

Extracapsular extension on multiparametric magnetic resonance imaging better predicts pT3 disease at radical prostatectomy compared to perineural invasion on biopsy

Luke Griffiths¹; Srinath Kotamarti^{1,2}; David Mikhail^{1,3}; Joseph Sarcona³; Ardeshir R. Rastinehad¹; Robert Villani¹; Jessica Kreshover¹; Simon J. Hall¹; Manish A. Vira¹; Michael J. Schwartz¹; Lee Richstone^{1,3}

¹Smith Institute for Urology, Northwell Health, New Hyde Park, NY, United States; ²Department of Urology, Maimonides Medical Center, Brooklyn, NY, United States; ³Department of Urology, Lenox Hill Hospital, New York, NY, United States

Cite as: Griffiths L, Kotamarti S, Mikhail D, et al. Extracapsular extension on multiparametric magnetic resonance imaging better predicts pT3 disease at radical prostatectomy compared to perineural invasion on biopsy. *Can Urol Assoc J* 2021 January 4; Epub ahead of print. <http://dx.doi.org/10.5489/cuaj.6909>

Published online January 4, 2021

Abstract

Introduction: Risk assessment for non-organ-confined prostate cancer (PCa) is important in the surgical planning for radical prostatectomy (RP). Perineural invasion (PNI) on prostate biopsy has been associated with adverse pathological outcomes at prostatectomy. Similarly, the identification of suspected extracapsular extension (ECE) on multiparametric magnetic resonance imaging (mpMRI) has been shown to predict non-organ-confined disease. However, no prior study has compared these factors in predicting adverse pathology at prostatectomy. We evaluated mpMRI ECE and prostate biopsy PNI on multivariable analysis to determine their ability to predict pathological stage at time of RP.

Methods: We retrospectively investigated the prostatectomy database at our institution to identify men who underwent prostate biopsy with pre-biopsy mpMRI and subsequent RP from 2013–2017. Multivariable regression analysis was performed to compare the association of mpMRI ECE (mECE) and PNI on prostate biopsy on the likelihood of finding pT3 disease on pathology post-prostatectomy.

Results: Of a total 454 RP between 2013 and 2017, 191 patients met our inclusion criteria. Stage pT2 and pT3+ were found in 120 (62.8%) and 71 (37.2%) patients, respectively. Patients with mECE had 4.84 cumulative odds of worse pathological stage on RP ($p=0.045$) compared to PNI on biopsy, which showed cumulative odds of 2.25 ($p=0.048$). When controlling only for those

patients without PNI, mECE was still found to be a significant predictor of pT3 disease at RP ($p=0.030$). However, in patients without mECE, PNI was not significant ($p=0.062$).

Conclusions: While mECE and biopsy PNI were both associated with worse pathological stage on RP, mECE had significantly higher cumulative odds compared to PNI. The significant predictive ability of mECE adds further clinical value to the use of mpMRI in PCa management. While validation in a larger cohort is required, these factors have important clinical implications with regards to early diagnosis of advanced disease and surgical planning.

Introduction

In patients with localized prostate cancer, nerve-sparing surgery offers improved post-operative functional outcomes and is considered the standard approach to radical prostatectomy (RP).^{1,2} Implementing a nerve-sparing approach, however, is not appropriate for every case and the decision to nerve spare is influenced by the estimated probability of extraprostatic extension (EPE) on prostatectomy.^{3,4} To optimize surgical and treatment planning, risk assessment for features of non-organ-confined disease is performed through nomogram assessment of preoperative clinical features, such as preoperative PSA, biopsy Gleason score, and clinical stage.⁵⁻⁹ However, preoperative estimates are often inaccurate, and in patients where the tumor extends outside of the prostate, the risk of positive surgical margin and adverse pathology may be particularly high.¹⁰

In an effort to improve existing predictive risk models, additional preoperative parameters have been studied for their utility. Perineural invasion is defined as the tracking of tumor cells along or around nerve fibers; in prostate cancer this extension is commonly reported on prostate biopsy pathology.^{11,12} While not traditionally utilized in nomogram assessment, perineural invasion (PNI) on prostate biopsy (PBx) is associated with EPE at RP as well as margin positivity and biochemical recurrence.¹³⁻¹⁶

