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*Original Article*

# Tumor suspicion on MRI incorporating T2 and Diffusion-weighted imaging predicts adverse pathology on radical prostatectomy

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**Abstract:** Objective: The objective of this study was to determine whether suspicion for tumor on pretreatment prostate magnetic resonance imaging (MRI) incorporating T2 and diffusion-weighted imaging (DWI) predicts more adverse pathology following radical prostatectomy (RP) in prostate cancer patients. Methods: A single-institutional retrospective analysis was performed on 745 patients who underwent 3.0 Tesla pelvic-phased-array MRI of the prostate that included T2 and DWI before RP between July 2009 and December 2015. Patients were grouped into no suspicion for tumor (NST), equivocal suspicion for tumor (EST), or strong suspicion for tumor (SST) based on MRI findings. Preoperative variables and post-operative pathology, including primary Gleason score (≥ 4 vs < 3), pathological stage (≥ pT3 vs < T3), surgical margin and lymph node positivity, were compared between the three groups. A univariate logistic regression analysis was used to assess the associations between preoperative parameters and surgical pathology. Multivariable logistic regression analyses were performed to determine whether MRI finding was an independent predictor of adverse pathology after RP. Results: The preoperative PSA level, Gleason score and clinical stage showed significant variations between the NST, EST, and SST groups. Tumor suspicion on MRI was significantly associated with primary Gleason pattern, pathologic stage, and surgical margin. On multivariate analysis, MRI findings were independently predictive of primary Gleason score ≥ 4, pathologic stage ≥ T3, and positive margin. Conclusion: Prostate cancer patients with increased tumor suspicion on MRI incorporating T2 and DWI seemed to have worse pathologic features after RP. MRI may have potential use as a surrogate biomarker for adverse pathology.

**Keywords:** Magnetic resonance imaging, pathology, prostatectomy, prostatic neoplasms, risk

## Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the sixth leading cause of cancer deaths in men worldwide [1]. Widespread use of prostate-specific antigen (PSA) for PCa screening has led to the increased detection of earlier stages of localized tumors, and some men have indolent small-volume, low-grade disease that are unlikely to result in significant morbidity or mortality [2]. However, most patients undergo radical prostatectomy (RP) or radiotherapy [3], which may carry a risk of urinary and sexual dysfunction that can significantly affect the quality of life.

As clinicians have grown aware of the hazards regarding the overtreatment of low-risk prostate cancer, active surveillance (AS) with selective delayed intervention has emerged as a viable option that can spares patients from morbidity related to the overtreatment of indolent disease [4]. Eligibility criteria for AS differ by institution and are most commonly based on the clinical features such as PSA, digital rectal examination, clinical stage, and biopsy results. However, regardless of the eligibility criteria used, a significant percentage of men enrolled in AS programs will show signs of disease reclassification over time [5]. The rates of Gleason score upgrading ranged from 20% to

**Table 1.** Comparison of preoperative clinical variables and pathologic outcomes in patients of prostate cancer stratified by tumor suspicion on MRI

| | | Group | | | |
|---|---|---|---|---|---|
| Patients | Total | NST | EST | SST | *P* value |
| No. of patients | 745 | 120 | 356 | 269 | |
| Age (year) | 67.1 ± 8.1 | 67.5 ± 6.4 | 67.0 ± 8.2 | 67.0 ± 8.9 | 0.825 |
| BMI (kg/m$^2$) | 23.5 ± 3.5 | 23.9 ± 3.6 | 23.6 ± 3.3 | 23.3 ± 3.9 | 0.321 |
| Smokers (%) | 250 (33.6) | 29 (24.2) | 116 (32.6) | 105 (39.0) | 0.014 |
| PSA (ng/ml) | 19.4 ± 26.0 | 21.6 ± 4.39 | 16.8 ± 18.5 | 22.0 ± 23.6 | 0.029 |
| Clinical stage ≥ T2 (%) | 632 (84.8) | 36 (30.0) | 336 (94.4) | 260 (96.7) | < 0.001 |
| Gleason ≥ 7 on biopsy (%) | 515 (69.1) | 76 (63.3) | 232 (65.1) | 207 (76.9) | 0.002 |
| Promary gleason pattern ≥ 4 (%) | 380 (51.0) | 47 (39.2) | 163 (45.8) | 170 (63.2) | < 0.001 |
| Positive margin (%) | 162 (21.7) | 22 (18.3) | 66 (18.5) | 74 (27.5) | 0.016 |
| Stage ≥ pT3 (%) | 253 (34.0) | 29 (24.2) | 110 (30.9) | 114 (42.4) | < 0.001 |
| Lymph node involvement (%) | 40 (5.4) | 4 (3.3) | 15 (4.2) | 21 (7.8) | 0.08 |

EST, equivocal suspicion for tumor; MRI, magnetic resonance imaging; NST, no suspicion for tumor; PSA, prostate-specific antigen; SST, strong suspicion for tumor.

