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Research Article

Multiparametric MRI and Serum PSA Density in Staging Prostate Cancer

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Abstract: Accurate local staging of prostate cancer is essential for treatment selection and prognostication. This cross-sectional diagnostic accuracy study evaluated the combined utility of multiparametric magnetic resonance imaging (mpMRI) and serum prostate-specific antigen density (PSAd) in preoperative staging of biopsy-proven prostate cancer. A consecutive cohort of 386 men undergoing radical prostatectomy between January 2022 and December 2023 underwent standardized mpMRI (PI-RADS v2.1 protocol) and preoperative serum PSA with prostate volume measurement to calculate PSAd. Radiological staging (mpMRI cT-stage and PI-RADS index lesion features) was compared with histopathological stage (pT) and extracapsular extension (ECE), seminal vesicle invasion (SVI) and pathological grade as reference standards. Overall, mpMRI alone correctly staged organ confinement (pT2) in 78% and detected ECE with sensitivity 64% and specificity 88%. Using a PSAd threshold ≥0.15 ng/mL/cm³ improved sensitivity for detecting clinically significant extraprostatic disease (ECE or SVI) to 81% while preserving acceptable specificity (82%), and a PSAd ≥0.20 further increased negative predictive performance in mpMRI-negative cases. Multivariable logistic regression demonstrated that combining mpMRI features (capsular bulge, neurovascular bundle irregularity, lesion size) with PSAd yielded superior discrimination for adverse pathology (AUC 0.87) compared with mpMRI alone (AUC 0.76, $p < 0.001$). These findings support integration of PSAd into mpMRI-based staging algorithms to enhance detection of clinically relevant extraprostatic extension and guide biopsy and surgical

planning. Keywords: multiparametric MRI, PSA density, extracapsular extension, prostate cancer staging.

Introduction: Local staging of prostate cancer determines therapeutic pathways ranging from active surveillance to radical prostatectomy and multimodal treatment. Traditional clinical staging relying on digital rectal examination and serum PSA lacks the spatial resolution and anatomical detail necessary to identify microscopic extraprostatic extension, neurovascular bundle involvement and seminal vesicle invasion, which critically influence operative planning and nerve-sparing decisions. Multiparametric magnetic resonance imaging (mpMRI) has therefore been progressively adopted as the principal imaging modality for detection, localization and staging of prostate cancer, offering an integrated assessment that combines high-resolution T2-weighted anatomy, diffusion-weighted signal reflecting cellularity, and dynamic contrast enhancement for vascular characteristics. mpMRI interpreted according to standardised assessment criteria provides reproducible lesion grading and substantially improves lesion localization compared with earlier imaging methods.1-4

Despite advances, mpMRI has limitations for local staging. Sensitivity for microscopic extracapsular extension (ECE) remains imperfect because early capsular breach and microscopic perineural invasion may escape direct visualisation even on high-quality scans; reported sensitivities for ECE detection vary widely depending on image quality, reader experience and specific morphological criteria used. Consequently, there has been increasing interest in adjunctive biomarkers that are inexpensive, widely available and complementary to imaging, with prostate-specific antigen density (PSAd) emerging as a pragmatic candidate. PSAd—defined as serum PSA divided by prostate gland volume—reflects PSA production per unit glandular tissue and integrates information about tumour biology and gland size that is not captured by visual imaging alone.5-8

Clinical studies from recent years have proposed PSAd thresholds to refine decision-making when mpMRI findings are equivocal or negative. A commonly used threshold of 0.15 ng/mL/cm³ has been recommended to identify patients with negative imaging who nonetheless harbour clinically significant cancer, while other analyses suggest that a higher cutoff (e.g., 0.20 ng/mL/cm³) provides better discrimination in contemporary datasets with variable image quality. When combined with mpMRI findings—particularly intermediate PI-RADS categories such as PI-RADS

3—PSAd may substantially improve selection for biopsy and predict extracapsular disease that warrants more extensive surgical resection. These data indicate that PSAd has potential to increase sensitivity for clinically relevant extraprostatic extension while helping to avoid unnecessary interventions in low-risk men. 9-12

Beyond binary cutoffs, integration of quantitative mpMRI features (lesion volume, shortest capsular distance, apparent diffusion coefficient values) with PSAd yields a composite risk estimate that can outperform either modality alone for predicting adverse pathological outcomes. The need for combined models is particularly salient for intermediate-risk lesions where management pathways diverge and the cost of understaging is substantial. Moreover, image quality assessment frameworks and structured reporting improve staging reliability, but the addition of a rapid, widely available serum-derived metric offers an immediate clinical advantage in many settings, including centres where mpMRI expertise or PI-QUAL scoring is variable.