Multi-parametric magnetic resonance imaging (mpMRI) is a PCa diagnostic tool that is increasingly popular and is being utilized to direct prostate biopsy and surgical planning.¹⁷ Preoperative mpMRI is useful for assessing the presence of significant cancer, predicting organ confined disease, and assessing seminal vesicle invasion.¹⁷ While having a low to moderate sensitivity, mpMRI has achieved high specificity and positive predictive values of up to 90% in detecting extracapsular extension and seminal vesicle invasion.¹⁸⁻²² Interestingly, while both PNI on PBx and mpMRI extracapsular extension (mECE) have been shown as independent predictors of adverse outcomes and non-organ-confined disease, no prior study has compared these factors together. To query whether PNI is a significant prognostic variable in the era of mpMRI, we evaluated and compared the ability of mECE and PNI on prostate biopsy to predict advanced pathological stage at time of RP.

Methods

Patient population

We retrospectively investigated the prostatectomy database at our institution to identify men who underwent radical prostatectomy from July 2013 through March 2017. Patients were included if they received an mpMRI and subsequent prostate biopsy before radical prostatectomy at our institution. Patients were excluded if they had missing information, incomplete mpMRI, if biopsy or mpMRI were conducted at an outside institution, or history of alternative or previous treatment for prostate cancer such as radiation therapy, cryoablation, or any neoadjuvant therapy. A subgroup analysis was performed to ascertain if mECE or PNI would reach significance in prediction of pT3 when excluding all mECE patients and then all PNI patients from the original cohort. All staging was assigned according to the 2017 American Joint Committee on Cancer (AJCC) staging criteria.²³

Protocol for mpMRI

Patients were referred for mpMRI in the setting of elevated PSA or PSA density. Urologists at our institution routinely obtained mpMRI prior to biopsy to utilize a fusion approach and for potential surgical planning. All patients underwent mpMRI (3T Verio, Siemens, Germany ®) of the prostate obtained with a 16-channel cardiac coil (Sense, Invivo ®) on the anterior pelvis and an endorectal coil (BPX-30, Medrad, Pittsburgh, PA ®) with its balloon filled with PFC-770 (3M, St. Paul, MN ®). Sequences obtained included tri-planar T2-weighted, diffusion-weighted imaging (DWI) (b-values 0, 500, 1000, and 1500) and separate b-2000 and dynamic contrast enhanced (DCE) sequences. All mpMRI were read by experienced genitourinary radiologists, who assigned risk scores using the PI-RADS v1 and PI-RADS v2 scoring system. If multiple suspicious lesions were present, the highest PI-RADS score reported was used. Extra-capsular extension on MRI was stratified based on radiology report into mECE present, mECE suspicious, or mECE absent. mECE ‘present’ was assigned if ECE was clearly seen, as described by the radiologist, with gross extension of disease. mECE ‘suspicious’ was assigned to reports including descriptions of “abutment”, capsular “bulging”, or “microscopic invasion cannot be ruled out”. mECE ‘absent’ was assigned when there was clearly no evidence of ECE on MRI.

Protocol for prostate biopsy

All biopsies were performed via transrectal technique by experienced urologists at our institution. MRI-Targeted images were processed on a Dynacad workstation (Invivo, Gainesville, FL®). MR/TRUS image fusion was performed using UroNav® software in conjunction with an IU-22 (Philips Health Care, Best Netherlands) end-fire ultrasound probe. During biopsies of the lesions, one core was obtained in the axial and sagittal planes for a total of two cores per lesion followed by 12-core systematic biopsy as per our institution’s protocol for MRI fusion biopsy. Patients without a targetable lesion identified on MRI received a standard

12-core transrectal ultrasound (TRUS) biopsy whereby 2 cores, medial and lateral, are taken from each sextant region in a standard fashion. All biopsy pathology slides were reviewed by our institution's experienced genitourinary pathologist.

