Does proximity of positive prostate biopsy core to capsular margin help predict side-specific extracapsular extension at prostatectomy?

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Introduction: *To determine whether quantifying the proximity of positive prostate biopsy cores to the capsular edge may aid in identifying patients at risk for extracapsular extension (ECE) at the time of radical prostatectomy (RP).*

Materials and methods: *We reviewed a single-surgeon experience of 429 systematic transrectal prostate biopsies from 2010-2014. Marking ink was applied to the capsular edge ex vivo following specimen acquisition, and the proximity of cancer to the stained capsular edge was measured. Primary outcome was ECE at RP. Demographics, PSA, DRE findings, Gleason score, core location and involvement, and RP pathology were recorded. Predictors of ECE were identified using multivariable logistic regression. Receiver operating characteristic (ROC) analyses were performed to assess the predictive value of variables alone and in combination.*

Results: *One hundred and one patients who underwent staining during biopsy received RP (202 hemiprostates). Thirty-three patients (40 hemiprostates) exhibited ECE. There were 343 positive stained biopsy cores. Mean proximity of carcinoma to capsule was 4.7 mm. On univariable analysis, proximity of positive core ≤ 1 mm to capsule was predictive of side-specific ECE (OR 2.86, p = 0.013), though significance was lost in multivariable models. Area under the curve (AUC) for proximity was 0.571 alone and 0.804 in combination with PSA, cT stage, and total biopsy Gleason score.*

Conclusion: *Proximity of positive biopsy core to capsular margin may supply additional information in predicting ECE but requires validation in a larger cohort. Implementation of a staining technique at the time of systematic biopsy may be helpful in counseling patients and determining utility of nerve-sparing approaches.*

Key Words: prostate cancer, prostate biopsy, extracapsular extension, prostatectomy, nerve-sparing

Introduction

Transrectal ultrasound guided (TRUS) biopsy is currently the gold standard to diagnose prostate cancer and provides critical histological information to guide clinical decision-making and patient counseling. In addition to histology, extracapsular extension (ECE) is an important prognostic indicator of prostate cancer-specific mortality.[1]

Preoperative knowledge of the likelihood of ECE at radical prostatectomy (RP) can aid in counseling patients regarding mortality risk and assist in identifying patients eligible for nerve-sparing (NS) RP techniques. Preservation of erectile function without jeopardizing cancer control can be a considerable quality-of-life concern for many patients.[2-4] Existing predictive nomograms for ECE incorporate clinical and histological characteristics at biopsy, including serum prostate specific antigen (PSA), clinical tumor stage, biopsy Gleason score, percent of positive cores and percent of cancer in biopsy specimens.[5-8] Additional predictors of ECE include location of positive cores,[9] presence of cancer at the peripheral end of biopsy samples,[10,11]

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and preoperative magnetic resonance imaging (MRI) findings.[12,13] Despite the range of predictors identified, nomograms yield a predictive accuracy of only 70.2%-84.0% for ECE,[5-8] and in 14.8% of cases NS is abandoned intraoperatively due to unexpected ECE detected on frozen section.[14]

In the present study, we sought to determine whether quantifying the proximity of positive cores to capsular margin during systematic biopsies may aid in preoperatively identifying patients at risk for ECE at RP. Such evidence may help identify patients suitable for NS approaches and yield prognostic information.

Materials and methods

Patients

Following institutional review board approval, we reviewed a single surgeon experience of 429 consecutive systematic TRUS biopsies performed in an outpatient clinic setting between October 1, 2010 and August 31, 2014 utilizing a staining technique described below. Patients who were found to harbor malignancy and who subsequently elected to undergo primary surgical treatment with RP were included for analysis. Patients with incomplete data were excluded.

TRUS biopsy technique

Indications to proceed with biopsy were based on a shared decision between provider and patient following a discussion of associated risks and benefits in the setting of PSA values, digital rectal exam (DRE) findings, and patient life-expectancy. A standard 12-core biopsy template protocol was utilized for all biopsies. A sterile needle guide and needle were used for each procedure. All patients received a pre-procedure rectal enema and antibiotic. Prior to triggering the biopsy needle for sample acquisition, the engaged needle was confirmed to indent the prostatic capsule on real-time sonography. Following specimen acquisition, the capsular edge of each biopsy core was marked ex vivo with either blue or orange standard pathology margin inks to differentiate lateral or medial cores, respectively. All biopsy samples were reviewed by a single genitourinary pathologist, and the distance in millimeters from any positive core to the marked capsular edge was quantified. Our staining technique is depicted schematically in Figure 1.

