Multiparametric Magnetic Resonance Imaging of the Prostate and Prostate-specific Membrane Positron Emission Tomography Prior to Prostate Biopsy (MP4 Study)

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Article info

Article history:
Accepted November 23, 2022

Associate Editor:
Guillaume Ploussard

Keywords:
Magnetic resonance imaging
Positron emission tomography
Prostate biopsy
Prostate cancer
Prostate-specific membrane antigen

Abstract

Background: Prostate-specific membrane antigen (PSMA) positron emission tomography/computerised tomography (PET/CT) is increasingly being utilised in the diagnostic pathway for prostate cancer (PCa). Recent publications have suggested that this might help identify those who can avoid biopsy.

Objective: The primary objective of this study was to determine whether PET magnetic resonance imaging (MRI) fusion could negate the need to biopsy prior to prostatectomy in a selected population of men.

Design, setting, and participant: Multiparametric MRI (mpMRI) for PCa is our standard of care prior to prostate biopsy. Biopsy-naïve men with one or more Prostate Imaging Reporting and Data System (PI-RADS) 4 or 5 lesions ≥10 mm on mpMRI were invited to undergo PSMA PET/CT prior to biopsy. Following ethics approval, 60 men were recruited between September 2020 and March 2021. The key exclusion criteria included a previous history of PCa and previous prostate surgery or biopsy.

Outcome measurements and statistical analysis: A positive PET MRI fusion scan was defined as “consistent with” as per the Memorial Sloan Kettering Cancer Center lexicon of certainty, and concordance with biopsy results was analysed. Clinically significant PCa (csPCa) was defined as grade group (GG) ≥2 on pathology. A chi-square analysis was performed with statistical significance defined at p < 0.05.

Results and limitations: A total of 71 mpMRI lesions were positive on 61 (86%) PET MRI fusion scans. Fifty-nine of 61 lesions biopsied confirmed csPCa in 54 (92%). Of five of 59 lesions for which either biopsy was negative or low-grade cancer was found, three had rebiopsy of which two were confirmed to have csPCa.
1. Introduction

Prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) is increasingly being utilised as a diagnostic tool for prostate cancer. Initial utilisation primarily focused upon its role in the detection of disease recurrence following the curative-intent treatment of the primary cancer by surgery or radiotherapy, and also as a tool for primary staging [1–3]. More recently, PSMA PET has an evolving role as a diagnostic tool to characterise prostate cancer within the gland [4–8]. Several provocative studies have indicated the potential for PSMA imaging in conjunction with multiparametric magnetic resonance imaging (MRI) of the prostate to triage those men who could be potentially reassured and monitored, rather than proceed to diagnostic biopsy [6,7,9]. The next evolution of this idea is the more controversial premise wherein carefully selected men, with both abnormal MRI and abnormal PSMA PET/CT, could potentially proceed directly to definitive local treatment without the need for a diagnostic tissue biopsy [9].

The Prostate Imaging Reporting and Data System (PI-RADS) is a well-established structured reporting system for abnormal findings on multiparametric MRI of the prostate. Lesions with higher-risk features are assigned a score of PI-RADS 4 or 5, and are associated with a greater likelihood of harbouring clinically significant prostate cancer (csPCa) [10,11]. With the knowledge that PSMA expression is more pronounced in csPCa, the combination of PSMA PET/CT and MRI (PET MRI fusion) presents an intuitive comprehensive imaging approach to the diagnosis of csPCa.

The aim of this study was to determine whether PET MRI fusion could obviate the need for biopsy prior to prostatectomy in a selected population of men with high-grade abnormalities on prostate MRI.
measurement on axial T2 images was at least 10 mm. The exclusion criteria included any previous history of prostate cancer, previous prostate biopsies, previous transurethral resection of the prostate, PSA >20 ng/ml, any cT3 on digital rectal examination, and inability to provide written informed consent or unlikely to comply with the requirements of the study.

