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Diagnostic value of MRI-based PSA density in predicting transperineal sector-guided prostate biopsy outcomes

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Abstract

Purpose: Prostate specific antigen (PSA) density (PSAD) has potential to increase the diagnostic utility of PSA, yet has had poor uptake in clinical practice. We aimed to determine the diagnostic value of magnetic resonance imaging-derived PSAD (MR-PSAD) in predicting transperineal sector-guided prostate biopsy (TPSB) outcomes.

Materials and Methods: Men presenting for primary TPSB from 2007 to 2014 were considered. Histological outcomes were assessed and defined as: presence of any cancer or significant cancer defined as presence of Gleason 4 and/or maximum tumour core length (MCCL)≥4mm (G4); or Gleason 4 and/or MCCL≥6mm (G6). Sensitivity, specificity and positive and negative predictive values were calculated and receiver operating characteristics (ROC) curves were generated to compare MR-PSAD and PSA.

Results: 659 men were evaluated with mean age 62.5±9 years, median PSA 6.7ng/ml (range 0.5-40.0), prostate volume 40cc (range 7-187) and MR-PSAD 0.15ng/ml/cc (range 0.019-1.3). ROC area under the curve (95% CI) was significantly better for MR-PSAD than PSA for all cancer definitions ($p<0.001$): 0.73 (0.70–0.76) vs 0.61 (0.57–0.64) for any cancer; 0.75 (0.71–0.78) vs 0.66 (0.62–0.69) for G4; 0.77 (0.74–0.80) vs 0.68 (0.64–0.71) for G6. Sensitivities for MR-PSAD <0.1ng/ml/cc were 85.0%, 89.9% and 91.9% for any, G4 and G6 cancer, respectively.

Conclusion: MR-PSAD may be better than total PSA in determining risk of positive biopsy outcome. Its use may improve risk stratification and reduce unnecessary biopsies.

Introduction

Despite the ubiquity of prostate specific antigen (PSA) as a screening tool for prostate cancer, its use as a serum marker suffers from limitations, including an inability to accurately distinguish between benign and malignant conditions. This holds particularly true in the 'diagnostic grey zone,' or PSA range of 4-10ng/ml and has led to increasing numbers of men undergoing biopsies for benign disease or small volume, low-risk prostate cancer that may not require treatment [1]. Given the potentially significant morbidity associated with prostate biopsy, screening investigations that decrease this burden merit further study [2].

PSA density (PSAD) has long had potential to improve the diagnostic utility of serum PSA alone by improving specificity whilst preserving sensitivity, but has had poor uptake in clinical practice [3]. Transrectal ultrasound (TRUS) is routinely used to estimate prostate volume, but is subject to human error resulting in variations in calculated volumes, with differences between two consecutive volume estimates ranging from 15.5-25.5% [4,5]. Further, if performed at the time of biopsy, its use for screening is limited, while undertaking separate pre-biopsy volume assessments are inconvenient, uncomfortable and expensive. Alternative methods of volume estimation, including digital rectal examination have proven notoriously unreliable [6].

Previous studies evaluating PSAD have used transrectal prostate biopsies as the reference standard, with protocols ranging from 6 to 12 cores [7-9]. In addition to potentially reduced accuracy in volume calculation, the transrectal method is flawed, given that a third of men with no or low-risk cancer by this sampling method are subsequently found to have significant disease on transperineal biopsy [10,11]. One reason for this is the difficulty in accessing the prostate via the transrectal approach. The anterior aspect of the prostate is difficult to sample, particularly in larger prostates, while access to the apical region is limited by the needle angle achievable through the rectum [12,13]. Transperineal prostate biopsy avoids these problems and allows for systematic investigation of the prostate, with studies showing high overall detection rates [11,14].

Traditionally, magnetic resonance imaging (MRI) has been used as a staging investigation for confirmed prostate cancer, but is frequently performed pre-biopsy to prevent post-biopsy haemorrhagic artefact [15]. The addition of multiparametric MRI (mpMRI) sequences such as diffusion weighted imaging (DWI) and dynamic contrast enhancement (DCE) has led to some centres performing MRI as part of the initial diagnostic pathway [16,17]. In fact, the recent PROMIS (Prostate MR imaging study) randomised controlled trial found mpMRI to have greater sensitivity (93%) compared to conventional TRUS-guided transrectal biopsy (48%) [18]. With pre-biopsy MRI, prostate

volume can be estimated accurately and noninvasively, with studies demonstrating improved accuracy in MR-derived volume assessment and reduced intraobserver variability compared to TRUS [19,20]. The majority of prostate MRI studies have focussed on the utility of additional sequences, excluding the additional utility of PSAD [16,21].