RP technique

Patients found to harbor localized malignancy were counseled regarding management options, including active surveillance, RP, and radiation therapy, contextualized per their perceived risk stratification. RP was performed by a single surgeon in all cases using a robotic-assisted laparoscopic approach. Bilateral pelvic lymph node dissection (PLND) was performed in most cases; decision to forego PLND was based on perceived risk. The decision to pursue a NS approach (none, unilateral, or bilateral) was based on several factors including baseline erectile function, patient desire, PSA, clinical stage, biopsy Gleason score, tumor burden, location of positive cores, and, when obtained, preoperative MRI. RP specimens were reviewed by a single pathologist for dominant Gleason pattern (2005 consensus)[15] and pathologic stage (American Joint Committee on Cancer (AJCC) 2010 TNM classification).[16]

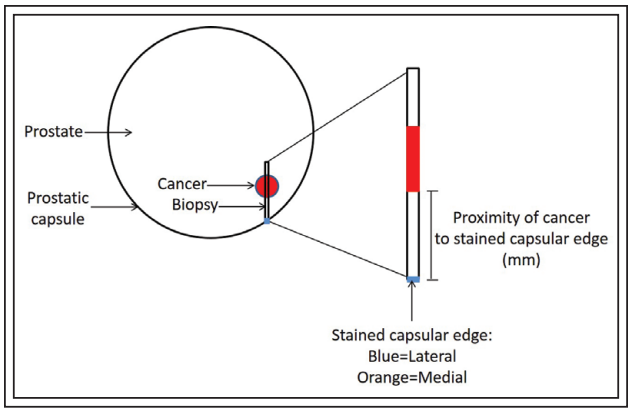

Figure 1. Schematic illustrating staining technique with representative positive biopsy core (inset). Capsular edge was stained at the time of sample acquisition with either blue (lateral cores) or orange (medial cores) ink. Proximity of cancer (shown in red) to stained capsular edge was measured in millimeters.

Data analysis

Patient demographics and comorbidities, PSA values, DRE findings, TRUS volume, Gleason score, positive cores, core location, % core involvement, and proximity of positive cores to stained capsular edge were collected and analyzed using descriptive statistics. Pathologic data from the RP specimen was also evaluated, including pT stage, pN stage, and Gleason score.

Our primary outcome was ECE at RP. We performed both side-specific (hemiprostatic) and core-specific subgroup analysis evaluating laterality of positive cores in relation to ECE, as well as extent of ECE. Independent-sample Mann-Whitney U tests were used to compare continuous variables, and chi-square tests were used to compare categorical

TABLE 1. **Patient characteristics and pathologic data from radical prostatectomy specimens**

Patient characteristics	
Total patients (#)	101
Median age (years)	63
Ethnicity (#)	
Caucasian	90
African-American	7
Asian	2
Hispanic	2
Median Charlson score	2
Family history of prostate cancer (#)	29
5ARI use (#)	4
LUTS (#)	49
PSA at biopsy (mean ± SD), ng/mL	6.53 ± 3.96
Positive DRE (#)	18
DRE suspicious for cT3 disease (#)	8
TRUS volume (ml), mean ± SD	43.75 ± 24.12
Median Gleason score on biopsy	7
Median time to surgery (IQR), mos.	1.7 (1.3-2.3)
Radical prostatectomy data	
pT stage (#)	
pT2a	9
pT2b	3
pT2c	56
pT3a	25
pT3b	7
ASAP	1
pN stage (#)	
pN0	93
pN1	3
pNX	5
Median Gleason score at prostatectomy	7
+ ECE (#)	33 (13 left-sided, 13 right-sided, 7 bilateral)

5ARI = 5-alpha reductase inhibitor; LUTS = lower urinary tract symptoms; PSA = prostate-specific antigen; TRUS = transrectal ultrasound; ECE = extracapsular extension; SD = standard deviation; IQR = interquartile range

variables. We also calculated corresponding prediction scores for side-specific ECE using the dynamic Memorial Sloan Kettering Cancer Center (MSKCC) nomogram, which takes into account preoperative PSA, primary and secondary biopsy Gleason patterns, clinical stage, and number of positive and negative biopsy cores.[8] We evaluated proximity of positive biopsy cores to capsular edge as both a continuous and categorical variable, including a range of proximity thresholds (0, 1, 2, 3, 4, and 5 mm). Receiver operating characteristic (ROC) analysis was additionally used to determine the optimal proximity threshold for our models. Corresponding area under the curve (AUC) values were calculated for individual and combined predictive features based on prior ECE nomograms.[6]

