



Original Article

# Multi-parametric MRI of the prostate: Factors predicting extracapsular extension at the time of radical prostatectomy



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**Abstract** *Objective:* Extracapsular extension (ECE) of prostate cancer is a poor prognostic factor associated with progression, recurrence after treatment, and increased prostate cancer-related mortality. Accurate staging prior to radical prostatectomy is crucial in avoidance of positive margins and when planning nerve-sparing procedures. Multi-parametric magnetic resonance imaging (mpMRI) of the prostate has shown promise in this regard, but is hampered by poor sensitivity. We sought to identify additional clinical variables associated with pathologic ECE and determine our institutional accuracy in the detection of ECE amongst patients who went on to radical prostatectomy.

*Methods:* mpMRI studies performed between the years 2012 and 2014 were cross-referenced with radical prostatectomy specimens. Predictive properties of ECE as well as additional clinical and biochemical variables to identify pathology-proven prostate cancer ECE were analyzed.

*Results:* The prevalence of ECE was 32.4%, and the overall accuracy of mpMRI for ECE was 84.1%. Overall mpMRI sensitivity, specificity, positive predictive value, and negative predictive value for detection of ECE were 58.3%, 97.8%, 93.3%, and 81.5%, respectively. Specific mpMRI characteristics predictive of pathologic ECE included primary lesion size ( $(20.73 \pm 9.09)$  mm, mean  $\pm$  SD,  $p < 0.001$ ), T2 PIRADS score ( $p = 0.009$ ), overall primary lesion score ( $p < 0.001$ ), overall study suspicion score ( $p = 0.003$ ), and MRI evidence of seminal vesicle invasion (SVI) ( $p = 0.001$ ).

*Conclusion:* While mpMRI is an accurate preoperative assessment tool for the detection of ECE, its overall sensitivity is poor, likely related to the low detection rate of standard protocol MRI for

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microscopic extraprostatic disease. The additional mpMRI findings described may also be considered in surgical margin planning prior to radical prostatectomy.

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## 1. Introduction

The presence of pathologic extracapsular extension (ECE) of prostate adenocarcinoma after radical prostatectomy is a poor prognostic factor associated with recurrence and progression, as well as an increased risk of prostate cancer-related mortality [1,2]. ECE may also contribute to positive surgical margins during prostatectomy, an independent predictor of prostate specific antigen (PSA) progression after surgery [3]. While some suggest robot-assisted radical prostatectomy (RARP) may safely be performed in pathologic T3 (pT3) disease, preoperative concern for ECE often impacts the decision to pursue a nerve-sparing procedure, a decision that may detrimentally affect erectile function and quality of life after surgery [4].

Accurate clinical staging is essential to the clinician when counseling regarding treatment modalities and surgical planning. However, existing staging tools are woefully inaccurate. Transrectal ultrasonography (TRUS) and digital rectal exam (DRE), even in combination, are hampered by insufficient sensitivity and specificity for extraprostatic disease [5]. Additional predictive tools, such as pretreatment algorithms like the Partin tables and the Memorial Sloan Kettering (MSK) nomogram, were developed for the prediction of pathologic stage [6,7]. These widely used tools consider factors, such as biopsy Gleason score, clinical staging, and PSA, in their analyses. Variability in reported accuracy rates of these nomograms and their inability to predict site-specific ECE necessitates a more clinically applicable, accurate tool for the differentiation of extraprostatic and organ-confined (OC) prostate cancer [6–10].

In recent years multi-parametric magnetic resonance imaging (mpMRI) of the prostate has emerged as an integral tool in the staging and, more recently, diagnosis of prostate cancer. Although its role is not currently clearly defined in management algorithms, both the National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) recommend its use as a staging adjunct in high-risk disease [11,12].

mpMRI may provide prognostic information integral to treatment counseling and the management of expectations. When combined with clinical nomograms, mpMRI has been shown to improve the overall diagnostic accuracy of OC prostate cancer [13]. Alone, mpMRI has been shown to outperform the Partin tables in the detection of ECE and prediction of organ-confined disease [14,15]. Moreover, patients with clinical T3 disease on MRI have twice the risk of prostate cancer-specific mortality (PCSM) versus those with clinical T1/T2 and occult pT3 disease upstaged on final pathology [16]. Unfortunately, reported sensitivity and specificity of mpMRI in the detection of ECE is variable. Additionally, correlation studies of mpMRI and histopathology have demonstrated inconsistent tumor volume

estimation, particularly in large tumors, in which size is often underestimated [17,18].

Despite these limitations, mpMRI represents an important step forward in the clinical staging of prostate cancer. It is our aim to identify specific mpMRI variables that predict an increased likelihood of ECE and pT3 disease following prostatectomy in patients with clinically localized prostate cancer.