54% and pathologic upstaging from 6% to 26% [6-9]. These findings have raised concerns regarding the adequacy of current techniques to differentiate appropriately between candidates for conservative management and those who require definitive treatment.

MRI has been the mainstay of prostate imaging, and provides incremental value to biopsy and digital rectal examination for PCa detection, localization and staging [10]. Diffusion-weighted imaging (DWI) is an unenhanced technique that quantifies random Brownian motion properties of water molecules in tissues and enables the characterization of PCa cellularity [11]. It has been shown that combined T2-weighted imaging (T2-WI) and DWI is significantly better than T2-WI alone for detecting prostate cancer, and DWI quantification calculated by apparent diffusion coefficient (ADC) has been shown to be a promising technique for investigating tumor aggressiveness [12]. However, some cancerous lesions still cannot be detected on prostate MRI [13].

Based on this, we hypothesized that a detectable lesion on MRI might be related to more aggressive PCa, and undertook this retrospective study to evaluate the correlation between combined T2-WI and DWI results and postoperative pathology findings.

## Methods

With institutional review board approval, data from 1266 patients who underwent RP and also had prebiopsy MRI of the prostate including T2-WI and DWI from January 2009 to December 2015 at our institute were reviewed. After excluding patients with missing data and/or preoperative treatment, a total of 745 patients were eligible for our study. The database includes information on age at surgery, BMI, tobacco smoking, clinical stage, biopsy Gleason score, preoperative PSA, and surgical pathology, which included primary Gleason score, pathological stage, surgical margin and lymph node positivity.

All patients underwent prostate MRI at 3T. The MRI protocol was composed of routine T1-weighted imaging, T2-WI and DWI. All MR images were retrospectively reviewed by a single radiologist with 5 years of experience in prostate MRI. The radiologist blinded to patients' clinical information to minimize bias, although he was aware that all patients had undergone RP for biopsy-proven PCa. Based on a combined assessment of T2WI and DWI, cases were assigned to one of the following 3 categories: no suspicion for tumor (NST), equivocal suspicion for tumor (EST), or strong suspicion for tumor (SST) [14].

Continuous quantities are reported as means ± standard deviations and were compared between groups by using one-way analysis of variance followed with Tukey's multiple comparison test. Discrete quantities were compared between groups by using $\chi^2$ tests. A univariate logistic regression analysis was used to

**Table 2.** Univariate analysis for prediction of adverse pathology

| Preoperative clinical variables | Dominant Gleason ≥ 4 | | Stage ≥ pT3 | | Positvie margin | | LN positivity | | Reference group |
|---|---|---|---|---|---|---|---|---|---|
| | 95% CI | β value | 95% CI | β value | 95% CI | β value | 95% CI | β value | |
| Tumor suspicion on MRI | 1.71 (1.34-2.12)* | 0.54 | 1.55 (1.24-1.95)* | 0.44 | 1.39 (1.07-1.80)* | 0.33 | 1.70 (1.03-2.79) | 0.53 | No suspicion for tumor |
| Age > 65 years | 1.16 (0.86-1.56) | 0.15 | 1.19 (0.87-1.64) | 0.17 | 1.29 (0.89-1.87) | 0.26 | 2.06 (0.97-4.40) | 0.72 | Age ≤ 65 years |
| BMI > 25 kg/m$^2$ | 1.28 (0.90-1.81) | 0.25 | 1.14 (0.79-1.64) | 0.13 | 1.36 (0.92-2.01) | 0.31 | 0.89 (0.42-1.87) | -0.12 | BMI ≤ 25 kg/m$^2$ |
| Smokers | 1.09 (0.81-1.48) | 0.09 | 1.34 (0.97-1.84) | 0.29 | 0.85 (0.59-1.24) | 0.16 | 1.07 (0.55-2.08) | 0.07 | Non-smokers |
| PSA > 10 ng/ml | 2.15 (1.59-2.92)* | 0.77 | 2.21 (1.59-3.09)* | 0.80 | 1.41 (0.97-2.04)* | 0.34 | 3.61 (1.49-8.70)* | 1.28 | PSA ≤ 10 ng/ml |
| Gleason ≥ 7 on biopsy | 6.88 (4.77-9.92)* | 1.99 | 2.79 (1.92-4.03)* | 1.02 | 2.09 (1.37-3.19)* | 0.74 | -† | | Gleason < 7 on biopsy |
| Clinical stage ≥ T2 | 1.56 (1.04-2.35)* | 0.45 | 1.88 (1.18-2.99)* | 0.63 | 1.18 (0.71-1.95) | 0.16 | 1.65 (0.57-4.72) | 0.50 | Clinical stage T1 |

CI, confidence interval; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; *$P$ < 0.05; †No patients of Gleason score < 7 had lymph node metastasis.