Univariable and multivariable logistic regression models were used to identify predictors of side-specific ECE in both a hemiprostatic and core-specific fashion. We performed two multivariable analyses for each: one controlling for predictors found to be significant on univariable analysis and one controlling for pre-defined variables of PSA, total biopsy Gleason score, and cT3 stage. All statistical analyses were conducted using SPSS version 22.0 (IBM, Armonk, NY, USA). P values are 2-sided with statistical significance defined as $p < 0.05$.

Results

Of 429 patients who underwent TRUS biopsy using our staining technique, 101 underwent RP and had pathologic and staining data available. Patient characteristics and RP pathology are summarized in Table 1. Median age in our cohort was 63 years. Mean (± SD) PSA at diagnosis was 6.5 ng/mL ± 4.0 ng/mL. Eighteen patients were noted to have positive DRE, 8 of whom were suspected of having cT3 disease. Thirty-three patients were found to have ECE, including 7 bilateral cases.

There were 202 corresponding hemiprostates available for side-specific analysis, which we stratified and compared by the presence of ipsilateral ECE, Table 2. Patients with ECE were noted to have higher total and primary Gleason pattern on biopsy ($p < 0.001$), a greater number of positive cores ($p < 0.001$), and a higher MSKCC preoperative prediction score (67.1% versus 45.5%, $p < 0.001$) versus those who did not harbor ECE. The proximity of a positive biopsy core ≤ 1 mm to the capsule was also notably more prevalent in patients with ECE (41.7% versus 20.0%, $p = 0.015$).

Out of 1,212 stained prostate biopsy cores from 101 RP patients, 343 cores were noted to harbor malignancy. Analysis of cores overall and sub-stratified by location is summarized in Table 3. Mean proximity of stain to capsule was 4.7 mm ± 3.6 mm (range 0-20), with 19.5% of cores ≤ 1 mm from capsule and 80.5% of cores > 1 mm from capsule. ECE ipsilateral to the side of positive core was found in 113 cores (32.9%). We compared the radial extent of ECE on RP specimens to the proximity of cancer to the stained capsular margin on biopsy cores and found that the corresponding scatterplot is best fit with a negative logarithmic regression function,

yielding a correlation coefficient value of r = -0.4961, Figure 2. These data highlight that the extent of ECE appears greater in cases in which positive biopsy cores are found at or within 1 mm of the capsular margin, whereas the magnitude of ECE seemingly diminishes as the distance from the capsular margin increases.

On ROC analysis, we found that proximity of positive core to capsule by itself yielded an AUC of 0.571 (95% CI 0.453-0.689), which was comparable to PSA alone (AUC 0.525) and cT stage alone (AUC 0.572) in our cohort, as shown in Table 4. Based on the ROC for proximity to capsule, we felt a 1 mm cut off was optimal, with a corresponding sensitivity of 41.7% and specificity of 80.0% for detecting ECE, Figure 3a. Recalculating AUC using this threshold yielded 0.608. AUC for Gleason pattern and number of positive cores ranged between 0.7 and 0.8. Figure 3b displays ROC curves for combined predictive features, including the MSKCC ECE predictive model(8) (AUC 0.763), PSA/cT stage/total biopsy Gleason score (AUC 0.803), and PSA/cT stage/total biopsy Gleason score/proximity to capsule (AUC 0.804).

