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Abstract

Background:

Pre-biopsy multiparametric magnetic resonance imaging (mpMRI) for the detection of clinically significant prostate cancer (csPCa) is now standard of care for suspected prostate cancer. However, due to the limited positive predictive value (PPV) of mpMRI (50-60%), many unnecessary prostate biopsies are still performed. Further, although mpMRI has a high negative predictive value (NPV) of 85-95%, false negatives occasionally delay diagnosis and treatment. Prostate specific membrane antigen (PSMA) positron emission topography (PET)/computed tomography (CT) is commonly used in pre-treatment staging and localising post-treatment recurrence but has recently been observed to show promising accuracy for detecting the intra-prostatic focus of csPCa.

Objectives

The primary objectives of this study are:

- To determine the additive value of PSMA-PET/CT when combined with mpMRI in detecting csPCa in men undergoing initial biopsy for suspicion of PCa
- To determine the proportion of men who could have avoided prostate biopsy with positive mpMRI (PI-RADS ≥ 3) but negative PSMA-PET/CT

The secondary objectives of this study are:

- To determine the proportion of men who had csPCa detected only by PSMA-PET/CT or only by systematic prostate biopsy.
- Comparison of index lesion identification by template biopsies vs targeted lesions identified on mpMRI or PSMA-PET/CT
- To assess whether there may be a health-economic benefit or harm if PSMA-PET/CT is incorporated into the diagnostic algorithm; and
- To develop a nomogram which combines clinical, imaging and biomarker data to predict the likelihood of csPCa.

Methods:

The PRIMARY trial is a multicentre, prospective cross-sectional study that meets criteria for level 1 evidence in diagnostic test evaluation. PRIMARY will investigate if a limited (pelvic only) ^{68}Ga -PSMA-PET/CT in combination with routine mpMRI can reliably discriminate men with csPCa from those without csPCa. We conducted a power calculation based on pilot data and will recruit up to 600 men who will have ^{68}Ga -PSMA-PET/CT (PSMA, the index test), mpMRI (MRI, the standard test) and transperineal template + targeted (PSMA and/ or MRI) biopsies (TPB, the reference test). The conduct and reporting of the MRI and PSMA-PET/CT will be blinded to each other.

Outcome and Significance:

The PRIMARY trial will measure and compare sensitivity, specificity, PPV and NPV of both mpMRI and PSMA-PET/CT against TPB. The results will be used to determine the proportion of men who could safely avoid biopsy without compromising detection of clinically significant cancers. Furthermore, we will assess whether there is a health economic benefit in incorporating PSMA-PET/CT into the diagnostic algorithm.

Conclusions:

This trial will provide robust prospective data to determine the diagnostic ability of PSMA-PET/CT in addition to mpMRI. It will establish if certain patients can avoid biopsy in the investigation of PCa.

Introduction

Prostate cancer (PCa) is one of the most commonly diagnosed cancers in men. However, the detection and diagnosis of PCa in current urological practice remains controversial. There is significant sampling error and morbidity associated with prostate biopsy and it is difficult to differentiate between aggressive and indolent disease (1, 2). Therefore, there has been an increased interest in the use of imaging to facilitate detection of significant PCa and reduce unnecessary biopsies.

The use of multiparametric magnetic resonance imaging (mpMRI) has been shown to have an acceptable diagnostic accuracy in the detection of clinically significant PCa (csPCa) (3). A prospective cross-sectional study from our institution demonstrated sensitivity of 93-96% and specificity of 47-53% for PCa, such that MRI could reduce over-detection of insignificant PCa by one-third and allow biopsy to be deferred in one-quarter (4, 5). The PROMIS trial showed the sensitivity and specificity of mpMRI to detect any amount of grade group 2 PCa to be 88% and 45% respectively (6). In addition, the PRECISION trial showed that an mpMRI directed pathway increased the detection rate of clinically significant disease from 26 to 38% and reduced the detection rate of clinically insignificant disease from 22 to 9%, when compared to a 12-core TRUS-guided biopsy (7). Given this, the use of mpMRI will lead to significant improvements in the detection and diagnosis of PCa. However, it is important to note that the positive predictive value (PPV) of mpMRI is low at 34-68%, leading to unnecessary biopsies, and mpMRI still misses a small number of clinically significant cancers (3, 6, 8). EAU and NICE guidelines (9, 10) recommend mpMRI before prostate biopsy and there has been a steady increase in its use worldwide.