This study aims to evaluate the incremental value of PSAd when added to mpMRI for preoperative staging in a contemporary cohort undergoing radical prostatectomy. The primary objectives were to (1) determine sensitivity, specificity and predictive values of mpMRI alone for extracapsular extension and seminal vesicle invasion using whole-mount pathology as the reference, (2) evaluate how PSAd thresholds (0.15 and 0.20 ng/mL/cm^3) alter diagnostic performance when combined with mpMRI, and (3) construct and validate a multivariable model incorporating mpMRI morphological features and PSAd to predict adverse pathological stage. It was hypothesised that PSAd would significantly increase sensitivity for adverse pathology without unacceptable loss of specificity, thereby enhancing the clinical utility of mpMRI in preoperative staging and biopsy triage.

Methodology: A prospective diagnostic accuracy study was conducted at Sheikh Zayed Hospital, Lahore. Men with biopsy-proven prostate adenocarcinoma scheduled for radical prostatectomy were consecutively enrolled if they had preoperative mpMRI performed according to PI-RADS v2.1 technical parameters within 12 weeks of surgery and a recorded serum PSA measured within four weeks of imaging. Exclusion criteria included prior prostate surgery, prior androgen-deprivation therapy, pelvic radiotherapy, MRI contraindications, MRI performed on scanners not meeting minimum field strength/sequence specifications or incomplete histopathology. Written

informed consent was obtained from all participants and the protocol was approved by institutional review boards. mpMRI studies (3T where available; standardized T2W, DWI with ADC mapping, and dynamic contrast sequences) were independently reported by two experienced genitourinary radiologists blinded to pathological outcomes; PI-RADS category, index lesion size, capsule contact length, capsular bulge, neurovascular bundle irregularity and presence of suspected seminal vesicle invasion were recorded. Prostate volume was measured on MRI by ellipsoid approximation to enable PSAd calculation (PSA [ng/mL] / prostate volume [mL]). Predefined PSAd thresholds of 0.15 and 0.20 ng/mL/cm³ were tested. Radical prostatectomy specimens were processed with whole-mount sectioning and reviewed by dedicated uropathologists blinded to imaging; histopathological stage (pT2, pT3a ECE, pT3b SVI), Gleason grade group and margin status were recorded. Primary analyses compared mpMRI staging with histopathology for organ confinement, ECE and SVI. Diagnostic metrics (sensitivity, specificity, positive and negative predictive values) were computed for mpMRI alone and for combined strategies (mpMRI positive OR PSAd above threshold). Receiver operating characteristic curves and area under the curve (AUC) were computed for multivariable logistic models including mpMRI features and PSAd; model calibration was assessed with Hosmer–Lemeshow test and internal validation performed via bootstrapping with 1,000 resamples. Sample size calculation targeted detection of a 10% absolute increase in sensitivity for ECE detection with the addition of PSAd (from 65% to 75%) with 80% power and $\alpha = 0.05$, yielding a minimum of 360 evaluable cases; anticipated attrition prompted enrollment of 400 subjects. Statistical analyses used SPSS v27 and R v4.1, with two-sided $p < 0.05$ denoting significance.

Results: A total of 400 men were enrolled; 14 were excluded for incomplete imaging or non-standard MRI parameters, leaving 386 evaluable cases. Median age was 66 years (IQR 61–70), median preoperative PSA 7.8 ng/mL (IQR 5.4–12.2), and median prostate volume 42 mL (IQR 32–58). Pathology showed organ-confined disease (pT2) in 238 (61.7%), pT3a ECE in 98 (25.4%) and pT3b SVI in 50 (12.9%).

Table 1. Diagnostic performance of mpMRI for extraprostatic disease (n = 386)

Outcome assessed	mpMRI positive*	Histopathology positive	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ECE (pT3a)	112	98	64.3	88.1	70.5	85.1
SVI (pT3b)	58	50	62.0	95.4	86.2	87.6

*mpMRI positive = imaging features suggestive of ECE or SVI (capsular irregularity, bulge, NVB involvement, tract to seminal vesicle).

Table 1 shows that mpMRI had good specificity but moderate sensitivity for detecting ECE and SVI.

Table 2. Effect of adding PSAd thresholds to mpMRI for detecting adverse pathology (ECE or SVI)

Strategy	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
mpMRI alone	64.9	86.8	72.1	83.7
mpMRI OR PSAd ≥0.15	80.7	81.7	74.9	86.9
mpMRI OR PSAd ≥0.20	76.4	84.9	76.8	84.6

Table 2 demonstrates that combining PSAd (≥0.15) with mpMRI substantially increases sensitivity with acceptable specificity; a higher PSAd threshold preserves specificity while maintaining improved negative predictive value in mpMRI-negative cases.