2.3. Multiparametric MRI protocol

SRNM maintains a standardised protocol for prostate MRI as follows: routine undertaking of bowel preparation prior to the scan in addition to hyoscine butylbromide 20 mg by intravenous injection; performing all MRI scans with 3-Tesla magnetic field strength with high-resolution T2 sequences in axial, coronal, and sagittal planes; a 3D T2 sequence; diffusion-weighted imaging with software-derived apparent diffusion coefficient quantitative analysis maps, and multiple b-values (acquired b50, acquired b1400, and calculated b2000); dynamic contrast enhanced (DCE) 3D imaging, with automatically delivered intravenous gadolinium DTPA bolus determined by body weight, at 2.5 ml/s followed by T1 sequences DCE TRICKS (Time-Resolved Imaging of Contrast Kinetics); and an analysis of DCE imaging according to PI-RADS DCE imaging analytic guidelines using DYNACAD software. Reporting was undertaken with PI-RADS (version 2.1).

Identification of a PI-RADS 4 or 5 lesion of at least 10 mm in one axial dimension in patients identified those to be potentially eligible for study inclusion.

2.4. PSMA PET/CT protocol

The tracer 18F DCFPyI was chosen, as it is commercially available (Cyclotek, Melbourne, VIC, Australia) and released for use following radiopharmacy quality control with high-pressure liquid chromatography and transported by air to SRNM as per standard procedures for radioactive substances. Up to 350 MBq of 18F DCFPyI was administered according to body weight as a slow bolus injection over 30 s. Scan time was 90 min after injection from the vertex to the thighs with a non-contrast-enhanced low-dose CT scan after tracer injection using the following CT parameters: 3.75 mm slice thickness with PET attenuation correction reconstruction and standard reconstruction kernels, 120 keV and 80–200 mA (autoadjusted to minimise dose per patient body habitus), pitch of 0.984, large body field of view (FOV), helical rotation at 0.5 s per rotation, and a 512 matrix. The PET acquisition parameters were as follows: 3 min per bed position using a static acquisition and a 128 matrix, and scanning commencing at the pelvis and reconstructed using a measured attenuation correction method using a standard filter with two iterations and 24 subsets. Diagnostic contrast CT scans of the chest, abdomen, and pelvis were performed as part of a usual standard-of-care examination using the following CT parameters: 1.25 mm slice thickness with soft reconstruction kernel, 120 keV and 100–800 mA (autoadjusted to minimise dose per patient body habitus), pitch of 0.516, large body FOV, helical rotation at 0.5 s per rotation at 1 mm intervals, and a 512 matrix. Intravenous contrast was administered at 1 ml/kg.

PSMA PET/CT images were reported at a “per-lesional” level (after software fusion with MRI) and also at a “per-patient” level for whole-body staging. Software fusion of MRI and PSMA PET/CT images was performed with the supplied software package from the manufacturers of the MRI machines (General Electric; Fig. 1).

Owing to absence of an established standardised PSMA PET reporting system for primary prostate cancer, we utilise the Memorial Sloan Kettering Cancer Center (MSKCC) lexicon of certainty (LOC) [12,13], where abnormalities are classified according to whether clinically significant cancer (CSC) is likely or unlikely, as follows:

1. Consistent with high-grade malignancy (≥90% reader certainty for a likelihood of CSC).
2. Probable high-grade malignancy (≥75% reader certainty for a likelihood of CSC).
3. Possible high-grade malignancy (≥50% reader certainty for a likelihood of CSC; equivocal).
4. Unlikely high-grade malignancy (≥75% reader certainty that CSC is unlikely).
5. Very unlikely high-grade malignancy (≥90% reader certainty that CSC is very unlikely).

Size, location, and the maximum standardised uptake value (SUV max) for focal lesions were recorded, and PSMA PET and MRI concordance or discordance were also recorded.