The addition of novel imaging or biomarkers may increase the detection of PCa missed by mpMRI. Prostate-specific membrane antigen (PSMA) is a cell surface transmembrane glycoprotein expressed on the cell surface by the majority of PCa cells, with its expression increasing in higher grade malignancy (11, 12). Recently, PSMA-PET/CT imaging has become increasingly utilised in the detection of metastatic disease, especially in patients with biochemical recurrence after local treatment (13-21).

Eiber et al (22) showed in 53 patients that ⁶⁸Ga PSMA-PET/CT had both a higher sensitivity and specificity than mpMRI for the detection of high-grade intraprostatic PCa. This study showed that simultaneous ⁶⁸Ga PSMA PET/MRI (AUC 0.88) outperformed

mpMRI (0.73) or PET (0.83) alone. Several other series demonstrated the improved diagnostic accuracy of intraprostatic PSMA-PET/CT in detecting PCa (23-25). Most recently, Scheltema et al (26) evaluated the ability of PSMA-PET/CT to detect intermediate-grade intraprostatic PCa and to determine if PSMA-PET/CT improved the diagnostic accuracy of mpMRI. They showed in 56 patients that with an SUV_{max} of 3.95 the sensitivity of intraprostatic PSMA was 94% and specificity was 100%. Furthermore, in a retrospective review of 205 men who underwent mpMRI, PSMA PET/CT, and radical prostatectomy, Kalapara et al reported that both mpMRI and PSMA PET/CT detected index lesions in 89-91% of cases (27). Whilst this data is promising, to our knowledge there are no high-quality prospective studies evaluating the efficacy of intraprostatic detection of PCa by PSMA PET/CT in the pre-biopsy setting.

This trial is a multicentre, prospective validating paired-cohort study which aims to determine the accuracy of ⁶⁸Ga-PSMA-PET/CT of the pelvis for detection of csPCa prior to diagnostic biopsy, in men undergoing biopsy based on PSA, DRE and MRI.

The current diagnostic pathway

Men suspected of having PCa are typically those with one or more risk factors including an elevated PSA/PSA density, an abnormal digital rectal examination, a family history, a genetic risk factor, or a specific ethnicity. In the post PROMIS and PRECISION era, many urologists perform a multiparametric MRI (mpMRI) of the prostate prior to considering biopsy. If the mpMRI reveals a suspicious or equivocal lesion, then a targeted +/- systematic biopsy is performed. If the scan is negative, then a biopsy may be avoided with shared decision-making. However, if the patient with a PIRADS 1-2 on mpMRI has risk factors (so called "red flags") such as a PSA >10 ng/ mL, high PSA density, high PSA velocity, BRCA-2 mutation, a family history of PCa in a first-degree relative or an abnormal DRE, then a systematic biopsy is still considered (Figure 1) (28).

Design and methods - the PRIMARY trial protocol

Overview

This is a multicentre, cross-sectional clinical trial which aims to assess the additive effect of PSMA-PET/CT scan to mpMRI in the diagnosis of PCa. The goal of the trial is to provide high quality evidence to establish whether PSMA-PET/CT scan should be added to mpMRI in the diagnosis of PCa in men undergoing biopsy.

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Objectives

The primary and secondary objectives are listed in table 1.

Patients and methods

The study is approved (HREC/18/SVH/239) by the St Vincent’s Hospital Human Research Ethics Committee (EC00140) and is registered on the Australian New Zealand Clinical trials registry (ANZCTRN12618001640291). The St Vincent’s Curran Foundation, St Vincent’s Clinic Foundation, St Vincent’s Prostate Cancer Centre and the Sydney Partnership for Health, education, research and enterprise (SPHERE) will fund this clinical trial. This study will be conducted according to local regulations and laws, the ethical principles in the Declaration of Helsinki and the principles of Good Clinical Practice. The trial schema is shown in Figure 2, and a schedule of events in Table 2.