Statistical methods

Univariable analysis was performed to determine if there were differences in age, PSA at MRI, prostate volume, PIRADS score, and ECE between pT2 and pT3+. A Mann-Whitney U test was run for non-normally distributed continuous variables and chi square was run for nominal parameters. A cumulative odds ordinal logistic regression with proportional odds was run to determine the effect of 6 variables on pathological cancer staging after radical prostatectomy. These variables included age, PNI on PBx, mECE, PI-RADS, PSA, and MRI prostate volume. A binomial logistic regression analysis was performed on all the variables to ascertain the likelihood of subjects having positive margins. PI-RADS, PSA, age, and prostate volume were analyzed as continuous variables. Proportional odds were assessed by a full likelihood ratio test comparing the fitted model to a model with varying location parameters. The model fit was tested through a deviance goodness-of-fit test. Collinearity of the independent variables was assessed and ruled out through inspection of correlation coefficients and tolerance/VIF values. SPSS 24.0.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis with $p < 0.05$ considered statistically significant.

Results

During the study period, 454 patients underwent RP at our institution. 191 patients met our inclusion criteria with baseline characteristics shown on Table 1. Stage pT2 and pT3 were found in 120 (62.8%) and 71 (37.2%) patients after prostatectomy. Biopsy pathology classified 28 (14.7%), 81 (42.4%), and 82 (42.9%) patients into Gleason grade group 1, 2, and 3-5 respectively. Prostate needle biopsy PNI was positive in 55 (22.8%) and absent in 136 (71.2%) of patients. On mpMRI, mECE was found in 12 (6.3%), suspicious mECE in 32 (16.8%), and mECE absent in 147 (77%) patients (Table 1).

Multiparametric MRI findings for mECE and suspicious mECE were compared to final pathology to determine sensitivity, specificity, PPV, and NPV of detecting pT3 disease (Table 2). mECE present had sensitivity, specificity, PPV, and NPV of 14.1% (95% CI 7.3-24.8), 98.3% (95% CI 93.5-99.7), 83.3% (95% CI 50.9-97.1), and 65.9% (95% CI 58.4-72.7), respectively. On the other hand, mECE suspicious resulted in a sensitivity, specificity, PPV and NPV of 23.9% (95% CI 14.9-35.8), 87.5% (95% CI 79.9-92.6), 53.1% (95% CI 35.0-70.5), and 66% (95% CI 58.1-73.2), respectively.

Univariable analysis revealed statistical significance between pT2 and pT3+ groups with regards to PSA, PNI, PIRADS, and ECE. Age and prostate volumes did not reach significance (Table 1). On multivariable analysis, PNI on PBx predicted 2.25 times higher odds of pT3

disease [$p=0.045$, 95% CI 1.101 - 3.431]. Similarly, presence of extracapsular extension on MRI also predicted pT3 disease with an odds of 4.84 times [$p = 0.048$, 95% CI 1.02 – 23.17]. However, ECE suspicious on MRI did not significantly predict advanced stage at prostatectomy compared to absent ECE on MRI ($p = 0.814$). Increased PI-RADS and PSA at MRI were both associated with an increase in the odds of predicting advanced stage PCa on RP (OR of 2.20, 95% CI [1.29 – 3.752] and 1.10, 95% CI [1.012 – 1.184], respectively) as seen in Table 3. Age was not associated with an increased odds of predicting pathological stage ($p = 0.542$). When assessing for surgical margin status on binary logistic regression, only mECE present was statistically associated with an increased likelihood of exhibiting positive surgical margins with an OR of 6.57 [$p = 0.031$, 95% CI (1.19 – 36.15); Table 4]. Fifty (90.9%) patients with PNI did not have mECE; of these, 28 (56.0%) were pT3.

In subgroup analysis, when controlling only for those patients without PNI ($n = 136$), 7 (5.1%) patients had mECE; of these, 5 (71.4%) were pT3. Within this cohort, mECE was still found to be a significant predictor of pT3 disease at RP ($p=0.03$). When analyzing mECE absent patients ($n = 174$), 50 (90.9%) had PNI on pBx; of these, 28 (56.0%) were pT3 PNI on PBx ($n=50$). This cohort, however, did not significantly predict pT3 disease ($p=0.062$).

