-PSMA PET/CT in Patients with Prostate Cancer. J Nucl Med. 2018 Apr;59(4):625–31.

18. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol. 2016 Jan;69(1):16–40.

19. Mottet N, van den Bergh R, Briers E, et al. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer. EAU Guidelines. 2019 Mar.

20. Leapman MS, Cowan JE, Simko J, et al. Application of a Prognostic Gleason Grade Grouping System to Assess Distant Prostate Cancer Outcomes. Eur Urol. 2017 May;71(5):750–9.

21. He J, Albertsen PC, Moore D, Rotter D, Demissie K, Lu-Yao G. Validation of a Contemporary Five-tiered Gleason Grade Grouping Using Population-based Data. Eur Urol. 2017 May;71(5):760–3.

22. Berger I, Annabattula C, Lewis J, et al. 68Ga-PSMA PET/CT vs. mpMRI for locoregional prostate cancer staging: correlation with final histopathology. Prostate Cancer Prostatic Dis. 2018 Jun;21(2):204–11.

23. Johnson DC, Raman SS, Mirak SA, et al. Detection of Individual Prostate Cancer Foci via Multiparametric Magnetic Resonance Imaging. Eur Urol. 2018 Nov 30.

24. Hofman MS, Murphy DG, Williams SG, et al. A prospective randomized multicentre study of the impact of gallium-68 prostate-specific membrane antigen (PSMA) PET/CT imaging for staging high-risk prostate cancer prior to curative-intent surgery or radiotherapy (proPSMA study): clinical trial protocol. BJU Int. 2018 Nov;122(5):783–93.

25. Rhee H, Thomas P, Shepherd B, et al. Prostate Specific Membrane Antigen Positron Emission Tomography May Improve the Diagnostic Accuracy of Multiparametric Magnetic Resonance Imaging in Localized Prostate Cancer. J Urol. 2016 Oct;196(4):1261–7.

26. Fendler WP, Schmidt DF, Wenter V, et al. 68Ga-PSMA PET/CT Detects the Location and Extent of Primary Prostate Cancer. J Nucl Med. 2016 Nov;57(11):1720–5.

27. Koerber SA, Utzinger MT, Kratochwil C, et al. 68Ga-PSMA-11 PET/CT in Newly Diagnosed Carcinoma of the Prostate: Correlation of Intraprostatic PSMA Uptake with Several Clinical Parameters. J Nucl Med. 2017 Dec;58(12):1943–8.

28. Minner S, Wittmer C, Graefen M, et al. High level PSMA expression is associated with early PSA recurrence in surgically treated prostate cancer. Prostate. 2011 Feb 15;71(3):281–8.

29. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018 May 10;378(19):1767–77.

30. Lopci E, Saita A, Lazzeri M, et al. 68Ga-PSMA Positron Emission Tomography/Computerized Tomography for Primary Diagnosis of Prostate Cancer in Men with Contraindications to or Negative Multiparametric Magnetic Resonance Imaging: A Prospective Observational Study. J Urol. 2018 Feb 1.

31. Herlemann A, Wenter V, Kretschmer A, et al. 68Ga-PSMA Positron Emission Tomography/Computed Tomography Provides Accurate Staging of Lymph Node Regions Prior to Lymph Node Dissection in Patients with Prostate Cancer. Eur Urol. 2016 Oct;70(4):553–7.

32. Finley DS, Deane L, Rodriguez E, et al. Anatomic excision of anterior prostatic fat at radical prostatectomy: implications for pathologic upstaging. Urology. 2007 Nov;70(5):1000–3.

33. Lawrentschuk N, Haider MA, Daljeet N, et al. “Prostatic evasive anterior tumours”: the role of magnetic resonance imaging. BJU Int. 2010 May;105(9):1231–6.

34. Bratan F, Melodelima C, Souchon R, et al. How accurate is multiparametric MR imaging in evaluation of prostate cancer volume? Radiology. 2015 Apr;275(1):144–54.