With improved prostate volume measurement afforded by MR imaging and more accurate reference standard of transperineal sector prostate biopsy (TPSB), we revisited the value of PSAD. The aim of the present study was to determine the predictive value of MRI-derived PSA density (MR-PSAD) for prostate adenocarcinoma, with 24-40 core TPSB as the reference standard. Our null hypothesis was MR-PSAD does not confer additional diagnostic benefit over conventional serum PSA.

Patients and Methods

This study was approved by the local governance boards as a prospective audit and adheresto the Standards for Reporting Diagnostic Accuracy (STARD) [22].

Patients

Consecutive patients from three institutions, referred between January 2007 and August 2014 for primary TPSB, were considered. Patient data was reviewed from a prospectivelycollected database. Initial patient referral was for elevated PSA and/or abnormal digital rectal examination (DRE). Patients who had undergone prior prostate biopsies (trans-rectal or transperineal), a PSA >30 mcg/L on presentation or no pre-biopsy MRI available were excluded from the study.

Magnetic Resonance Imaging Protocols (Index Test and Assessment of Prostate Volume)

Patients underwent a pre-biopsy MRI in one of three centres using 1.5 Tesla machines and 8-channel phased array body coils. Indication for pre-biopsy MRI included disease staging in the event of positive biopsy and more recently, identification of suspicious lesions. All protocols included axial oblique, sagittal and coronal T2-weighted imaging and were optimised for the staging of prostate cancer. An example T2-weighted MRI protocol is shown in Supplementary Table 1. Prostate volume was calculated by a dedicated uroradiologist at the respective centre, using the ellipsoid approximation method: □/6 x length x height x width. MR-PSAD was defined as serum total PSA divided by MRI-derived

prostate volume [23].

Transperineal Sector-Guided Prostate Biopsies (Reference Standard)

All patients underwent transperineal sector-guided biopsies as previously described by Vyas et al.,

regardless of MRI findings [11]. A total of 24 to 40 cores, preferentially targeting the peripheral zone, were taken from the anterior, mid and posterior sectors; additional basal cores were taken in prostates greater than 30cc. All cores were analysed by dedicated uropathologists, with histological reporting following the classic Gleason grading based on most frequent pattern.

Outcomes

Primary outcomes of interest was any prostate cancer detected by TPSB. Two additional outcomes which represented significant cancer were assessed as follows: Gleason pattern 4 and/or maximum cancer core length (MCCL) of >4mm, referred to as Definition G4 and Gleason pattern 4 and/or MCCL >6mm, referred to as Definition G6 [16]. These lengths of core involvement were selected as they are representative of a lesion volume of 0.2ml (4mm) and 0.5ml (6mm) [24]. These volumes are below the calculated threshold of 1.3ml for significant tumour volume, as per the European Randomised study of Screening for Prostate Cancer [16,24].

Data Analysis

Statistical analyses were performed using MedCalc v12.5 (MedCalc Software bvba, Ostend, Belgium). Receiver operator characteristic (ROC) curves were generated and area under the curve (AUC) was estimated separately for PSA and MR-PSAD as predictors of each outcome of interest. Diagnostic performance for PSA and MR-PSAD were compared based on the difference between the two AUCs using the De Long et al. method. Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) with 95% confidence intervals were calculated using the epiR package for R version 3.1.2 (R Project for Statistical Computing, Vienna, Austria). Tests were considered statistically significant at $p<0.05$.

Results

A total of 659 patients were identified from the three study centres. Excluded patients included non-primary referral, PSA >30 ng/ml on presentation (n = 20) or no pre-biopsy MRI available (n = 13). In total, 374 (56.8%) patients were diagnosed with *any cancer*, 278 (42.2%) with Definition G4 cancer and 248 (37.6%) with Definition G6 cancer. Baseline demographics are summarised in Table 1.