Initial Visit

All patients will have been referred to a urologist for a suspicion of prostate cancer, based on an abnormal PSA or digital rectal examination (DRE). Patients will be screened by their urologist for eligibility onto the study based on the inclusion and exclusion criteria listed in table 1. A limited pelvic PSMA PET/CT will be performed prior to prostate biopsy in men alongside the standard workup for prostate cancer. An initial total of 207 men will be recruited from up to 9 centres, which will be extended to 578 men if interim analysis shows improvement in PPV.

mpMRI procedures

All men will undergo an mpMRI organized by their urologist or primary care physician prior to PSMA-PET/CT scan and prostate biopsy. This must have been completed within 6 months of biopsy. The mpMRI will be reported by local radiologists according to the Prostate Imaging-Reporting and Data System, version 2 (PI-RADS v2), on a scale from 1 to 5. Location of suspicious areas (scoring ≥ 3) will warrant descriptions of location and size to allow for targeted biopsies. The corresponding PSMA PET/CT report will not be available to the reporting clinician, partially blinding the reporter to avoid bias.

PSM- PET/CT procedures

PSMA-PET/CT procedures will be undertaken at St. Vincent’s Theranostics and nuclear medicine department, Sydney, Peter MacCallum Cancer Centre Nuclear Medicine department, Melbourne or the Netherlands Cancer Institute, Amsterdam. All PET

cameras will be harmonised for both dose calibration and intensity score assessment. ⁶⁸Ga-PSMA (H-BED CC-11), will be produced on-site compliant to the Good Laboratory Practices procedure. Radio-pharmacy quality control undertaken using a high-pressure liquid chromatography (HPLC) and ⁶⁸Ga-PSMA (H-BED CC-11) 1.8- 2.2mbq/kg administered. A limited field of view PSMA PET of the pelvis (3 minutes/bed stop) will be undertaken a minimum 60 minutes post injection with a non-contrast-enhanced low dose CT scan (pelvis only) performed 60 minutes post tracer injection.

PSMA PET images will be clinically reported at a per patient and per lesion level by highly experienced prostate imagers across 2 sites. All reports will be read blinded by 2 experienced PSMA PET specialists. All abnormalities will be classified as '*definitely malignant*', '*probably malignant*', '*probably normal*' or '*definitely normal*' based on experienced clinical decision using the double read system. Quantitative analysis will be factored into the interpretation with a minimum PSMA intensity score (SUV max) of 3.3 required to define significant malignancy. Extent and location of lesions will be documented. Additionally, the first 60 cases will be double read between involved reporting sites using the certainty scoring system, to derive Cohens Kappa for the detection of significant malignancy. The PSMA reporting template form is attached in supplementary figure 1. For the purposes of localisation, the prostate will be divided into quadrants. The corresponding mpMRI report will not be available to the reporting clinician, partially blinding the reporter to avoid bias.

An additional quantitative analysis of the PSMA-PET/CT will also be undertaken determining SUV max /Tumour to background ratio (TBR) and metabolic volume of prostatic quadrants to determine ROC cut-offs for malignancy. The benefit of the SUV max 3.3 minimum cut-off for significant malignancy will be assessed using ROC analysis at the interim analysis of 200 men. If required, this minimum SUV max cut-off may be adjusted.

Biopsy

Trans-perineal prostate biopsies, with mpMRI/PSMA-PET/CT targeting of ROIs will be performed as per the treating urologist's usual practice. No specific template for biopsy is prescribed for the purposes of the study; however, a thorough systematic sampling of the prostate is required, with a minimum of 18 cores dependent on prostate volume. Up to three identified lesions on PSMA or mpMRI will be targeted, if available, using either software assisted or cognitive fusion techniques, with each lesion having 2-4 cores.