## 2. Materials and methods

### 2.1. Study design

We queried our prospectively maintained, Institutional Review Board-approved database of 1722 3-T (T) mpMRI studies performed within the Northwell Health System between the years 2012 and 2014. 3-T MRI included use of both endorectal and phase array cardiac coil. Functional analyses, consisting of dynamic contrast enhanced (DCE) and diffusion weighted imaging (DWI) modalities, are standard. Positive mpMRI was defined as the presence of one or more radiographically detected lesions. Primary and secondary lesions (based on overall size in mm) were assessed for peripheral versus central location, laterality, associated apparent diffusion coefficient (ADC) and prostate imaging reporting and data system (PIRADS) scores. In this scoring system each parameter (T2 Weighted Imaging (T2WI), DWI, DCE) is graded on a 5-point Likert scale. An additional overall 5-point score is given to the lesion as a whole, corresponding to the risk of clinically significant cancer, per the recommendations of the European Society of Urogenital Radiology (ESUR) [19]. Additional MRI variables such as capsular bulging, overt ECE and seminal vesicle involvement (SVI), and number of visualized lesions were also assessed. mpMRI studies were cross-referenced with radical prostatectomy specimens received within study duration. All prostatectomy specimens were centrally reviewed by dedicated uropathologists. mpMRI accuracy was defined as concordance between MRI findings suggestive of and pathologic evidence of ECE.

### 2.2. Statistical analysis

Descriptive statistics are presented as counts and percentages for categorical variables and as means and SD for continuous variables. The association of baseline clinical, biochemical, and MRI-related variables with pathology-proven prostate cancer ECE (present or absent) was analyzed with Student's *t* test for continuous data and chi-square test for categorical variables in univariable analysis. The following clinical and biochemical variables analyzed included: PSA (continuous, in  $\mu\text{g/L}$ ), prostate volume (continuous, in mL), fusion biopsy (yes or no), MRI result

(positive or negative), overall suspicion score (1–5), abutting capsule (yes or no), bulging (yes or no), ECE on MRI (yes or no), SVI on MRI (yes or no), number of lesions (continuous), and primary and secondary lesions size (continuous, in mm), zone (central or peripheral), laterality (right, middle, or left), ADC (continuous, in  $10^{-6}$  mm<sup>2</sup>/s), T2 PIRADS score (1–5), diffusion PIRADS score (1–5), enhancement PIRADS score (1–5) and overall lesion score (1–5). We also evaluated the predictive properties of ECE on MRI to identify pathology-proven prostate cancer ECE. Estimates are presented with 95% confidence interval (CI). All statistical analyses were two-tailed and performed using R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). A  $p < 0.05$  was considered statistically significant.

### 3. Results

A total of 74 patients underwent radical prostatectomy after mpMRI, and the descriptive pathologic statistics are presented in Table 1. OC disease (pT2) was found in 49 (66.2%) patients. Overall prevalence of ECE was 32.4% ( $n = 24$ ), with five cases being indeterminate on final pathology. Of the patients with ECE, eight had disease with SVI. One patient had solitary SVI. Two specimens, both pT3b, demonstrated lymphovascular invasion.

**Table 1** Radical prostatectomy characteristics found on surgical pathology ( $n = 74$ ).

Characteristic	Value
Prostate size (g) <sup>a</sup>	51.8 ± 19.7
Gleason score	
6	18 (24.3)
7	42 (56.8)
8	11 (14.9)
9	2 (2.7)
10	1 (1.4)
Tumor quantification	
Minimal (<10%)	5 (6.8)
Moderate (10%–50%)	64 (86.5)
Extensive (>50%)	5 (6.8)
Tumor stage	
pT2	49 (66.2)
pT3a	16 (21.6)
pT3b	9 (12.2)
Extracapsular extension	
Absent	45 (60.8)
Present	24 (32.4)
Indeterminate	5 (6.8)
Positive surgical margins	
Absent	54 (73.0)
Present	19 (25.7)
Indeterminate	1 (1.4)
Seminal vesicle invasion	
Absent	65 (87.8)
Present	9 (12.2)
Lymphovascular invasion	
Absent	72 (97.3)
Present	2 (2.7)

<sup>a</sup> Data presented as mean ± SD, and  $n$  (%) for other parameters.

The overall accuracy of mpMRI for ECE was 84.1%. mpMRI sensitivity, specificity, positive predictive value, and negative predictive value for detection of ECE were 58.3%, 97.8%, 93.3%, and 81.5%, respectively.