35. Rhee H, Thomas P, Shepherd B, et al. Prostate Specific Membrane Antigen Positron Emission Tomography May Improve the Diagnostic Accuracy of Multiparametric Magnetic Resonance Imaging in Localized Prostate Cancer. J Urol. 2016 Oct;196(4):1261–7.

36. Reynolds HM, Williams S, Jackson P, et al. Voxel-wise correlation of positron emission tomography/computed tomography with multiparametric magnetic resonance imaging and histology of the prostate using a sophisticated registration framework. BJU Int. 2018 Dec 10.

Table 1: Demographic and pathological features of cohort (n=205)

Demographics		
Age (years)		67 (IQR, 61 – 72)
PSA (ng/mL)		7.18 (4.90 –10.20)
PSAD		0.204 (0.145 – 0.305)
Features on mpMRI		
PIRADS Score	**2**	10 (4.9%)
	3	14 (6.8%)
	4	93 (45.4%)
	5	88 (42.9%)
Pathological features on RP		
Index tumour ISUP Grade Group	**GG 2**	72 (35.1%)
	GG 3	87 (42.4%)
	GG 4	10 (4.9%)
	GG 5	36 (17.6%)
Pathological T-stage	**pT2**	78 (38.0%)
	pT3a	86 (42.0%)
	pT3b	41 (20.0%)
Index tumour volume		2.8 cc (1.5 – 5.8)
Zonal location	**Peripheral zone only**	145 (70.7%)
	Transition zone only	20 (9.8%)
	Both	40 (19.5%)
• Figures shown as median (*interquartile range*), or n (%) • PSA = prostate specific antigen; PSAD = PSA density; RP = radical prostatectomy; ISUP = International Society of Urological Pathology; GG = ISUP Grade Group		

Table 2: Clinical and tumour characteristics in men with non-avid 68Ga-PSMA PET/CT or non-visible lesions on mpMRI

Variable		**68Ga-PSMA PET/CT**	**mpMRI**
n		12	11
Age		71 (65 – 69)	65 (63 – 69)
PSA (ng/mL)		5.25 (3.63 – 8.43)	9.90 (4.94 – 18.60)
PSAD		0.114 (0.075 – 0.143)	0.260 (0.159 – 0.380)
Pathological features on RP			
Index TV		1.4 (0.8 – 2.2)	1.2 (0.6 – 2.8)
ISUP GG	**2**	9 (75.0%)	6 (54.5%)
	3	1 (8.3%)	4 (36.4%)
	4	1 (8.3%)	0
	5	1 (8.4%)	1 (9.1%)
pT-stage	**pT3**	7 (58.3%)	4 (36.4%)
Index tumour location – zone	**Peripheral zone only**	10 (83.3%)	8 (72.7%)
	Transition zone only	2 (16.7%)	2 (18.2%)
	Both	0	1 (9.1%)
Index tumour location – left/right	**Right-sided only**	6 (50.0%)	5 (45.4%)
	Left-sided only	4 (33.3%)	3 (27.3%)

Table 3: Sagittal and coronal location of index tumours on RP accurately localised by ^{68}Ga-PSMA PET/CT and mpMRI

Plane	**Location**	68Ga-PSMA PET/CT	mpMRI	No. of index tumours on RP
Sagittal	**Left only**	70 (93.3%)	66 (88.0%)	**75**
	Right only	48 (85.7%)	46 (82.2%)	**56**
	Bilateral	69 (93.2%)	70 (94.6%)	**74**
Coronal	**Anterior only**	31 (86.1%)	31 (86.1%)	**36**
	Posterior only	116 (89.9%)	111 (86.0%)	**129**

Figure 1: Tumours detected and missed on mpMRI and 68Ga-PSMA PET/CT with RP histological comparison. A) PET/CT and mpMRI both positive; B) PET/CT positive and mpMRI negative; C) PET/CT negative and mpMRI positive; D) PET/CT and mpMRI both negative.