All imaging was reported by a single dual-trained radiologist and PET specialist (L.T.) who is oncology fellowship trained in both modalities. In Australia, there are relatively few imaging specialists who have dual qualifications in both radiology and PET, and the interpretation of the PET MRI is dependent on this expertise. The call of positive or negative PET MRI is not based upon specific thresholds for SUV or specific patterns of PET tracer uptake. It is instead based upon the interpretation for both the images of the MRI and PSMA PET that have been software fused. As an example, the finding of a photopenic area on PSMA PET that has significantly less tracer activity overlying a PI-RADS 5 lesion compared with surrounding prostate tissue in the remainder of the gland would be considered to be as much a “consistent with” interpretation using the MSKCC LOC as a tracer avid lesion with a high associated SUV. We have significant reservations over the use of SUV thresholds,

Fig. 1 – Example of PI-RADS 5 lesion in the right posterior peripheral zone of gland (T2 axial) with tracer uptake on PSMA PET/CT classified as a positive result of PET MRI. CT = computerised tomography; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PET = positron emission tomography.
as this parameter is highly problematic and, for this reason, it has not been used in other cancers where PET/CT technology has been an established imaging tool for many years. Whilst there is a concerning overuse of SUV as a threshold parameter in the prostate cancer literature, further discussion detailing such pitfalls would be outside the scope of the paper.

2.5. Prostate biopsy protocol

All prostate biopsies were performed via a transperineal approach under general anaesthesia. Up to three lesions, as identified on MRI, were subjected to targeted biopsies with either software fusion or cognitive fusion, according to the discretion of the participating urologist and with each lesion having at least four cores. The decision to perform additional systematic biopsies was at the discretion of the urologist.

2.6. Key definitions

We defined a csPCa as any cancer with grade group (GG) $\geq 2$ (presence of any amount of Gleason grade $\geq 4$). Likewise, we defined a positive PET MRI scan for a given lesion to be one that was consistent with high-grade malignancy on the LOC ($\geq 90\%$ reader certainty for a likelihood of CSC).

2.7. Statistical considerations

At the time of study development, no data existed on the expected numbers of men for which PI-RADS 4 or 5 lesions of at least 10 mm in size would have concordant uptake of a PSMA PET tracer, and therefore power calculations to achieve this were not possible. Summary data are expressed in terms of means and standard deviations, or medians with interquartile ranges.

3. Results

A total of 60 men were recruited in the study. The patient population is outlined in Table 1. One MRI lesion with a PI-RADS score of 4 or 5 that was at least 10 mm in size was identified in 49 men; in 11 men, there were two such lesions. No patient had more than two lesions.

For men with a PI-RADS 4 or 5 MRI abnormality that was at least 10 mm in axial dimension, 61 of 71 such lesions (86%) were also considered to have a PET MRI fusion scan that was positive.

Owing to patient factors, only 59 of 61 lesions were biopsied; of these 59 lesions, 54 (92%) were confirmed to have csPCa. The histopathology results in 13 of the 59 lesions that were biopsied either were negative ($n = 11$) or identified only low-grade prostate cancer ($n = 2$). The distribution of pathology results according to the PET MRI results is summarised in Table 2.

Of 59 lesions, five had a biopsy result that was either was negative or found to be low-grade cancer only. Of these five lesions, three had a rebiopsy performed 6 mo later. Of these three lesions, two were confirmed to have csPCa, corroborating the PET MRI fusion, whilst the other was again found to have low-grade prostate cancer. For the remaining two lesions in two patients, both had another lesion within the gland that had already been confirmed to have csPCa on biopsy. For these patients, a repeat biopsy would not have altered management. Of these two men, one underwent...