ROC curves are shown in Figures 1-3. MR-PSAD was significantly better than total PSA alone, for all definitions studied. For *any cancer*, the area under the curve (AUC) for PSA and MRPSAD was 0.61 (95% CI 0.57-0.64) and 0.73 (95% CI 0.70-0.76, p<0.0001*), respectively. For Definition G4 significant cancer, the AUC for PSA was 0.66 (95% CI 0.62-0.69) and MR-PSAD was 0.75 (95% CI 0.71-0.78, p<0.0001). For Definition G6 significant cancer, the AUCs were 0.68 (95% CI 0.64-0.71) and 0.77 (95% CI 0.74-0.80, p<0.0001) for PSA and MR-PSAD, respectively. Table 2 shows MR-PSAD performance (sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)) at different threshold values for detecting prostate cancer at different cancer definitions.

Using a threshold value of 0.1ng/ml/cc would have prevented 166 biopsies, compared to a biopsy-all strategy, at the expense of 28 or 20 missed significant cancers, using Definitions G4 and G6, respectively. Alternatively, a threshold of 0.15ng/ml/cc would prevent 328 biopsies, at the expense of 84 or 65 missed significant cancers, using Definitions G4 or G6, respectively.

Discussion

We present a contemporary study demonstrating improved prediction of TPSB outcome using MR-PSAD, compared to PSA alone. For the prediction of any prostate cancer, we demonstrated a significant difference between the ROC curve AUC for MR-PSAD vs PSA (0.73 vs 0.61, p<0.0001). Additionally, the AUCs for MR-PSAD were significantly greater (P<0.0001) than PSA for two definitions of significant cancer.

Current PSA screening for prostate cancer is plagued by low specificity; a high proportion of men undergo unnecessary prostate biopsy, potentially leading to patient morbidity and anxiety [25]. While studies have suggested that PSAD is a better predictor of prostate biopsy outcome than PSA uptake in clinical practice has been poor [3,8,26]. Our study makes use of MR-derived prostate volumes and TPSB as the reference standard. MR-derived prostate volumes represent an improvement both in convenience and accuracy over traditionally used transrectal volumes, whereas TPSB are an improvement over transrectal biopsies, with enhanced prostate sampling apically and anteriorly [14,19,20].

To reduce unnecessary biopsies, MR-PSAD must discriminate between no or low volume, insignificant prostate cancer, and significant disease. Sensitivity for MR-PSAD is good; at a threshold of 0.1ng/ml/cc, we demonstrate 85.0% sensitivity for any cancer, improving to 89.9 and 91.9% for our definitions of significant cancer, respectively. Specificity for MRPSAD improved as the cut-off values increased; specificity for any cancer at cut-off values 0.1, 0.15 and 0.2ng/ml/cc were 38.6, 69.1 and 83.5%, respectively. The difficulty lies in the selection of an appropriate threshold value. As MR-PSAD threshold values rise, so will false negative rates and missed cancers. We note that significant cancers are missed at both the 0.1 and 0.15ng/ml/cc thresholds.

Our study, the largest to utilise MRI-calculated prostate volumes, compares favourably to previously published studies, summarised in Table 3 [9,27-31]. Similar AUC values are seen across the studies; we note however, wide variation in MR-PSAD cut-off values, sensitivities and specificities obtained. The study by Mueller-Lisse et al. appears to be an outlier [29]. The authors compared prostate cancer and known benign prostatic hyperplasia (BPH), finding high sensitivity and specificity using MR-PSAD at a low cut-off of 0.07ng/ml/cc. This low cut-off may arise from the selected population; while the authors did not publish average prostate volumes for each group, the BPH group was likely to have particularly low MR-PSAD, given their high prostate volumes.

MR-PSAD compares favourably to previous, large (>1000 patients) PSAD studies utilising TRUS-guided volumes and biopsies, although we recognise the difficulties in comparing studies given the wide variation in study protocols and populations. Elliot et al. showed in 1708 men a statistically higher ROC curve AUC for PSAD vs PSA for all cancer (0.737 vs 0.633, $p<0.001$), high grade (Gleason 3+4 or higher) (0.766 vs 0.673, $p<0.001$) and high volume (>50% of cores involved, 0.843 vs 0.755, $p<0.001$) disease[8]. A cut-off of 0.073ng/ml/cc was required to reach 95% sensitivity for high grade cancer. A separate study of 1809 patients by Stephan et al. subgrouped PSA into ranges; the ROC curve AUC for PSAD was significantly greater than PSA across all groups [26]. When sensitivity was set at 90 or 95%, PSAD had significantly higher specificity compared to PSA alone.