**Table 3.** Multivariate analysis for prediction of adverse pathology

| Preoperative clinical variables | Dominant Gleason ≥ 4 | | Stage ≥ pT3 | | Positvie margin | | LN positivity | | Reference group |
|---|---|---|---|---|---|---|---|---|---|
| | 95% CI | β value | 95% CI | β value | 95% CI | β value | 95% CI | β value | |
| Tumor suspicion on MRI | 1.94 (1.43-2.64)* | 0.66 | 1.49 (1.11-2.01)* | 0.40 | 1.54 (1.11-2.13)* | 0.43 | 1.67 (0.91-3.07) | 0.52 | No suspicion for tumor |
| Age > 65 years | 1.18 (0.82-1.73) | 0.17 | 1.26 (0.88-1.82) | 0.23 | 1.50 (1.00-2.25) | 0.41 | 2.27 (1.00-5.17) | 0.82 | Age ≤ 65 years |
| BMI > 25 kg/m$^2$ | 1.27 (0.86-1.89) | 0.24 | 1.11 (0.76-1.63) | 0.10 | 1.37 (0.92-2.06) | 0.32 | 0.86 (0.40-1.86) | -0.15 | BMI ≤ 25 kg/m$^2$ |
| Smokers | 0.88 (0.60-1.28) | -0.13 | 1.17 (0.81-1.68) | 0.16 | 0.66 (0.44-1.00) | -0.41 | 0.96 (0.47-1.97) | -0.04 | Non-smokers |
| PSA > 10 ng/ml | 2.03 (1.40-2.94)* | 0.71 | 2.04 (1.40-2.98)* | 0.71 | 1.37 (0.91-2.05) | 0.31 | 2.80 (1.13-6.96)* | 1.03 | PSA ≤ 10 ng/ml |
| Gleason ≥ 7 on biopsy | 6.29 (4.15-9.55)* | 1.84 | 1.93 (1.28-2.92)* | 0.66 | 1.95 (1.23-3.09)* | 0.67 | -† | | Gleason < 7 on biopsy |
| Clinical stage ≥ T2 | 0.76 (0.43-1.34) | -0.28 | 1.18 (0.65-2.16) | 0.17 | 0.82 (0.44-1.54) | -0.20 | 1.06 (0.27-4.19) | 0.06 | Clinical stage T1 |

CI, confidence interval; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; *$P$ < 0.05; †No patients of Gleason score < 7 had lymph node metastasis.

assess the associations between the preoperative parameters and surgical pathology. To test MRI results as an independent predictor for each adverse pathologic features, we carried out multivariable logistic regression analyses adjusted for age (> 65 years vs ≤ 65 years), BMI (> 25 kg/m$^2$ vs ≤ 25 kg/m$^2$), clinical stage (T1 vs ≥ T2), PSA (≥ 10 ng/ml vs < 10 ng/ml) and Gleason score on biopsy (≥ 7 vs < 7). Statistical analyses were conducted using SPSS 16.0. For all tests, a *P* value of 0.05 was considered to indicate a significant difference.

## Results

Preoperative demographics, and clinical and pathological characteristics of patients as stratified by MRI suspicion are listed in **Table 1**. Non-significant association was demonstrated between MRI findings and age and BMI, while the preoperative risk factors, including PSA level, Gleason score ≥ 7 on biopsy and clinical stage, showed significant variations between the NST, EST, and SST groups (P < 0.05). Analysis of pathologic outcomes demonstrated that tumor suspicions were significantly associated with postoperative adverse pathology findings, including primary Gleason score ≥ 4, positive surgical margins and pathologic stage ≥ T3, and it showed a stepwise increases in the ability to detect prostate tumors on MRI with worse pathology. Although not statistically significant, a slight trend towards higher lymph node positivity was also noted with increased tumor visibility on MRI (P = 0.08).

At univariate logistic regression analysis, tumor suspicion on MRI, PSA, Gleason score on biopsy and clinical stage were significant predictors of adverse pathology after RP, while age and BMI were not significant predictors (**Table 2**). We further conducted multivariate analysis controlling for preoperative variables, including age, BMI, PSA, Gleason score on biopsy and clinical stage (**Table 3**). The results suggested that higher tumor suspicion on MRI were independently predictive of primary Gleason score ≥ 4 pathology (odds ratio [OR] 1.94, 95% confidence interval [CI] 1.43-2.64), stage ≥ pT3 (OR 1.49, 95% CI 1.11-2.01), as well as positive margin (OR 1.54, 95% CI 1.11-2.13), while it was not independently correlated with lymph node positivity.