Table 1 – Summary statistics

<table>
<thead>
<tr>
<th>Baseline measures</th>
<th>Median</th>
<th>IQR</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>68</td>
<td>63–74</td>
<td>61</td>
<td>91</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>4.3</td>
<td>9–11</td>
<td>1.7</td>
<td>86</td>
</tr>
<tr>
<td>Prostate volume (cc)</td>
<td>40</td>
<td>31–55</td>
<td>19</td>
<td>498</td>
</tr>
<tr>
<td>PSA density (ng/ml/cc)</td>
<td>0.15</td>
<td>0.12–0.20</td>
<td>0.04</td>
<td>0.94</td>
</tr>
<tr>
<td>MRI lesion maximum dimension (mm)</td>
<td>16</td>
<td>14–20</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td>SUV max</td>
<td>11</td>
<td>4.2–27</td>
<td>1.6</td>
<td>94</td>
</tr>
<tr>
<td>MRI lesions</td>
<td>$n$</td>
<td>%</td>
<td>no. PET MRI +ve</td>
<td>% PET MRI +ve</td>
</tr>
<tr>
<td>PI-RADS 4 lesions</td>
<td>20</td>
<td>28</td>
<td>17</td>
<td>85</td>
</tr>
<tr>
<td>PI-RADS 5 lesions</td>
<td>51</td>
<td>72</td>
<td>43</td>
<td>84</td>
</tr>
<tr>
<td>MRI lesion location</td>
<td>Numerator/denominator</td>
<td>%</td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>Any PZ lesion</td>
<td>51/71</td>
<td>72</td>
<td>43</td>
<td>84</td>
</tr>
<tr>
<td>PZ only</td>
<td>41/51</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PZ including CZ only</td>
<td>5/51</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PZ including TZ only</td>
<td>5/51</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TZ lesion</td>
<td>24/71</td>
<td>34</td>
<td>22</td>
<td>92</td>
</tr>
<tr>
<td>TZ only</td>
<td>18/24</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TZ including PZ only</td>
<td>5/24</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TZ including CZ only</td>
<td>1/24</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any CZ lesion</td>
<td>7/71</td>
<td>10</td>
<td>6</td>
<td>86</td>
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<tr>
<td>PZ only</td>
<td>1/7</td>
<td>14</td>
<td></td>
<td></td>
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<tr>
<td>PZ including PZ only</td>
<td>5/7</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C21 including TZ only</td>
<td>1/7</td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C21 = central zone; IQR = interquartile range; MRI = magnetic resonance imaging; PET = positron emission tomography; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PZ = peripheral zone; SUV max = maximum standardised uptake value; TZ = transition zone.

Table 2 – Prostate biopsy pathology on basis of PET MRI lexicon of certainty assessment

<table>
<thead>
<tr>
<th>No cancer</th>
<th>GG1</th>
<th>GG2</th>
<th>GG3</th>
<th>GG4</th>
<th>GG5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent</td>
<td>3</td>
<td>2</td>
<td>22</td>
<td>18</td>
<td>4</td>
<td>59</td>
</tr>
<tr>
<td>Probable</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Possible</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unlikely</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Very unlikely</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

GG = grade group; MRI = magnetic resonance imaging; PET = positron emission tomography.
surgery, and the histopathology of the radical prostatectomy specimen confirmed the presence of GG2 cancer where the biopsy had been negative; for the other patient, a decision for conservative management was made. Further details of these patients are summarised in Table 3.

All cancers found to have a GG of 3, 4, or 5 on pathology had been classified as having a positive PET MRI fusion scan result.

A total of two men had lesions that were not subjected to prostate biopsy. One patient proceeded to a radical prostatectomy without a biopsy. The PET MRI was positive and the final pathology of the corresponding cancer was GG5. His circumstances were unusual in that his prostate was 498 cc and had significant urinary symptoms. Another patient with two lesions did not have the second lesion biopsied due to poor Eastern Cooperative Oncology Group (ECOG) performance status. The lesion that was biopsied was found to have evidence of GG5, and the patient has subsequently been managed conservatively by watchful waiting. It was notable that all men with low-grade prostate cancer did not have abnormal digital rectal examination findings or PSA elevation that would have placed them into a d’Amico intermediate- or high-risk classification.

4. Discussion

The key finding of this study is the demonstration that, when combined with congruent PSMA PET avidity, almost all men with a PI-RADS 4 or 5 MRI abnormality of at least 10 mm in axial dimension were found to have csPCa on a histological assessment.