On univariable hemiprostatic logistic regression analysis, Table 5, significant predictors for ECE included total biopsy Gleason score (OR 1.77, $p < 0.001$), primary Gleason pattern (OR 2.74, $p < 0.001$), number of positive cores (OR 1.59, $p < 0.001$), and proximity of positive core ≤ 1 mm from capsule (OR 2.86, $p = 0.013$). On multivariable models, proximity of core to capsule was no longer significant, and the strongest predictor remained total biopsy Gleason score. On core-specific univariable logistic regression analysis, Table 6, significant predictors for ECE included family history

TABLE 2. **Side-specific analysis stratified by presence of extracapsular extension (ECE)**

	ECE (side-specific)	**No ECE (side-specific)**	**p value***
Total hemiprostates	40	162	--
African American race (%)	5.0	7.4	0.741
Median Charlson score (IQR)	2 (2-3)	2 (1-3)	0.097
Family history of prostate cancer (%)	17.5	31.5	0.117
Median PSA at diagnosis (IQR), ng/mL	5.57 (4.47-7.29)	5.59 (4.26-7.26)	0.622
+DRE (%)	30.3	17.0	0.091
cT3 on DRE (%)	18.2	6.5	0.095
Median age (IQR), years	64.3 (58.0-69.0)	62.5 (55.2-69.1)	0.186
Median total biopsy Gleason score (IQR)	7 (6-8)	6 (0-7)	< 0.001*
Median primary Gleason pattern on biopsy (IQR)	4 (3-4)	3 (0-3)	< 0.001*
Median positive cores (IQR) [out of 6]	3 (1-4)	1 (0-2)	< 0.001*
Median time to surgery (IQR), mos.	1.7 (1.2-2.3)	1.7 (1.3-2.3)	0.491
Median proximity to capsule (IQR), mm	3.0 (0.5-6.0)	3.5 (1.5-7.0)	0.208
Proximity to capsule 0 mm (%)	13.9	5.3	0.137
Proximity to capsule ≤ 1 mm (%)	41.7	20.0	0.015*
Proximity to capsule ≤ 2 mm (%)	47.2	38.9	0.430
Proximity to capsule ≤ 3 mm (%)	52.8	49.5	0.845
Proximity to capsule ≤ 4 mm (%)	55.6	63.2	0.431
Proximity to capsule ≤ 5 mm (%)	72.2	70.5	1.000
Proximity to capsule > 1 mm and ≤ 5 mm (%)	30.6	50.5	0.050
Proximity to capsule > 5 mm (%)	27.8	29.5	1.000
Median MSKCC nomogram prediction score for side-specific ECE (IQR), %	67.1 (50.0-80.8)	45.5 (38.3-57.2)	< 0.001*

*statistical significance defined for $p < 0.05$
PSA = prostate specific antigen; ECE = extracapsular extension; IQR = interquartile range

TABLE 3. **Characteristics of positive stained biopsy cores overall and sub-stratified by location**

Core location	# Positive cores	Gleason score (median)	% Core involvement (mean ± SD)	Median proximity of core to capsule (mm), [range]
All cores	343 (166 R, 177 L)	7	31.1 ± 26.3	4 [0-20] Mean ± SD: 4.7 ± 3.6
R lateral base	29	7	30.1 ± 25.1	3 [1-11]
R medial base	23	7	35.6 ± 30.7	5 [0-14]
L lateral base	30	7	27.9 ± 25.6	5 [0-11]
L medial base	30	7	30.4 ± 25.4	5 [0.5-13.5]
R lateral mid	34	7	35.4 ± 24.1	2 [0.5-12]
R medial mid	28	7	42.1 ± 27.4	1.5 [0-10]
L lateral mid	27	7	35.3 ± 32.2	4 [0-12]
L medial mid	31	7	34.7 ± 27.5	3 [0-17]
R lateral apex	27	6	22.4 ± 24.8	7 [0.5-15]
R medial apex	25	7	26.1 ± 19.8	6 [1-14]
L lateral apex	31	6	26.7 ± 26.7	5 [0.5-20]
L medial apex	28	6	28.0 ± 24.5	5 [0-14]

R = right; L = left; SD = standard deviation

(p = 0.002), PSA (p = 0.010), suspicious DRE (p < 0.001), age (p = 0.009), Gleason score (p < 0.001), percent core involvement (p < 0.001), and proximity to capsule ≤ 1 mm