Discussion

To our knowledge, this is the first study to compare PNI and mECE together in a predictive model for at least pT3 disease at time of RP. In particular, we found mECE to have an increased likelihood of predicting pT3 compared to that of PNI on prostate biopsy. Additionally, in our population mECE also was shown to be an independent predictor of positive surgical margins. Importantly, when PNI was present but there was no ECE on MRI, there was no significant increase in pT3 disease.

Historically, preoperative risk stratification methods have implemented certain clinical and laboratory elements to predict oncologic outcomes. Common methods such as the Partin Tables or D'Amico Risk Stratification for prostatectomy oncologic outcomes include the use of PSA, Gleason score, and clinical staging.^{5,9,24} While these stratification methods do not use PNI on PBx, PNI has been shown to be associated with adverse pathological outcomes at time of RP.^{13,14,16} A recent retrospective review by Celik *et al.* stratified post-prostatectomy patients based on RP pathological stage, PNI presence on PBx, and D'Amico risk stratification. The authors suggested the presence of PNI is an important predictive marker due to positive correlation with local invasive disease after RP in all stratification groups, especially highlighting that those with intermediate D'Amico risk and positive PNI should have increased suspicion for locally advanced disease.¹³ An earlier review conducted by Delancey *et al.* in 2013, also sought to determine the effect of PNI on adverse pathological features at time of RP, as well as to determine survival outcomes in these patients. On multivariable models controlling for biopsy Gleason score, PSA, and clinical stage, they found patients with PNI on PBx had 2.27,

2.64, and 1.64 increased odds of having extraprostatic extension, seminal vesical involvement, and positive surgical margins, respectively. Additionally, their analysis of survival outcomes showed decreased disease free and overall survival times.¹⁴ While our results for predicting pT3 are in line with these findings showing similar increased odds of 2.25, association of positive surgical margins did not achieve significance. This is likely related to controlling for different factors between our models (Table 3).

In another study examining PNI, Cozzi *et al.* conducted a systematic review and meta-analysis in which they also found patients with PNI on PBx had a significant association with pT3 tumors at time of RP.¹⁶ Of their 7981 patients reported, they found PNI positivity on PBx to be 15.8%, and in patients with PNI, pT3 pathology was found in 53.4% of RP specimens. These findings agree with similar studies which showed just over half of patients with PNI having pT3.^{14,15} While the present study found an increased PNI positivity rate of 22.8%, this is similar to previously published rates of PNI.^{13-15,25} Our findings of an increased rate at 60% of PNI patients having pT3 disease may be attributed to our population having an overall higher rate of pT3 at 37.1% compared to 27.9% as seen in Cozzi *et al.* Clearly, presence of PNI on PBx has been implicated as a predictor of non-organ confined disease, and consequently, some have agreed nerve sparing techniques should not be performed in such patients.

In our cohort, we looked to evaluate if the presence of PNI on PBx holds significance in the age of high-resolution imaging. Specifically, would mpMRI prediction of ECE exceed PNI on PBx as a predictor of non-organ confined disease? Furthermore, does the presence of PNI even maintain predictive significance when mpMRI fails to show mECE?

Our study demonstrated mECE was, in fact, a better predictor of adverse pathology compared to PNI on PBx. The continued rise in mpMRI usage for pre-surgical evaluation and management of prostate cancer has allowed for further exploration into how these tools can be incorporated in predicting patient outcomes. While the impact of PIRADS has been well studied, mECE provides a logical tool to identify patients at risk for adverse postoperative pathology. In a study examining whether findings of mECE were associated with upstaging or upgrading at prostatectomy by Hedge *et al.*, they followed the mECE T3 staging based on findings of asymmetric bulging, irregular margins, or direct extension of the lesion into periprostatic fat or neurovascular bundle staging as reported previously by Roethke *et al.*^{26,27} On multivariable logistic regression, they found a 4.81 adjusted odds ratio for increased likelihood of pT3 after RP compared to pT2. These findings are in line with our study results of 4.84 increased odds of pT3 compared to pT2 when mECE is present. Interestingly, our mECE suspicious group did not achieve significance for independently predicting pT3 at time of RP. This finding perhaps could be attributed to the inclusion of PIRADS scoring into the regression model.