1 Targeted and systematic biopsies will be performed with MRI and PSMA data made
2 available to the treating urologist. Targeted and systematic biopsies will be labelled
3 appropriately and sent for histopathological analysis
4

5 *Histopathology*

6 Specimens will be labelled based on location and if applicable whether they were
7 targeted by PSMA, mpMRI or both. The preferred provider of each site will review
8 histopathology.
9

10 Clinical data collected

- 11 • Number of cores
- 12 • Location – Identification of the ‘index’ lesion (the largest and pathologically
13 highest-grade tumour focus)
- 14 • Histological type of prostate cancer
- 15 • ISUP grade group
- 16 • Number of cores positive per site (right/left) or other (e.g. midline, targeted)
17 and total
- 18 • At least one of the following
 - 19 ○ The total percentage of cancer in one core
 - 20 ○ The greatest percentage of cancer in one core
 - 21 ○ The longest length of cancer in one core
- 22 • Perineural invasion, intraduct and cribriform patterns (present/absent)
- 23 • Acinar or ductal adenocarcinoma
- 24 • Involvement of adipose tissue (identified/present)
25

26 *Follow-up*

27 Patients will follow-up with their urologist after biopsy to discuss results. For the subset
28 of patients proceeding to radical prostatectomy (RP), histopathological concordance
29 with the identified lesions on each of the imaging modalities will be analysed. The
30 proportion of men with change in ISUP grade group following RP will also be recorded.
31

32 *Sample Size and Power Calculation*

33 Initial sample size calculation has been based on potential improvement of the positive
34 predictive value (PPV) with PMSA PET/CT to diagnose clinically significant prostate
35 cancer. Single proportion sample size formula was used to determine a required initial
36 sample size of 207 to achieve a power of 95% and $p = 0.05$. This is based on the

1 following assumptions (i) expected sensitivity of PSMA PET/CT to be 0.94 for ISUP 2 or
2 above disease (26, 29) (ii) Expected specificity of 0.97 for ISUP 2 or above disease (26,
3 29) (iii) expected prevalence of 0.69. To allow for a 5% patient drop-out rate, 220
4 patients will be initially recruited to the study. There are no published studies that have
5 examined the diagnostic accuracy of PSMA in screening setting to optimally derive a
6 robust power calculation. Hence, at the interim analysis of the data, the power
7 calculation will be adjusted if required. This interim analysis will also assess the PPV
8 of PSMA/MRI for the detection of defined significant malignancy on
9 histopathology. Based on this interim analysis and power calculation adjustment, the
10 study will be extended to evaluate a potential improvement of negative predictive value
11 (NPV). Based on initial assumptions, 578 patients are required to achieve a power of
12 95%. 600 patients would therefore be recruited to allow for a 5% patient drop out.
13

14 *Quality of life indicators*

15 Patients will be asked to fill in questionnaires related to the experience of undergoing
16 mpMRI, PSMA-PET/CT and prostate biopsy. These will be given to the patient at
17 enrolment, after PSMA PET/CT scan and after prostate biopsy.
18

19 *Procedure funding*

20 As part of informed consent, participants will be briefed on the costs involved in this
21 study:

- 22 - MRI – funded through the Medicare rebate scheme and patient (if ineligible for
23 rebate)
- 24 - PSMA – funded through the clinical trial
- 25 - Biopsy – funded through the Medicare rebate scheme, private health insurance
26 and patient (as per usual practice)

27 Participants will not be paid for their participation, and no participating clinician or
28 researcher will be paid outside of the normal wages.
29

30 *Blinding*

31 The reporting MRI radiologist will be blinded to the PSMA PET/CT results. The
32 reporting nuclear medicine physician will be blinded to the MRI results (they will be
33 sent directly to the urologist and will not be available through any result database
34 available to the nuclear medicine physician). The urologist will not be blinded to any of
35 the results, as they will be using the clinical and imaging findings to make clinical

1 decisions and perform targeted biopsies, as well as discussing findings with the patients
2 as clinically indicated. The anatomical pathologist reporting the biopsies will be aware
3 of the type of modality used to target biopsies if applicable. Otherwise, they will not
4 have direct access to the mpMRI or ⁶⁸Ga-PSMA PET results. Patients will be blinded to
5 the PSMA-PET/CT results until after their biopsies, as the results will be sent directly to
6 the urologist who will discuss the PSMA PET results together with the biopsy results.