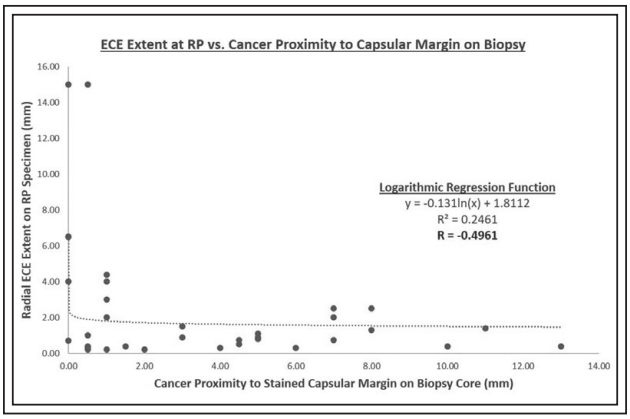

Figure 2. Scatterplot comparing radial extent of extracapsular extension (EPE) on prostatectomy specimen to proximity of cancer to stained capsular margin on biopsy core. The dotted line reflects the best-fit logarithmic regression function, which yielded a correlation coefficient value r = -0.4961. The extent of ECE is greatest at smaller distances of positive biopsy cores from the capsular edge and diminishes as the distance increases.

(OR 1.92, p = 0.026). On multivariable analysis, proximity of positive to core to capsule was no longer a statistically significant predictor for ECE. Our strongest predictors when controlling for other univariate predictors included positive DRE (OR 3.34, p = 0.001) and Gleason score on biopsy (OR 4.19, p < 0.001). In our pre-defined multivariable model, Gleason score (OR 4.69, p < 0.001) and cT3 (OR 4.55, p = 0.001) remained significant predictors for ECE.

Discussion

NS approaches during RP can significantly improve the quality of life of patients by preserving potency and potentially hastening recovery of continence.[2-4] Oncologic control, however, remains the principal objective of primary therapy for prostate cancer. The decision to spare the neurovascular bundle in potent patients must be risk-appropriated based on the perceived likelihood of ECE, especially given its prognostic role in predicting prostate cancer-specific mortality.[1] Various nomograms have emerged based on these variables to predict ECE;[5-8] however, they yield an estimated predictive accuracy of only 70.2%-84.0%. In a recent study, von Bodman et al found that in 14.8% of cases, NS RP is abandoned intraoperatively

TABLE 4. **Individual and combined predictive accuracy for side-specific ECE based on ROC analysis**

	Predictive features	AUC (95% CI)
Individual	PSA at diagnosis	0.525 (0.428-0.622)
	DRE-based cT stage in each lobe	0.572 (0.458-0.686)
	Total biopsy Gleason score	0.797 (0.721-0.874)
	Primary Gleason pattern on biopsy	0.771 (0.692-0.850)
	Secondary Gleason pattern on biopsy	0.753 (0.674-0.831)
	Number of positive cores	0.729 (0.648-0.809)
	Proximity to capsule	0.571 (0.453-0.689)
	Proximity to capsule ≤ 1 mm	0.608 (0.496-0.721)
In combination	MSKCC ECE predictive model	0.763 (0.674-0.853)
	PSA, cT stage, total biopsy Gleason score	0.803 (0.715-0.890)
	PSA, cT stage, total biopsy Gleason score, proximity to capsule	0.804 (0.705-0.903)

AUC = area under the curve; CI = confidence interval; MSKCC = Memorial Sloan Kettering Cancer Center; ECE = extracapsular extension; PSA = prostate-specific antigen; DRE = digital rectal exam

due to unexpected ECE detected on frozen section,[14] though their cohort is notably limited to 236 patients from a single institution. In addition, the perceived risks of NS techniques and their association with positive surgical margins are debated. For example, in a multi-institutional cohort of 6,120 patients who underwent RP, Preston et al concluded that bilateral NS is associated with increased risk of positive surgical margins in patients with pT2 disease;[17] however, their adjusted risk was not statistically significant (p = 0.069), as noted by Boehm and Graefen, who argue that NS is oncologically safe when patient selection is based on objective criteria.[18] In line with this latter argument, Palisaar et al noted in an earlier analysis that positive surgical margins are largely related to cancer volume rather than NS procedures.[19]