Utilizing mECE in predictive models has also shown a potential benefit. Dominguez *et al.* implemented mECE findings using a 1.5T mpMRI in patients with intermediate and high D'Amico risk to establish an AUC of 0.7 for predicting non-organ confined disease at time of

RP.¹⁸ Taking a step further, when comparing these mECE against the Partin tables, Gupta *et al.* found that mECE had an AUC of 0.82 compared to those of the Partin table's at 0.62 ($p = 0.04$) in terms of predicting adverse pathologic stage.²⁸ Interestingly, sensitivity of mECE in predicting pT3 using a 3.0T MRI scanner is variable and generally low across literature ranging from 35-74%, and our study was no different, reporting sensitivities of 14.1% and 23.9% for mECE present and mECE suspicious, respectively. However, specificity is consistently reported as robust for the prediction of pT3 with mECE, as we confirmed in our study, finding a specificity of 98.3% for mECE presence.^{22,29,30}

The present study was not without its limitations. As a retrospective study, it is subject to inherent biases including selection bias as a possible explanation for our higher observed pT3 rate at RP. Evaluating for both PNI and mECE decreased the included sample size, resulting in large confidence intervals, specifically for mECE. Further validation with a larger cohort is warranted. Unlike the PIRADS scoring system, reporting for mECE does not follow a strict standardized procedure and is vulnerable to subjectivity and interobserver variability between radiologists. Evaluating mECE presents a challenge due to inherent subjectivity of proper characterization; although similar, a non-standardized and heterogenous approach to MRI staging amongst studies exists in the literature.^{18,22,26,28} Unfortunately, there does not exist a standardized stratification for mECE at this time. Furthermore, there are a plethora of possible descriptions for addressing ECE that fall in between “no ECE” and “ECE present.” We attempted to account for this by stratifying the groups to separately analyze the less straight forward ‘mECE suspicious’ reported lesions. Although during this time period, many institutions did not routinely obtain mpMRI prior to prostate biopsy, our institution routinely obtained mpMRI prior to biopsy on patients with elevated PSA to allow for fusion biopsy approach. When challenged, we were often able to obtain high insurance approval rates through peer-to-peer authorization discussions.

Our findings support mECE as having the potential to significantly predict the presence of pT3 disease on radical prostatectomy. When excluding all patients with mECE present, PNI positivity on its own did not significantly predict pT3 disease. Conversely, when all PNI patients were excluded, mECE still retained its significance in predicting pT3. Although the development of an accepted standardized reporting system for extracapsular extension is necessary for inclusion into a nomogram for risk assessment, our study further supports the use of MRI pre-operatively in perioperative surgical and treatment planning for organ confined prostate cancer.

Conclusions

While mECE and PNI on PBx were both associated with worse pathological stage on RP, mECE had significantly higher cumulative odds compared to PNI. The significant predictive ability of ECE on multivariable analysis, and when controlling for only non-PNI patients, adds further clinical value to the use of mpMRI in prostate cancer management. In patients with no suspicion

for ECE on mpMRI, PNI is not associated with increased risk for T3 disease. This has potential implications when selecting patients for nerve sparing prostatectomy. While validation in a larger cohort is required, these factors may have important clinical implications with regards to early diagnosis of advanced disease, while also highlighting the necessity for selective nerve sparing to be further explored.