Table 2 summarizes characteristics of prostate MRI, broken down by pathology-proven ECE. The five patients with indeterminate ECE result on pathology were excluded from this analysis. Additional mpMRI characteristics associated with pathologic ECE were primary lesion size ( $20.73 \pm 9.09$  mm, mean ± SD,  $p < 0.001$ ), T2 PIRADS score ( $p = 0.009$ ), overall primary lesion score ( $p < 0.001$ ), overall study suspicion score ( $p = 0.003$ ), and MRI evidence of SVI ( $p = 0.001$ ). Neither MRI presence of capsular abutment nor bulging was significantly associated with pathologic ECE ( $p = 1.000$  and  $p = 0.173$ , respectively).

### 4. Discussion

mpMRI is a well-established adjunct in the clinical staging of prostate cancer, improving detection of ECE versus that of clinical nomograms, which routinely understage 25%–30% of patients [20]. In this study, we have demonstrated the excellent specificity, but limited sensitivity, of mpMRI for the presence of ECE and pT3 disease. The limited sensitivity reported in many prior studies examining mpMRI prediction of ECE reflects the inability of MRI to detect microscopic capsular penetration.

In their meta-analysis of 75 studies encompassing 9796 patients, de Rooij et al. [21] sought to comprehensively examine the staging accuracy of MRI of the prostate. Excellent overall specificity of 91% and 88%, for the detection of ECE and overall T3 staging, was found respectively. In contrast, overall sensitivity was less reliable at 57% and 61%, respectively. This study included a variety of differing MRI protocols, many of which employed a single or no functional components (i.e., DWI, DCE, or MR spectroscopic imaging (MRSI)), an integral component of prostatic MRI [21]. Both the American Society of Radiology (ACR) and the European Society of Uroradiology recommend use of two or more functional studies [19,22]. On whole in the subset of protocols using functional phases, some of which included only one functional component, overall sensitivity and sensitivity were improved (62%) and reduced (86%), respectively, in overall clinical T staging.

DWI and determination of ADC is particularly fundamental in evaluation of peripheral zone lesions and has shown superior sensitivity vs. T2WI alone [23–28]. Cancer on DWI presents with lower ADC values than that of normal tissue, the degree of which may be correlated to Gleason score [29,30]. Underscoring the importance of DWI further, Giganti et al. [31] generated a novel nomogram combining mpMRI, including ADC from DWI, along with clinical factors aiming at side-specific ECE prediction. Sensitivity was significantly improved vs T2WI (88% vs. 54%). Interestingly, in our study, T2WI PIRAD scoring was predictive of ECE while DWI was not. While T2WI has shown independent concordance with pathologic ECE, the absence of DWI concordance is puzzling [27]. ADC of secondary lesions, when observed, was also found to be predictive of pathologic ECE, while primary lesion's ADC was not. It is well established that DWI is superior to T2WI for evaluation of

**Table 2** Prostate MRI characteristics by pathology-proven prostate cancer extracapsular extension.

Variable	Extracapsular extension		p-Value
	Absent	Present	
n (%)	45 (65.2)	24 (34.8)	N/A
MRI <sup>a</sup>			0.067
Negative	13 (28.9)	2 (8.3)	
Positive	32 (71.1)	22 (91.7)	
Overall suspicion score <sup>a</sup>			0.003
2	5 (20.8)	1 (6.3)	
3	6 (25.0)	1 (6.3)	
4	11 (45.8)	4 (25.0)	
5	2 (8.3)	10 (62.5)	
Abutting capsule <sup>a</sup>			1.000
No	43 (95.6)	23 (95.8)	
Yes	2 (4.4)	1 (4.2)	
Bulging <sup>a</sup>			0.173
No	43 (95.6)	20 (83.3)	
Yes	2 (4.4)	4 (16.7)	
MRI: extracapsular extension <sup>a</sup>			<0.001
No	44 (97.8)	10 (41.7)	
Yes	1 (2.2)	14 (58.3)	
MRI: seminal vesicle invasion <sup>a</sup>			0.001
No	45 (100.0)	18 (75.0)	
Yes	0 (0.0)	6 (25.0)	
Number of lesions <sup>b</sup>	1.0 ± 0.9	1.4 ± 0.9	0.119
Primary lesion			
Lesion size (mm) <sup>b</sup>	11.55 ± 4.88	20.73 ± 9.09	<0.001
Zone <sup>a</sup>			1.000
Central	6 (19.4)	5 (22.7)	
Peripheral	25 (80.6)	17 (77.3)	
Laterality <sup>a</sup>			0.007
Right	20 (64.5)	5 (22.7)	
Left	9 (29.0)	12 (54.5)	
Middle	2 (6.5)	5 (22.7)	
ADC ( $\times 10^{-6}$ mm <sup>2</sup> /s) <sup>b</sup>	752.6 ± 241.2	623.1 ± 166.9	0.069
T2 PIRADS score <sup>a</sup>			0.009
3	5 (29.4)	1 (8.3)	
4	11 (64.7)	4 (33.3)	
5	1 (5.9)	7 (58.3)	
Diffusion PIRADS score <sup>a</sup>			0.773
3	1 (5.9)	0 (0.0)	
4	3 (17.6)	1 (8.3)	
5	13 (76.5)	11 (91.7)	
Enhancement PIRADS score <sup>a</sup>			0.164
1	1 (5.9)	0 (0.0)	
2	2 (11.8)	0 (0.0)	
3	3 (17.6)	0 (0.0)	
4	11 (64.7)	12 (100.0)	
Overall lesion score <sup>a</sup>			<0.001
3	4 (23.5)	0 (0.0)	
4	13 (76.5)	3 (25.0)	
5	0 (0.0)	9 (75.0)	