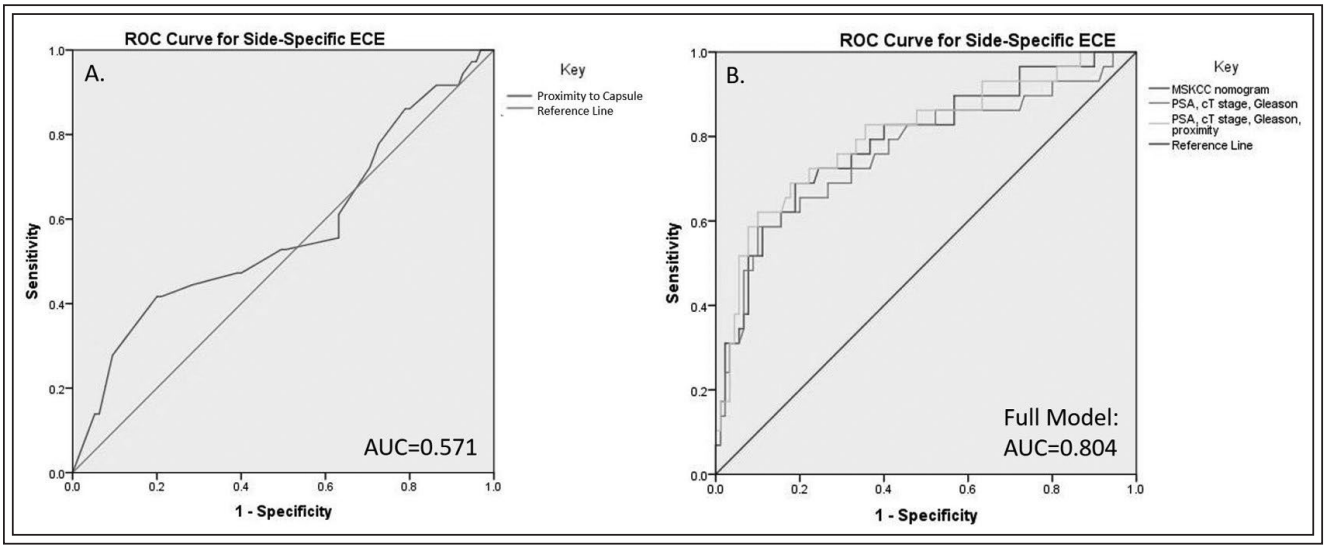

Figure 3. Receiver operating characteristic (ROC) curves for prediction of side-specific extracapsular extension (ECE). (**A**) Proximity of positive biopsy core to capsular edge individually yields an area under the curve (AUC) of 0.571. A 1 mm cutoff corresponds to a sensitivity of 41.7% and specificity of 80.0% in predicting ECE. (**B**) Combined ROC curves are displayed for comparison, including the dynamic Memorial Sloan Kettering Cancer Center (MSKCC) predictive model (AUC 0.763); PSA, cT stage, total biopsy Gleason score (AUC 0.803); and PSA, cT stage, total biopsy Gleason score, proximity to capsule (AUC 0.804).

TABLE 5. **Univariate and multivariate logistic regression analyses for predictors of side-specific ECE by hemiprostatic analysis**

	Variable	OR (CI)*	p value**
Univariate analysis	African American race	0.66 (0.14-3.07)	0.594
	Charlson score	1.14 (0.92-1.42)	0.225
	Family history of prostate cancer	0.46 (0.19-1.11)	0.085
	PSA at diagnosis	1.03 (0.95-1.12)	0.522
	+DRE	2.12 (0.90-4.99)	0.084
	cT3 on DRE	2.68 (0.91-7.89)	0.073
	Age	1.03 (0.99-1.08)	0.190
	Total biopsy Gleason score	1.77 (1.30-2.41)	< 0.001**
	Primary Gleason pattern on biopsy	2.74 (1.69-4.47)	< 0.001**
	Positive cores	1.59 (1.29-1.95)	< 0.001**
	Time to surgery	0.84 (0.59-1.19)	0.327
	Proximity to capsule (continuous)	0.95 (0.85-1.06)	0.322
	Proximity to capsule 0 mm	2.90 (0.79-10.71)	0.109
	Proximity to capsule ≤ 1 mm	2.86 (1.24-6.56)	0.013**
	Proximity to capsule ≤ 2 mm	1.40 (0.65-3.04)	0.391
	Proximity to capsule ≤ 3 mm	1.14 (0.53-2.46)	0.736
	Proximity to capsule ≤ 4 mm	0.73 (0.34-1.59)	0.426
	Proximity to capsule ≤ 5 mm	1.09 (0.46-2.55)	0.849
	Proximity to capsule > 1 mm and ≤ 5 mm	0.43 (0.19-0.97)	0.043**
	Proximity to capsule > 5 mm	0.92 (0.39-2.16)	0.849
Multivariate analysis based on univariate predictors	Total biopsy Gleason score	3.80 (1.90-7.61)	< 0.001**
	Positive cores	0.97 (0.69-1.35)	0.836
	Proximity to capsule ≤ 1 mm	1.84 (0.69-4.91)	0.223
Multivariate analysis based on predetermined variables	PSA at diagnosis	1.02 (0.92-1.13)	0.750
	Total biopsy Gleason score	3.51 (1.84-6.71)	< 0.001**
	cT3 on DRE	2.64 (0.60-11.65)	0.199
	Proximity to capsule ≤ 1 mm	1.70 (0.67-4.37)	0.267

