BJU Int 2022; **130:** Supplement 3: 5–7 doi:10.1111/bju.15736

BJUI
BJU International

Research Communication

High prostate-specific membrane antigen (PSMA) positron emission tomography (PET) maximum standardized uptake value in men with PI-RADS score 4 or 5 confers a high probability of significant prostate cancer

In clinical practice, men with suspicion of prostate cancer are offered multiparametric MRI followed by a systematic and/or a targeted prostate biopsy. The PRECISION trial identified that MRI prior to prostate biopsy could identify targetable lesions, leading to a higher proportion of men diagnosed with clinically significant prostate cancer (csPCa) and a lower incidence of clinically insignificant disease. This trial has changed practice for many urologists and resulted in men either avoiding a prostate biopsy or proceeding to a targeted biopsy with a superior diagnostic yield.

It has been observed that a Prostate Imaging-Reporting and Data System (PI-RADS) classification of 4 or 5 confers a positive predictive value that is variable and considerably less than 100% [1]. This is due to differences in patient selection, underlying disease prevalence, MRI acquisition and sampling error associated with transperineal or transrectal prostate biopsy [2]. The proPSMA trial identified that prostate-specific membrane antigen (PSMA) positron emission tomography (PET) provides superior staging accuracy for nodal or metastatic disease compared to conventional imaging, while multiple retrospective studies have reported that PSMA PET combined with MRI improves intraprostatic disease detection of csPCa [3,4]. Furthermore, a study from Meissner et al. presented a case series of patients who forwent biopsy prior to surgery on the basis of highly suspicious MRI and PSMA PET imaging [5]. In this research communication, we performed an exploratory subanalysis of the PRIMARY trial to examine how PSMA PET intensity in men with PI-RADS score 4 or 5 on MRI can be used to predict the probability of csPCa.

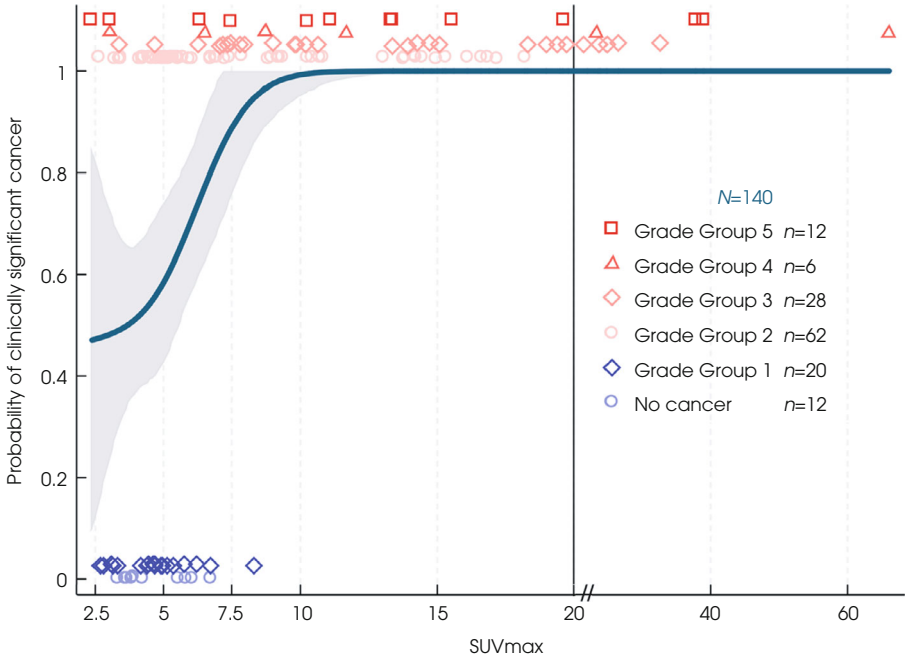
The PRIMARY trial was a prospective, multicentre study that investigated whether pelvic-only PSMA PET could improve the accuracy of pre-biopsy MRI triage in men with suspected prostate cancer [6]. Significant cancer was defined as International Society of Urological Pathology (ISUP) Grade Group ≥ 2 [7]. All PSMA PET scanners were harmonized and urologists were provided PSMA PET- and MRI-mapped lesions prior to biopsy to assign concordance. It was found that PSMA PET intensity (maximum standardized uptake value [SUVmax]) was associated with PI-RADS and biopsy grade. Analysis was carried out on a per-patient basis.

The analysed sample comprised 140 patients with PI-RADS 4 or 5 lesions and a recorded SUVmax. The majority (N = 108, 77%) had csPCa, with 44% having ISUP Grade Group 2 disease. SUVmax was associated with csPCa (median 8.0 vs 4.5; rank-sum test $P < 0.001$). The highest SUVmax in a patient without cancer was 6.8, and for ISUP Grade Group 1 it was 8.3. Of note, 53 patients (38%) had an SUVmax >8.7 and all had csPCa. SUVmax was observed to have a non-linear relationship with the probability of csPCa on locally weighted regression. Hence, it was entered into a logistic regression as a restricted cubic spline with internal knots at the tertiles. The resulting post-estimation predicted probabilities of csPCa and 95% CI are plotted in Fig. 1. The lower bound of the CI was estimated to be 95% at an SUVmax of 10 and >99% at an SUVmax of 13. The number of patients with an SUVmax ≥13 was 35 (25%).