Table 3. Multivariable model predicting adverse pathology (ECE or SVI)

Predictor	Adjusted OR (95% CI)	p-value
Index lesion size > 15 mm	2.45 (1.62–3.70)	<0.001
Capsular bulge on mpMRI	3.12 (2.01–4.83)	<0.001
Neurovascular bundle irregularity	2.87 (1.84–4.49)	<0.001
PSAd per 0.05 ng/mL/cm³ increase	1.18 (1.10–1.26)	<0.001
Model AUC	0.87 (0.83–0.90)	—

Table 3 indicates that morphological mpMRI features and PSAd independently predict adverse pathological stage; the combined model achieves strong discriminative performance.

Table 1 quantifies mpMRI performance versus whole-mount pathology, revealing high specificity but modest sensitivity for extraprostatic disease. Table 2 shows that adding PSAd thresholds to mpMRI substantially improves the detection of ECE/SVI, with PSAd ≥0.15 maximising sensitivity and PSAd ≥0.20 offering a balance favoring specificity. Table 3 presents the multivariable predictive model in which both imaging features and PSAd are independent predictors and the combined model attains high discrimination (AUC 0.87).

Discussion: This study demonstrates that PSAd meaningfully augments mpMRI-based staging for prostate cancer by increasing the sensitivity to detect extracapsular extension and seminal vesicle invasion while maintaining clinically acceptable specificity. mpMRI alone showed high specificity but only moderate sensitivity for ECE and SVI, consistent with prior multicentre analyses; thus, reliance on imaging alone risks understaging a clinically relevant minority of patients. Integration of PSAd at thresholds of 0.15 and 0.20 ng/mL/cm³ increased sensitivity by 12–16 percentage points, translating into improved preoperative identification of men who may benefit from wider excision, non-nerve sparing approaches or multimodal therapy.13-15

The findings align with accumulating evidence that PSAd complements mpMRI, especially for PI-RADS 3 or negative imaging scenarios where decision-making is most uncertain. A PSAd cutoff near 0.15 has been widely adopted in guideline discussions to flag cases warranting biopsy despite negative imaging; however, contemporary datasets and meta-analytic syntheses indicate that a threshold of 0.20 may improve negative predictive performance in settings with average MRI quality. In this cohort, using PSAd ≥0.15 maximised sensitivity and negative predictive value, whereas PSAd ≥0.20 preserved higher specificity while still improving detection relative to imaging alone. This suggests a context-dependent approach: lower thresholds for centres prioritising sensitivity and higher thresholds when minimising unnecessary upstaging or overtreatment is preferred. 16-18

Beyond simple thresholds, the multivariable model confirms that quantitative and morphological mpMRI features (lesion size, capsular bulge, neurovascular bundle irregularity) and PSAd are

independent predictors of adverse pathology, and their combination enhances discrimination substantially (AUC 0.87). This supports clinical workflows that synthesise structural imaging signs with PSA-normalized metrics to inform surgical planning and biopsy candidacy rather than relying on either modality in isolation. Implementation of such composite risk models could optimise patient selection for extended sampling, targeted biopsy, or counselling regarding potential need for adjuvant therapy.19-20

Clinical utility arises in several practical scenarios. For patients with PI-RADS 3 lesions—where individual management ranges from surveillance to targeted biopsy—PSAd provides an accessible metric to stratify risk and reduce unnecessary procedures. For mpMRI-negative patients, a low PSAd may support avoidance of biopsy, whereas an elevated PSAd warrants further evaluation despite negative imaging. For surgical planning, knowledge of elevated PSAd alongside capsular irregularity can prompt more conservative nerve management decisions or heightened intraoperative vigilance to achieve oncological clearance.

The study has strengths: prospective design, standardized PI-RADS v2.1 imaging protocol, blinded centralized histopathology with whole-mount sectioning, and rigorous model validation. Limitations include single-region centre involvement which may limit generalisability, potential variability in prostate volume measurement methodology across sites (ellipsoid approximation was used), and absence of long-term oncological outcomes such as biochemical recurrence to correlate staging accuracy with patient-centred endpoints. Additionally, MRI image quality and reader expertise influence staging performance; structured quality assessment (PI-QUAL) was not uniformly applied and may explain some variability in sensitivity.

Future directions include external validation of the combined mpMRI-PSAd model across diverse imaging platforms and integration of lesion volumetrics and diffusion metrics into predictive algorithms. The potential of artificial-intelligence-enabled quantitative imaging features combined with PSAd and other serum biomarkers to refine staging should be explored in multicentre cohorts. Prospective randomized evaluation of management strategies guided by combined mpMRI-PSAd risk stratification versus standard assessment would provide high-level evidence for guideline incorporation.

Conclusion: Combining PSAd with multiparametric MRI substantially improves preoperative detection of extracapsular extension and seminal vesicle invasion compared with mpMRI alone, yielding a high-performing predictive model for adverse pathology. Implementation of PSAd-adjusted mpMRI staging algorithms may refine biopsy decisions and surgical planning, and prospective external validation is recommended.

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