*OR = odds ratio; CI = confidence interval (95%)
**statistical significance defined for $p < 0.05$
ECE = extracapsular extension; PSA = prostate-specific antigen; DRE = digital rectal exam

In light of the need to more accurately predict ECE pre-operatively, we herein report a technique of staining the capsular margin during prostate biopsies in order to quantify the proximity of positive cores to the capsular edge. ROC analysis revealed an optimal proximity threshold of 1 mm, which, unlike other thresholds, was a significant predictor for side-specific ECE on univariable hemiprostatic and core-specific analysis, but not on multivariable analysis. Concordant with prior studies, our strongest multivariable predictors for ECE on both hemiprostatic and core-specific analysis was total biopsy Gleason score.[5-8] We further validated previous predictive nomograms[6,8] using our cohort and supplemented their predictive accuracy with our proximity data.

While the AUC for proximity to capsule by itself was only 0.571, we note that this was comparable to the AUC for both PSA alone and cT stage alone in our pilot study. It is conceivable that repeating the ROC analysis in a larger cohort would yield a greater AUC. In a cohort of 763 patients (1,526 hemiprostates), for example, Ohori et al found these variables to be individually predictive for side-specific ECE,[6] and they calculated AUCs of 0.627 and 0.695 for PSA and cT stage, respectively. Our ECE rates (32.7% per patient, 19.8% per hemiprostate) were nonetheless comparable to theirs (30% per patient, 17% per hemiprostate). Furthermore, just as our 1mm threshold yielded a low sensitivity (41.7%) despite an acceptable specificity (80.0%), Ohori et al noted that no single feature predicted the presence of ECE with both high sensitivity and specificity in their study. In their combined ROC, Ohori et al's standard model consisting of PSA, cT stage and total biopsy Gleason sum had an

TABLE 6. **Univariate and multivariate logistic regression analyses for predictors of side-specific ECE by core analysis**

	Variable	OR (CI)*	p value**
Univariate analysis	African American race	1.08 (0.48-2.40)	0.854
	Charlson score	1.00 (0.86-1.17)	0.968
	Family history of prostate cancer	0.43 (0.25-0.74)	0.002**
	PSA at diagnosis	1.08 (1.02-1.14)	0.010**
	+DRE	4.10 (2.34-7.20)	< 0.001**
	cT3 on DRE	6.72 (3.07-14.71)	< 0.001**
	Age	1.04 (1.01-1.07)	0.009**
	Total biopsy Gleason score	4.24 (2.86-6.28)	< 0.001**
	Primary Gleason pattern on biopsy	5.95 (3.57-9.91)	< 0.001**
	% core involvement	1.02 (1.01-1.03)	< 0.001**
	Proximity to capsule ≤ 1 mm	1.92 (1.08-3.41)	0.026**
Multivariate analysis based on univariate predictors	Family history of prostate cancer	0.72 (0.36-1.43)	0.344
	PSA at diagnosis	1.04 (0.95-1.13)	0.448
	+DRE	3.34 (1.62-6.88)	0.001**
	Age	1.02 (0.98-1.06)	0.459
	Total biopsy Gleason score	4.19 (2.47-7.09)	< 0.001**
	% core involvement	1.01 (0.99-1.02)	0.245
	Proximity to capsule ≤ 1 mm	0.70 (0.30-1.61)	0.400
Multivariate analysis based on predetermined variables	PSA at diagnosis	1.01 (0.92-1.10)	0.894
	Total biopsy Gleason score	4.69 (2.92-7.54)	< 0.001**
	cT3 on DRE	4.55 (1.88-11.00)	0.001**
	Proximity to capsule ≤ 1 mm	1.05 (0.51-2.17)	0.891

*OR = odds ratio; CI = confidence interval (95%)
**statistical significance defined for $p < 0.05$
ECE = extracapsular extension; PSA = prostate specific antigen; DRE = digital rectal exam

AUC of 0.788, versus 0.803 in our study. Supplementing their standard model with proximity to capsule as an additional variable yielded an AUC of 0.804, which was an improvement over the dynamic MSKCC ECE predictive model[8] when applied to our cohort (AUC 0.763). Our ability to include additional variables individually in our combined model, such as number of positive cores and percent core involvement, may have unfortunately been limited by sample size.