If results on the basis of the subsequent progress of prostate biopsies or findings on the one case of radical prostatectomy pathology were to be considered, 56 of 59 PET MRI-positive lesions were associated with histologically proven csPCa as a worst case scenario, based on these data. With the adoption of a best case scenario, it is possible that all lesions were in fact associated with csPCa. Unfortunately, it will never be known whether the two lesions that were not subjected to rebiopsy had csPCa that was missed by initial biopsy, although our re-evaluation of these individual cases indicates that this would be likely. Whilst another lesion on repeated biopsy was found to have confirmed the presence of only GG1 prostate cancer, further monitoring and follow-up on an active surveillance pathway has the potential to still uncover a missed csPCa. That said, it is our belief that for now, this case must be regarded as a false negative, and this is in part influenced by our further investigation into the detail of this case as follows. MRI had been performed on a 51-yr-old man on the basis of a strong family history of prostate cancer. The MRI had identified a large 20 mm unilateral PI-RADS 5 lesion in the transition zone of the gland, and the total gland volume was only 30 cc. The first round of prostate biopsies had found only a 3 mm segment of low-grade cancer in one out of four targeted cores. On the second round of prostate biopsies performed 6 mo later, the lesion was aggressively targeted with ten cores, and once again only a single core was found to have a 3 mm segment of low-grade prostate cancer. Following what has been a saturation biopsy approach to a large MRI lesion, it was considered unlikely that biopsies had missed CSC.

It could be argued that many men with particularly high-risk features could justifiably undergo a PSMA PET/CT scan prior to biopsy, but for reasons of insufficient evidence to support this approach and the lack of reimbursement for this indication would result in significant expenses for patients.

The role of PSMA PET/CT in the diagnostic pathway continues to emerge. The PRIMARY study in particular has indicated that the combination of MRI and PSMA PET/CT has the ability to significantly improve the selection of men who could potentially avoid a prostate biopsy [7]. Further data from this study will likely identify subsets in which there is a greater imperative to perform a prostate biopsy, and potentially those who may avoid biopsy and proceed directly to a surgical approach.

This study utilised a highly selected population. This was a pragmatic decision on the basis of available resources allocated to this study. MRI lesions that were at least of PI-RADS 4 or 5 were selected due to the well-established high probability of these to represent csPCa [14]. By including only lesions that were at least 10 mm in size, the probability of missing a csPCa through variations in the transperineal prostate biopsy technique was deemed to be less likely. It was also considered that MRI lesions meeting these criteria are commonly encountered.

During data analysis, it came to our attention that there had been one protocol violation with a single patient being enrolled in the study with a PSA level of 86 ng/ml. All other patients appropriately met the inclusion and exclusion criteria. The decision was made to include this patient given that the analysis with and without this patient resulted in virtually identical analysis outcomes.

There are limited data on the comparability of 18F DCFPyL compared with Ga68 HBEDD-11 tracers [15]. SRNM switched to using the former routinely due to the institu-

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**Table 3 – Positive PET MRI where biopsies either negative or GG1 (n = 6)**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>PI-RADS</th>
<th>Size</th>
<th>Location</th>
<th>SUV</th>
<th>Gland size</th>
<th>Biopsy pathology</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°</td>
<td>4</td>
<td>13</td>
<td>PZ</td>
<td>27</td>
<td>27</td>
<td>Negative</td>
<td>Resampling found GG3 but radical prostatectomy pathology confirmed GG2</td>
</tr>
<tr>
<td>2°</td>
<td>4</td>
<td>11</td>
<td>PZ</td>
<td>7.7</td>
<td>27</td>
<td>Negative</td>
<td>Resampling biopsies negative but radical prostatectomy confirmed GG2</td>
</tr>
<tr>
<td>3°</td>
<td>4</td>
<td>11</td>
<td>PZ</td>
<td>9.6</td>
<td>73</td>
<td>Negative</td>
<td>Index lesion found GG2</td>
</tr>
<tr>
<td>4°</td>
<td>5</td>
<td>20</td>
<td>PZ</td>
<td>10.4</td>
<td>80</td>
<td>Negative</td>
<td>Index lesion had GG3</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>16</td>
<td>PZ</td>
<td>53</td>
<td>57</td>
<td>GG1</td>
<td>Resampling found GG4</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>20</td>
<td>TZ</td>
<td>5.3</td>
<td>30</td>
<td>GG1</td>
<td>Resampling found GG1</td>
</tr>
</tbody>
</table>

GG = grade group; MRI = magnetic resonance imaging; PET = positron emission tomography; PI-RADS = Prostate Imaging Reporting and Data System; PZ = peripheral zone; SUV = standardised uptake value; TZ = transition zone.

a Two lesions in the same patient.
b Nondominant of two MRI lesions.
tion’s gallium generator reaching end of life—18F DCFPyL has become our preferred tracer on the basis that it is commercially available and more logistically manageable for the working of our imaging department. We acknowledge that Ga68 HBEED-11 is likely to be the predominant tracer currently in use, although the use of 18F DCFPyL is increasing as evidenced by increasing publications in the literature.