8 **Outcomes**

10 *Accuracy*

11 The study endpoints are detailed in Table 1.

12
13 The diagnostic accuracy in the detection of csPCa will be evaluated using two definitions
14 for the csPCa

15 (i) ISUP grade group ≥ 2 (with $>5\%$ Gleason pattern 4 overall, or $>10\%$ Gleason
16 pattern 4 in any core or $>6\text{mm}$ of PCa (any grade in a single core) (primary
17 definition)

18 (ii) Any PCa ISUP grade group ≥ 2 (alternate definition)

19
20 The mpMRI will be reported by local radiologists according to PI-RADS v 2, on a scale of
21 1 to 5. A PI-RADS score ≥ 3 will be recorded as positive and PI-RADS ≤ 2 as negative.
22 PSMA-PET/CT images will be clinically reported at a per patient and per lesional level.
23 All abnormalities will be classified as 'definitely malignant', 'probably malignant',
24 'probably normal' or 'definitely normal'. Lesion analysis of mpMRI and PSMA identified
25 lesions will be used to plot a ROC curve. A quantitative SUV max and qualitative tumour
26 to background SUV ratio (background will be taken as the SUV max of the gluteus
27 maximus) will be calculated for each prostate quadrant and used to determine optimal
28 SUV cut-off points for malignancy.

30 *Health economic analysis*

31 We will conduct a post hoc cost effectiveness analysis based on the long-term
32 implication of changes to the diagnostic classification of PCa that result from the
33 adoption of a PSMA PET CT based diagnostic pathway. The implications will relate to
34 health effects and the costs of the diagnostic pathway.

Costs for the delivery of PSMA-PET/CT will consider production costs on site, including personnel, equipment and quality assurance. Standard of care resources, including PSA measurements, mpMRI and prostate biopsy will be valued based on publicly available sources such as those published through the Medicare benefits schedule for publicly funded services in Australia.

A cost effectiveness model will be developed to assess whether the use of PSMA PET CT could have resulted in safe avoidance of prostate biopsy, which then has downstream cost savings, including hospital admissions, avoidance of postoperative complications and quality of life benefits. Resource use for both pathways will be assessed based on the number of scans (PSMA PET and mpMRI) undertaken and the number of transperineal biopsies undertaken. This will include the resource use associated with “unnecessary biopsies” (those conducted in men who do not have csPCa who could have avoided biopsy). In addition, resource use associated with the complications arising from each arm will be included. This data will be collected using the Eq-5D-5L instrument and a questionnaire relating to adverse events post imaging/biopsy (supplementary material 1).

This analysis will ultimately provide information relating to the implications of changes that PSMA PET CT has on over and under detection of PCa

Patient Impact

Analysis of the patients experience, including anxiety and symptomatology, of the PSMA-PET/CT + mpMRI will be compared to the experience of biopsy through standardized questionnaires at different time points in the study. The validated EQ-5D-5L questionnaire will be sent to patients at baseline, post PSMA/MRI and post biopsy as a general measure of health status and a comprehensive questionnaire relating to side effects will be sent after the imaging and biopsy investigations.

Risks of ⁶⁸Ga-PSMA-PET/CT

⁶⁸Ga-PSMA-11, is a small molecule PET radioligand now extensively evaluated in clinical trials(13, 21, 30-34). Based on FDA requirements, a single-organ dose of 0.05 Sv is allowed. This corresponds to an activity of 289.9 – 414 MBq (7 –11 mCi) of ⁶⁸Ga-PSMA for a 70-100 kg male patient. Accordingly, the effective dose expected to the whole body is 0.01 Sv, which is below the 0.03 Sv upper limit recommended by the FDA.

1 No adverse effects due to intravenous administration of ⁶⁸Ga-PSMA for imaging have
2 been reported in the published literature. The radiation dose due to the whole-body CT
3 component of the PET/CT is estimated to be 4.7mSv. This is anticipated to be
4 significantly reduced with the limited pelvic-only scan used in this trial.