ADC, apparent diffusion coefficient; MRI, magnetic resonance imaging; PIRADS, prostate imaging reporting and data system; PSA, prostate-specific antigen; SD, standard deviation.

<sup>a</sup> Data presented as n (%).

<sup>b</sup> Data presented as mean ± SD.

peripheral zone lesions [32]. The significance of these findings in the current study is not immediately apparent, but may owe to low study numbers.

mpMRI may enable more precise surgical strategy, as opposed to reliance on risk group stratification. Evidence of ECE on mpMRI should influence margin planning at the time of radical prostatectomy. Indeed, as many as 30%–50% of men categorized as high-risk by D'Amico criteria may have OC disease; however, these patients are likely to undergo non-nerve-sparing surgery due to the imprecise clinical risk assessment [33,34]. Analysis of ECE prediction based on ESUR scoring on mpMRI in prostate cancer patients stratified by NCCN risk groups demonstrated excellent predictive value, even amongst the high-risk cohort. Retrospective review showed 25.7% of men who had no evidence of ECE on mpMRI and who underwent a non-nerve-sparing procedure due to high-risk features, ultimately had OC disease at final pathology. Conversely, mpMRI was able to predict pathologic ECE in low or intermediate risk patients in patients who underwent nerve-sparing procedures and subsequently had a positive surgical margin [35].

Tamada et al. [36] retrospectively analyzed a group of 56 men with prostate cancer who underwent 3-T mpMRI prior to radical prostatectomy and found similar results. Positive surgical margins, found in 27% of patients, were linked with MRI findings suggestive of ECE, as well as lower tumor ADC and extension into the proximal or apical prostate. Despite this, small foci of ECE may not be detectable, especially when localized in the prostatic apex, again accounting for low sensitivity [37].

Ultimately, the ability of MRI to detect ECE has the most utility in surgical planning. In a recent study, investigators incorporated MRI in the preoperative decision to preserve or sacrifice the neurovascular bundles in a group of 353 men scheduled to undergo robotic radical prostatectomy. Following review, 26% of initial surgical plans were changed. In the procedures altered due to MRI findings, 91% of those changed to nerve sparing and 63% of those changed to neurovascular bundle resecting were appropriate, demonstrating the benefit of mpMRI staging in clinical practice [38].

In this study we have identified several independent mpMRI predictors of pathologic ECE. Unfortunately, we were unable to identify any correlation between these independent variables and pathologic ECE in the setting of negative mpMRI, given low study numbers. Van Holsbeeck et al. [39], Cornud et al. [40], and Baco et al. [41] found beneficial improvements in sensitivity (85.2% vs. 57.4%) and moderate decrease in specificity (83.9% vs. 91.9%) for mpMRI detection of ECE with the addition of "indirect signs", including capsular bulging and tumor contact length greater than >20 mm. An additional predictor not examined in our analysis, tumor contact length above a threshold of 20 mm has been shown to be superior to that of conventional MRI criteria [41]. MRI mean lesion size was found to be independently predictive of pathologic ECE. Larger index lesion size (>0.5 mL) has been correlated to increased risk of positive surgical margin after RALP [42]. This may indicate a potential role for wider surgical margins, even in the absence of discrete mpMRI evidence of ECE.

There are several limitations to this study. The overall number of patients with ECE included in the study was small and findings were generated through retrospective

review at a single institution. Also, MRI accuracy is dependent on experienced radiologic review. Inexperience may negatively impact the sensitivity and specificity of mpMRI by as much as 9% and 37%, respectively [43]. Our studies were read by one of two fellowship trained uro-radiologists. Further multi-institutional, prospective trials are necessary to confirm generalizability of the findings herein. Future research will need to address the role of mpMRI suspicion versus that of clinical risk stratification profiles and nomograms in the clinical assessment of ECE.

## 5. Conclusion

mpMRI is able to predict pathologic ECE with excellent specificity, but poor sensitivity. Several additional variables detected on mpMRI were found to be independently predictive of pathologic ECE in this study and may assist with preoperative staging.

## Conflicts of interest

The authors declare no conflict of interest.

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