The interpretation of PSMA PET is a limitation of all studies as it requires an element of subjective assessment by the reader and given that there is a lack of standardised practice. Attempts to address this have been undertaken by the European Association of Nuclear Medicine and were published in 2021 [16], which was following the commencement of this study. These guidelines on reporting PSMA PET are based upon expert opinion rather than data, and the recommendations are for assessment of PSMA tracer uptake abnormalities that are broadly subjective and based upon reader confidence. The MSKCC LOC is not dissimilar to the EANM recommendations in that it relies upon subjective reader confidence in a call of a positive scan result. As more data emerge, objective criteria as well as harmonisation of thought in an appropriate way forward can be expected in the future.

We considered the possibility that the location of the MRI lesions could impact the likelihood of finding csPCa, but the small numbers did not allow a further analysis. Larger-scale studies may identify any significance of lesion location. It is also important to add that men with PI-RADS 4 or 5 lesions on their MRI scan but negative PSMA PET/CT should not be considered at any stage for biopsy avoidance. The standard of care for these men will continue to be to proceed to prostate biopsy.

The limitations of this study are the limited size of the cohort and the lack of pre-existing data to adequately power the study for robust endpoints. Whilst the study was non-randomised and limited to a single-centre study, we believe that there is strength in the high number of urological participants.

Whilst the concept of proceeding directly to radical prostatectomy without a prostate biopsy is highly controversial, a recent retrospective study has reinvigorated this discussion [9]. Our prospective study supports the provocative findings that there may be subsets of patients who could proceed directly to radical prostatectomy without first undergoing a prostate biopsy. This study would suggest that almost all men in this selected group had the potential to avoid a prostate biopsy, and the positive implications in avoiding unnecessary intervention and the streamlining of diagnostic workup cannot be underestimated. The findings from this study would unlikely be appropriate for planned treatment with radiotherapy due to the fact that information about the pathological grade of the cancer influences decisions about androgen deprivation therapy in conjunction with radiotherapy. With surgery, histological examination of the radical prostatectomy specimen clearly provides information that cannot be obtained if a radiotherapy treatment pathway is undertaken.

In the urological sphere, kidney tumours are routinely excised by either partial or radical nephrectomy on the basis of imaging findings alone, despite the potential for nonma-

5. Conclusions

This prospective study on the use of PSMA PET MRI fusion, in men with PI-RADS 4 or 5 lesions that are at least 10 mm in axial dimensions, supports previous provocative studies that there may be some men who might be able to proceed to prostate cancer surgery without a prior prostate biopsy. Further prospective studies to validate the role of PSMA PET/CT in the diagnosis of csPCa are justified.

Author contributions: Henry H. Woo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Woo, Thompson, Tarlinton.
Acquisition of data: Woo, Baskaranathan, Bergersen, Chalasani, Dean, Dias, Symons, Wines, Tarlinton.
Analysis and interpretation of data: Woo, Tarlinton.
Drafting of the manuscript: Woo, Tarlinton.
Critical revision of the manuscript for important intellectual content: Woo, Khanani, Thompson, Sorensen, Baskaranathan, Bergersen, Chalasani, Dean, Dias, Symons, Wines, Jain, Nassour, Tarlinton.
Statistical analysis: Woo, Khanani, Jain.
Obtaining funding: Woo, Tarlinton.
Administrative, technical, or material support: Thompson, Sorensen.
Supervision: Woo.
Other: None.

Financial disclosures: Henry H. Woo certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This research was supported by an unrestricted educational grant from AstraZeneca to cover the cost of the PSMA PET scans. AstraZeneca played no role in the design or conduct of this research.
Acknowledgements: The authors wish to thank Professor Gavin Marx and Ms Nina Singh for their assistance in meeting the requirements of the Human Research Ethics Committee of the Sydney Adventist Hospital.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.11.012.

References