In contrast, a study of nearly 5000 men by Catalona et al. found that at a PSAD cut-off of 0.15ng/ml/cc, 47% of tumours were missed, with no improvement over PSA [7]. However, they highlight difficulty in accurately assessing prostate volume, with poor correlation ($r=0.61$) between estimated TRUS volume and pathological specimen weight. While we did not compare MRI-guided volumes to prostate specimen weights, researchers have suggested that MRI can offer improved volume estimation [20]. With increasing use of pre-biopsy mpMRI to detect clinically significant prostate lesions, the difficulty in obtaining volumes for PSAD has diminished. While only T2 sequences are required for disease staging and prostate volume assessment, our index test uses a

1.5 Tesla magnet and two straightforward and resource-friendly sequences: T2-weighted imaging and DWI [16,32]. We recently demonstrated a high sensitivity (97%) for Prostate Imaging – Reporting and Data System (PI-RADS) at a threshold score of ≤2[16]; therefore, in the absence of contraindications, all our patients now receive mpMRI prior to TPSB. This ability of MRI to detect clinically significant lesions has led to its adoption in many centres [33].

In addition to prostate cancer detection, there is evidence that PSAD can identify patients with adverse pathologic features and recurrence following management. Busch et al. demonstrated PSAD to be an independent predictor of recurrence-free survival in 1334 men undergoing radical prostatectomy [34]. PSAD was significantly increased in patients with Gleason >7 tumours, pT3 disease and positive surgical margins. In a separate study of men undergoing prostatectomy, Koie et al. found PSAD to be significantly linked with extracapsular extension and biochemical recurrence-free survival on multivariate analysis [35].

A practical solution to increase the specificity of MR-PSAD, whilst retaining sensitivity, involves combining MR-PSAD with the imaging findings of mpMRI. A recent paper by Washino et al.[31] utilised this approach, finding MR-PSAD and PI-RADS score (T2 and DWI) to be predictors for prostate cancer on multivariate analysis. Two high risk groups were identified: PI-RADS ≥4 and MR-PSAD ≥0.15 and PI-RADS 3 and MR-PSAD ≥0.30, which was associated with the highest clinically significant prostate cancer detection rates (76-97%) [31]. In contrast, patients with PI-RADS score ≤2 and MR-PSAD ≤0.15 yielded no clinically significant prostate cancer. Similarly, Kubota et al. [28] combined T2-weighted MR-imaging and MR-PSAD; MRI results were stratified into two groups: cancerous and non-cancerous. At a cut-off of 0.111, MR-PSAD had 96.8% sensitivity and 19.5% specificity. Inclusion of MRI findings allowed a greater MR-PSAD cut-off to be used (0.184); sensitivity remained at 95.2% but specificity doubled to 40.7%. Furthermore, Hansen et al. combined PSAD with mpMRI in a repeat biopsy setting [36]. At initial biopsy, patients had no or Gleason 6 prostate cancer. The authors found a low detection rate of Gleason ≥7 prostate cancer at PSAD ≤0.2 ng/ml/cc. This most affected indeterminate (Likert/PI-RADS 3) and high risk (Likert/PI-RADS 4-5) lesions. For Likert 3 lesions, the PPV rose from 0.09±0.06 to 0.44±0.19 when a 0.2 ng/ml/cc PSAD cut-off was used. For Likert 4-5 lesions, PPV rose from 0.47±0.08 to 0.66±0.10, further highlighting the benefit of PSAD in a pre-biopsy MRI setting [36].

The question does remain as to which cohort of patients may benefit most from pre-biopsy MRI, and in turn, MR-PSAD, given cost requirements for the procedure. A recent study by Klemann et al [37] suggests that the initial biopsy result itself holds important prognostic information regarding prostate cancer-specific mortality (PCSM). In patients with PSA ≤10ng/ml and negative initial biopsy,

the cumulative incidence of PCSM was 0.7% at 20 years. In men with initial negative biopsy and PSA between 10 and 20 ng/ml, this rises to 3.6% and 17.6% when PSA was ≥20ng/ml [37].