6 The total (combined ⁶⁸GaPSMA PET and CT) effective dose would thus be significantly
7 below the 10mSv range the Australian Radiation Protection and Nuclear Safety Agency
8 (ARPANSA) states has no direct effects on human health, and likely below 5mSv in any
9 one year as described in the Code of practice for exposure to humans to ionising
10 radiation for research purposes (35).

11 Overall, ⁶⁸Ga-PSMA PET/CT scan would carry a low to very low level of risk (less than 1
12 in 1000) and its use in the diagnosis of prostate cancer and prevention of invasive
13 biopsies would be justified.

15 *Adverse Events*

16 In the case of this protocol, adverse event reporting will be restricted to the study
17 period within 48 hours after the PSMA PET scan acquisition as investigations or
18 therapies outside of the PET are not considered part of the study intervention. Any
19 adverse events (defined as any adverse event experienced by the patient within two
20 hours after radiotracer administration) associated with PSMA-PET/CT will be recorded.

22 **Discussion**

24 There is increased interest in using novel imaging techniques to limit the need for
25 invasive prostate biopsies. While the use of prostate mpMRI is increasing, its use is
26 limited by its low specificity and PPV. PSMA-PET/CT has been shown in a number of
27 recent studies to have superior diagnostic accuracy to mpMRI to detect intraprostatic
28 csPCa (22, 26), an example of which is shown in Figure 3. However, these studies were
29 retrospective and there is significant heterogeneity between the different cohorts.
30 Conducting a prospective, multicentre cross-sectional study will provide essential data
31 on the diagnostic accuracy of PSMA-PET/CT in detecting csPCa. The detection of PCa
32 with imaging has the potential to reduce the number of invasive biopsies in men.

34 In current practice, many urologists utilise an MRI directed pathway (figure 1) as the
35 workup for men with a suspicion of having PCa. Despite this there are still a significant
36 number of men who do not harbour PCa undergoing unnecessary biopsies. In particular,

1 patients with a PIRADS 3 lesions have a 16-21% chance of harbouring clinically
2 significant disease (36). Conversely, some men with a PIRADS 1-2 mpMRI still harbour
3 PCa (6, 8). PSMA PET/CT may have a role in determining which men can truly avoid
4 prostate biopsy.

5
6 This study may help establish new diagnostic pathways using both mpMRI and PSMA-
7 PET/CT to better select which patients require a biopsy, those that do not and those
8 patients that can avoid immediate biopsy but still require close surveillance. We
9 hypothesize that it is likely that PSMA-PET/CT will be of additive diagnostic benefit to
10 mpMRI in men with PIRADS 2 to 4 lesions, However, it is unlikely to alter decision
11 making in men with a PIRADS 5 lesion or in men with a negative mpMRI and no red
12 flags.

13
14 The use of diagnostic imaging is increasing worldwide. Furthermore, it is important to
15 note that many malignancies are diagnosed with imaging alone and do not require a
16 tissue diagnosis in all cases. Although a biopsy-free diagnostic pathway is unlikely to
17 occur in PCa, the utilisation of imaging is expected to reduce the need for many
18 unnecessary biopsies. This will have significant benefit to patients in terms of reducing
19 the associated morbidity of biopsies and may also reduce healthcare costs associated
20 with PCa diagnosis. The long-term implications of including PSMA PET imaging in the
21 workup of prostate cancer with regard to overall and cancer specific survival has limited
22 published information, are not easily evaluable in the short term in this study, and is a
23 limitation of the study design(37).

24
25 The PRIMARY trial has commenced as of July 2019 and aims to complete recruitment
26 within 18 months. This study is innovative in that it will provide high level evidence to
27 answer the question of whether PSMA-PET/CT in addition to mpMRI can aid in reducing
28 unnecessary biopsies in men with a suspicion of prostate cancer. It will contribute
29 significantly to the global literature and has the potential to change the way PCa is
30 diagnosed.

31 32 **Acknowledgments**

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Conflict of Interest

None to disclose.

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