## Discussion

PCa is the most frequent cancer in men in almost all western countries [1]. Owing to the increasing awareness of its variable biologic aggressiveness, the biggest challenge in managing patients with newly diagnosed PCa is to identify aggressive cancers that need radical treatment, while spare those with indolent cancers [15]. The Gleason grading system is the pathological reference standard for measuring the aggressiveness of PCa. However, the Gleason score determined through biopsies is known to differ from those determined following radical prostatectomy [16]. More accurate techniques are needed to determine the aggressiveness of PCa.

Owing to its high soft-tissue contrast, high resolution, and ability to simultaneously image functional parameters, MRI provides the best visualization of the prostate compared to other imaging methods. In this respective study, we observed that suspicion on MRI using combined T2-WI and DWI was positively correlated with some adverse pathologic findings. For example, patients with strong suspicion for PCa were significantly more likely to have higher Gleason scores, which could be explained by the fact that the ADC from DWI has been confirmed to be valuable for differentiating tumor aggressiveness [12]. Furthermore, MRI suspicion was significantly related to pathologic stage and positive margin, and a borderline significant correlation was also noted between MRI suspicion and lymph node positivity. The fact that all every adverse features were suggestively linked with MRI findings argues against the possibility of a chance finding. In addition, we found a significant correlation between MRI suspicion and preoperative clinical risk factors for advanced disease including a higher likelihood of Gleason score ≥ 7 and more advanced clinical stage. Even after adjustment for these confounding factors, tumor suspicion remained the independent predictor of higher primary Gleason score, pathologic stage and risk of positive margin.

In recent years, with a rapidly growing body of evidence, MRI is suggested to be a noninvasive tool risk-stratification tool for prostate cancer. Our results were consistent with a prior study by Borofsky et al. [14] who also demonstrated a

statistically significant correlation with the MRI detected lesion suspicion level and adverse pathology findings. However, only 154 patients, who underwent MRI at 1.5T, were included in that study, and their conclusion was based on comparison of men with SST to a combined cohort of men with either NST or EST. Park et al. [17] found that the apparent tumor presence on combined T2, DWI, and dynamic contrast-enhanced MRI was an independent predictor of biochemical recurrence after radical prostatectomy. Shukla-Dave et al. [18] introduced a new risk-stratification nomogram for PCa incorporating multiparametric-MRI findings, which performed significantly better than the clinical-only models [7]. A recent systemic review concluded that multiparametric MRI was able to detect significant prostate cancer and may be used to target prostate biopsies [19].

Published studies have offered conflicting results on the potential relationship between MRI findings and pathologic outcome in low-risk prostate cancer. Guzzo et al. [20] showed that tumor identification on MRI could not differentiate between favorable and adverse pathologic features in men who would qualify for active surveillance. On the contrary, Borofsky et al. [14] demonstrated that it was indicative of adverse pathology on RP in these patients. In the present study, we did not perform subgroup analysis in low-risk prostate cancer because small number of patients fulfilled the criteria. In China, men are not routinely screened for prostate cancer using the PSA test, resulting in more patients with advanced prostate cancer when diagnosed. Also, whether it is appropriate to conduct conventional active surveillance for Asian men with low-risk prostate cancer has not reached an agreement [21], and most patients with clinically confined disease underwent curative treatment.

To our knowledge, this is the largest study analyzing MRI findings to pathologic outcomes in Chinese PCa patients in a single center. However, our study has several limitations. First, the retrospective nature of this study might have some impact on our results. We only included patients who had RP in our institute, and not all men underwent MRI preoperatively. Second, the 3-point grading scale for tumor suspicion on MRI was a potential limitation. A 5-point scale was recommended for communicating the probability of malignancy from a European Consensus Meeting [22], which we felt was unnecessary for the purpose of answering our question, while a 2-point scale (suspicion vs no suspicion), as a previous study did [20], may led to increased misclassification from diagnostic dilemma. Third, some surgical confounding factors were not considered in our study. For example, patients were operated by eight different surgeons with two surgical approaches (open and laparoscopic surgery), and there is no doubt that the surgeon and the surgical technique have an influence on surgical margins. In addition, we did not perform extended but limited pelvic lymph node dissection, which would miss some lymph node involved.

In conclusion, higher tumor suspicion on MRI incorporating combined T2 and DWI may help predict worse pathologic outcomes after RP. These findings suggest a role for MRI in pretreatment risk assessment. A larger prospective trial and further evaluation is certainly needed to confirm our results and elucidate the exact mechanism underlying the observed association.

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## Disclosure of conflict of interest

None.

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