Based upon this study, the ongoing use of PSA to triage patients for biopsy will continue to be important. In these patients with PSA <10, MRI may be of reduced benefit, given the low mortality within this cohort of patients; subsequent PSA surveillance and further prostate evaluation can be performed prudently. However, with higher PSA values, incidence of PCSM rises, despite negative initial biopsy. In this group of patients, it appears that the adoption of pre-biopsy mpMRI and utilisation of factors including MR-PSAD can increase PSA specificity. This increase can aid prostate cancer diagnosis in these patients, and potentially reduce the number of further biopsies required or allow for specific MRI-targeting.

The strengths of our study include a relatively large patient cohort drawn from three UK centres. It is limited to patients undergoing primary prostate biopsy; we include all patients with a PSA ≤30ng/ml, in contrast to the studies by Kubota and Mueller-Lisse, who only included patients with PSA levels ≤10ng/ml [28,29]. Furthermore, as MR-PSAD was calculated retrospectively, results did not affect the decision to proceed to biopsy and a heterogeneous range of patients have been studied.

Another strength was the reference standard: whole prostate glands were systematically examined by TPSB using 24-40 cores, providing improved diagnostic accuracy over 6-8 core transrectal biopsy. As many as a third of significant prostate cancers are missed at initial transrectal biopsy, likely due to tumour heterogeneity, as well as the challenges in sampling the anterior and apical prostate regions [11-14]. TPSB provides a practical reference standard, and allows for systematic interrogation of the prostate. While pathological examination of whole prostate specimens would be more accurate, TPSB allows for the inclusion of patients with both benign and malignant prostates.

We recognise the limitations in the retrospective nature of our study. MR-PSAD was calculated retrospectively and did not affect decision to biopsy. However, we were unable to completely exclude other factors involved in the biopsy decision-making process, e.g. family history, digital rectal examination, etc. Within our population, patients tend to present late, with raised PSA and lower urinary tract symptoms (LUTS) often due to benign prostatic hyperplasia (BPH). This group of patients will have low PSAD secondary to these large volume prostates, potentially biasing towards PSAD utility.

Data on the use of 5-alpha reductase inhibitors was not available; we do recognise the source of bias these medications produce by decreasing both PSA and prostate volume. PSA is reduced by a different rate to volume, adding variation to PSAD [38]. Similarly, body mass index (BMI) data was

not included; obesity can impact both serum PSA values and prostate volumes [39]. With lower PSA values and higher volumes, obese men produce lower PSAD values, which can positively influence the ability of PSAD to predict prostate cancer [39].

The ellipsoid method was used for calculation of prostate volume and may account for differences in PSAD thresholds used across studies. This calculation does require user intervention in measuring the prostate dimensions and is thus subject to inter-observer variation [4,5]. A potential solution lies in MRI segmentation for prostate volume calculation; fully-automated methods are able to yield highly accurate volumes, and reduce this user variation [40]. Despite this limitation, error was reduced by applying the same volume calculation across all patients; all prostate dimensions were calculated by senior uroradiologists. Finally, definitions of 'significant' cancers are based on previous study definitions. The long term implications of 'clinically insignificant' cancer are unknown. There has been a trend towards active surveillance of these patients; this management appears to offer a clear advantage in observing these patients, while reducing overtreatment and patient morbidity [41].

In summary, our study shows that MR-PSAD is superior to PSA alone at detecting prostate cancer at TPSB. Currently, pre-biopsy mpMRI protocols allow for accurate volume determination and PSAD calculation. MR-PSAD is a practical adjunct that allows urologists to help risk stratify patients for the presence of any and significant prostate cancer and to improve patient counselling prior to prostate biopsy.

Compliance with Ethical Standards

Funding: No funding was received for this study.

Conflict of interest: Findlay MacAskill declares that he has no conflict of interest. Su-Min Lee declares that he has no conflict of interest. David Eldred-Evans declares that he has no conflict of interest. Wahyu Wulaningsih declares that she has no conflict of interest. Rick Popert declares that he has no conflict of interest. Konrad Wolfe declares that he has no conflict of interest. Mieke van Hemelrijck declares that she has no conflict of interest. Giles Rottenberg declares that he has no conflict of interest. Sidath Liyanage declares that he has no conflict of interest. Peter Acher declares that he has no conflict of interest.

Ethical Approval: The study was approved by the local governance board as a prospective audit. This article does not contain any studies with human participants or animals performed by any of the authors.

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