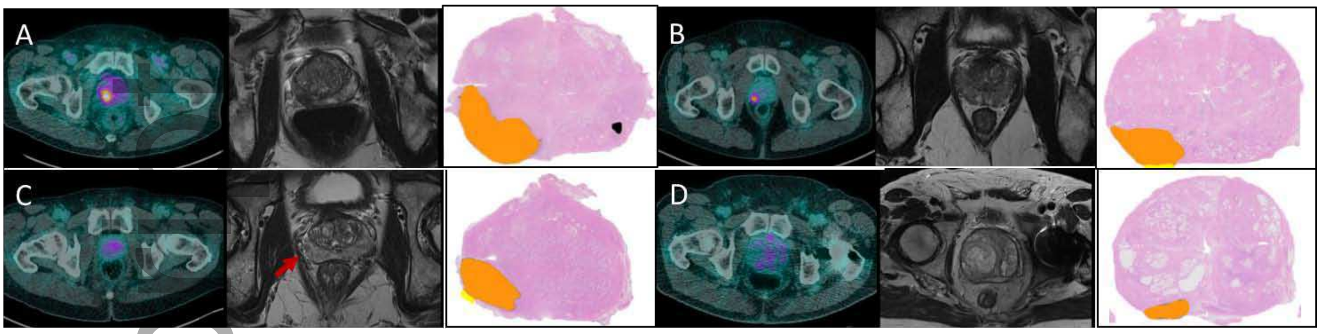

Figure 2: Example of non-avid lesion on 68Ga-PSMA PET/CT (A) compared with wholemount histopathology (B). 60 year old male, PSA 3.2 with no focal lesion on 68Ga-PSMA PET/CT. Final pathology on RP was ISUP GG 2, stage pT3a.

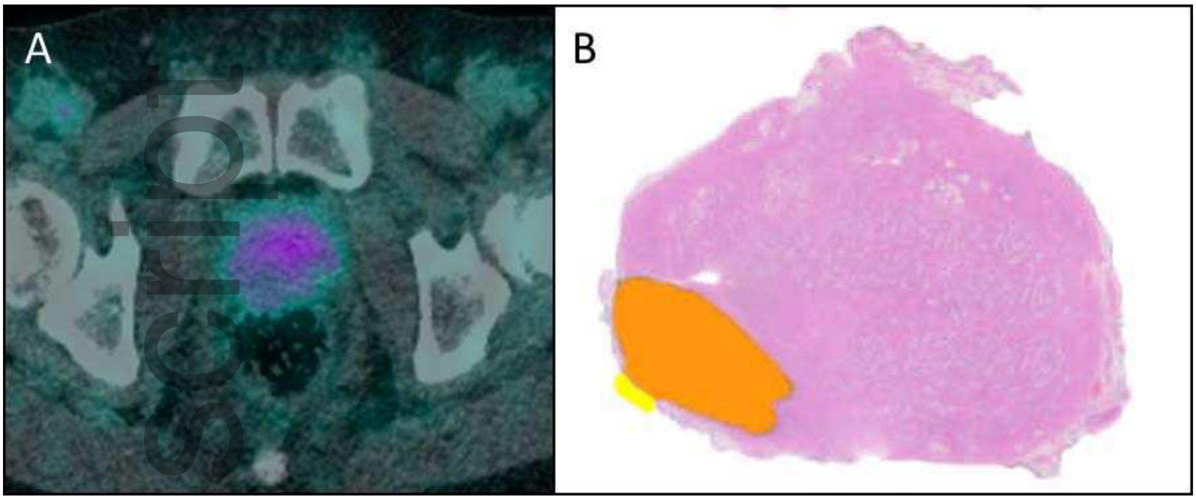

Figure 3: Localisation of index tumour by ISUP Grade Group