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Table 1. Baseline characteristics by pathological stage on radical prostatectomy					
Parameter	Total (n=191)	Pathological staging			p
		T2 (n=120)	T3a (n=56)	T3b (n=15)	
PSA (mean ± SD)	8.1±5.2	7.2±4.4	9.3±5.7	11.6±7.6	0.002
Age (mean ± SD)	61.8±7.1	61.8±7.1	61.1±7.5	63.3±5.9	0.630
Prostate volume RP (mean ± SD)	51.2±20.7	52.4±21.7	49.0±19.2	49.6±18.3	0.266
Prostate volume MRI (mean ± SD)	42.8±23.7	44.4±25.8	41.0±21.3	37.3±11.6	0.352
Extracapsular extension (MRI)					<0.001
	Present	12	2 (16.7%)	5 (41.7%)	5 (41.7%)
	Suspicious	32	15 (46.9%)	15 (46.9%)	2 (6.3%)
	Absent	147	103 (70.1%)	36 (24.5%)	8 (5.4%)
Perineural invasion on biopsy					<0.001
	Present	55	22 (40%)	25 (45.5%)	8 (14.5%)
	Absent	136	98 (72.1%)	31 (22.8%)	7 (5.1%)
PI-RADS					<0.001
	2	14	11 (78.6%)	2 (14.3%)	1 (7.1%)
	3	39	29 (74.4%)	8 (20.5%)	2 (5.1%)
	4	94	67 (71.3%)	23 (24.5%)	4 (4.3%)
	5	44	13 (29.5%)	23 (52.3%)	8 (18.2%)

p-values reflect univariable analysis comparing parameters to pT2 and pT3 disease. ECE: extracapsular extension; MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging–Reporting and Data System; PSA: prostate-specific antigen; RP: radical prostatectomy; SD: standard deviation.

Table 2. Multiparametric MRI findings for mECE present and suspicious in detecting pT3 disease	
Parameter	Percentage (95% CI)
mECE present	
Sensitivity	14.1% (7.3–24.8)
Specificity	98.3% (93.5–99.7)
PPV	83.3% (50.9–97.1)
NPV	65.9% (58.4–72.7)
mECE suspicious	
Sensitivity	23.9% (14.9–35.8)
Specificity	87.5% (79.9–92.6)
PPV	53.1% (35.0–70.5)
NPV	66% (58.1–73.2)
PBx PNI	
Sensitivity	46.5% (34.6–58.7)
Specificity	81.7% (73.6–88.1)
PPV	60.0% (48.8–70.2)
NPV	72.1% (67.1–76.5)

CI: confidence interval; mECE: multiparametric MRI extracapsular extension; NPV: negative predictive value; PBx PNI: prostate biopsy perineural invasion; PPV: positive predictive value.

Table 3. Multivariable cumulative odds ordinal regression predicting likelihood of pT3 on radical prostatectomy

Parameter	OR (95% CI)	p
PNI present (Bx)	2.25 (1.02–4.97)	0.045
PNI absent (Bx)	*	
ECE present (MRI)	4.84 (1.01–23.17)	0.048
ECE suspicious (MRI)	0.88 (0.29–2.66)	0.814
ECE absent (MRI)	*	
Age	1.02 (0.94–1.07)	0.542
Prostate volume (MRI)	0.99 (0.97–1.00)	0.135
PSA (MRI)	1.10 (1.01–1.18)	0.023
PI-RADS	2.20 (1.29–3.75)	0.004

*Variable used as referent. CI: confidence interval; ECE: extracapsular extension; MRI: magnetic resonance imaging; OR: odds ratio; PI-RADS: Prostate Imaging–Reporting and Data System; PNI: perineural invasion; PSA: prostate-specific antigen.

Table 4. Multivariable binomial regression predicting likelihood of positive surgical margins

Parameter	OR (95% CI)	p
Age	1.02 (0.97–1.08)	0.436
PNI (Bx)	1.70 (0.75–3.86)	0.209
PSA (MRI)	1.04 (0.96–1.13)	0.328
Prostate volume (MRI)	0.99 (0.98–1.01)	0.610
ECE not present (MRI)	*	
ECE suspicious (MRI)	2.18 (0.78–6.06)	0.135
ECE present	6.57 (1.19–36.15)	0.031

*Variable used as referent. CI: confidence interval; ECE: extracapsular extension; MRI: magnetic resonance imaging; OR: odds ratio; PNI: perineural invasion; PSA: prostate-specific antigen.