PRIMARY is the first prospective, multicentre trial investigating the use of mpMRI and PSMA PET prior to prostate biopsy and highlights the additional information offered by PSMA PET in the pre-biopsy setting. Incorporation of a PSMA PET intensity threshold into a subgroup of PI-RADS 4 or 5 men elevated the positive predictive value to 100%, although the PRIMARY study was not powered to analyse diagnostic performance in high-risk subgroups. MRI represented the first imaging method to identify significant malignancy pre-biopsy and was recently incorporated into the European Randomized Study of Screening for Prostate Cancer risk calculator. With further exploration, PSMA PET findings may also be included into similar risk stratification instruments.

This improved diagnostic certainty for significant malignancy over a high PI-RADS score has potential clinical implications. The combination of PSMA PET and mpMRI, developed as a combined score, could therefore identify men who can avoid a biopsy and proceed directly to radical treatment. While controversial, there are theoretical advantages to avoiding biopsy which carries a financial cost, complication rates and periprostatic bleeding, fibrosis and disturbance of surgical planes [8]. Therefore, imaging findings that are diagnostic of clinically significant prostate cancer with predictive values

Fig. 1 Predicted probability of clinically significant prostate cancer (csPCa) as a function of maximum standardized uptake value (SUVmax [navy line]) with 95% CI (grey shading). Individual patients shown as markers according to biopsy grade group. Red = csPCa; blue = no csPCa. NB axis break at SUVmax >20.



approaching 100% could make biopsies, which are fraught with risk, cost and human error, redundant. Of course, the economic case for hypothetically replacing a prostate biopsy with PSMA PET/CT, is variable from one health system to another. Although there may be an argument for this in countries such as Australia, where PSMA PET/CT is highly accessible and relatively affordable, this is not likely to be the case elsewhere.

If further studies confirm these results, the use of PSMA PET could challenge the traditional path to definitive treatment. Patients being evaluated for high-risk primary prostate cancer require the counsel of a multidisciplinary team and it can be envisaged that not all members would be comfortable providing guidance in the absence of a tissue grade. Some patients may be offered non-surgical treatment, such as radiotherapy, where a biopsy-proven ISUP Grade Group is unequivocally indispensable. Furthermore, there are limited data on the correlation between PSMA PET SUVmax uptake and ISUP Grade Group. Consequently, novel imaging alone cannot guide treatment options such as androgen deprivation therapy with radiotherapy, the necessity of nerve-sparing or the appropriateness of active surveillance. Even if prostatectomy is deemed most appropriate for the patient, prostate biopsy is often necessary to guide the need for pelvic lymph node dissection. Another important consideration when adding imaging modalities is the cumulative radiation dose. The exposure in the PRIMARY trial was limited by performing a pelvic-only PSMA PET [7]. However, patients with ISUP Grade Group 3–5 in our practice subsequently undergo a full-body staging PSMA-PET as a routine staging scan. Therefore, in our high-risk patients there would be no overall additional radiation burden for many men when substituting an earlier PET scan for prostate biopsy. It should be noted that the SUVmax used in this subanalysis is only reproducible with the same imaging parameters as described in the PRIMARY trial. These naturally may vary from site to site so external validity may be limited. Notwithstanding these limitations, the ability to make a rapid diagnosis on imaging alone and proceeding directly to treatment in certain cases would seem attractive to patients wishing to avoid delays and additional procedures for a highly probable clinically significant malignancy.

The introduction of PSA changed practice by allowing clinicians to diagnose prostate cancer at an earlier stage. More recently MRI has further refined the diagnostic process. PRIMARY confirms that PSMA PET could be the next step forward in evaluating men with suspected prostate cancer; patients with a suspicious MRI and an SUVmax over 13 were all found to have csPCa on biopsy. This result, combined with data from the recent retrospective series alone, suggests that there is a cohort in whom csPCa can be predicted with high confidence based on imaging alone. However, this concept must be considered hypothesis-generating, and additional prospective studies would be required to determine the clinical utility of the avoidance of biopsy in a highly selected group of patients.

Acknowledgements

Matthew Roberts is supported by a Clinician Research Fellowship from the Metro North Office of Research, Queensland Health. Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians. [Correction added on 19 May 2022, after first online publication: CAUL funding statement has been added.]

Disclosure of Interests

Matthew Roberts has received grants from the RBWH Foundation, the ANZUP Trials Group Ltd and Mundipharma Pty Ltd, consulting fees from Cook Medical and travel support from the Royal Australasian College of Surgeons and Urological Society of Australia and New Zealand. He has served on the advisory boards of Peter MacCallum Cancer Centre, Melbourne and Royal Brisbane and Women's Hospital and as a board member of the *BJUI*. James Thompson has received payment for a lecture from Abbvie. Michael Hofman has received grants from the Prostate Cancer Foundation and payment for lectures from Janssen, Astellas, Merck/MSD, AstraZeneca and AAA/Novartis. Declan Murphy has received consulting fees from Astellas, Bayer, Janssen, Ipsen, Ferring and AstraZeneca. Louise Emmett has received funding for this article from St Vincent's Currant Foundation, St Vincent's Clinic Foundation, CINSW and SPHERE.

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Abbreviations: csPCa, clinically significant prostate cancer; ISUP, International Society of Urological Pathology; PET, positron emission tomography; PI-RADS, Prostate Imaging-Reporting and Data System; PSMA, prostate-specific membrane antigen; SUV, max maximum standardized uptake value.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. An example of imaging predicting the final pathology in a 71-year-old presenting with a PSA rising to 4.7 μg/L.