The concept of staining prostate biopsy specimens after acquisition for localization of biopsy cores has been previously utilized[6,20-22] and may assist with predicting side-specific ECE.[6,10,11,23-25] As Bjurlin et al noted in their recent review, while identifying the laterality of positive biopsy cores may be helpful for predicting sites of ECE and assist with therapeutic planning, characterizing the exact location of cores may be less clinically meaningful.[23] Given this information, we elected to perform side-specific analysis of our stained cores and ECE, rather than a more in-depth location mapping of cores versus ECE sites. Furthermore, this side-specific approach is more clinically relevant for determining whether or not to perform bilateral, unilateral, or no NS approaches.

In 2011, Ponholzer et al introduced a novel technique of marking the peripheral end of prostate biopsy specimens to predict locally advanced prostate cancer or positive surgical margins (PM).[10] In this technique, following acquisition of biopsy samples, a nurse was responsible for marking the peripheral end of each biopsy core prior to submission for histopathological analysis, similar to our method. In a binary fashion, they evaluated whether or not carcinoma was present at the marked end. They found that patients with carcinoma present at the peripheral end of cores were significantly more likely to have both ECE and PM. In a subsequent multi-institutional validation study, they found that this remained predictive of PM but not ECE on logistic regression.[11]

There are some similarities between our staining technique and that of Ponholzer et al. If the peripheral ends of biopsy cores in their study are truly the

capsular edge, then carcinoma at the stained edge would be analogous to "0 mm" proximity in our study. Furthermore, while their approach is binary in nature, ours enables the ability to quantify the proximity of positive cores to the stained capsular edge and assess whether a positive core that is approaching (but not necessarily involving) the edge may hold poor prognostic value.

There are limitations to our pilot study including its retrospective nature and single institution cohort with a small sample size, which may have limited our ability to achieve statistical significance on multivariable analysis. The number of patients with ECE also limited the number of variables available for inclusion in our multivariate model given the risk of overfitting. Although we performed side-specific analysis based on perceived clinical relevance,[23] a more complex approach mapping core location based on prostate zone with sites of ECE may potentially increase the predictive accuracy.

Furthermore, all patients included underwent systematic, rather than targeted, biopsies; with the advent of multiparametric MRI-targeted approaches and genomic classifiers for adverse outcomes, staining of the biopsy cores may conceivably offer a complementary role for ECE prediction in patients who would benefit from undergoing targeted biopsies. Although we did not assess the incremental benefit of combining our staining technique with pre-operative MRI findings, recent findings have revealed some debate regarding the association of MRI findings and surgical margin rates.[26,27] In a small institutional cohort, the AUC for prediction of ECE by the addition of multiparametric MRI to clinical predictive models increased by 0.07-0.08.[28] Similarly, in another cohort, the AUC for ECE prediction increased by 0.08-0.12 with the addition of MRI depending on the clinical nomogram used.[29] However, Roethke et al noted that while MRI was felt to be an effective tool in predicting ECE in intermediate- to high-risk patients and influenced the decision to pursue NS approaches, it was not effective in low-risk patients, and the overall sensitivity and positive predictive value were only 41.5% and 69.0%, respectively.[30] Likewise, Martini et al described a nomogram to predict side-specific ECE for NS planning and found that multiparametric MRI was able to predict ECE correctly in only 40% of cases.[26,31] Recent data from Johns Hopkins revealed that MRI did not significantly decrease the rates of positive surgical margin, even in a subset in patients with non-focal ECE.[27] In addition, although we did not specifically perform a cost analysis, the cost of our staining technique is considerably less than that of an MRI or genomic testing. Nonetheless, combining our technique with MRI would be the next logical step, and a cost-per-biopsy comparison may provide further insights regarding the costs and benefits of implementing this technique.

The advantages of our technique include negligible added cost and time, safety, ease of learning, and ability to be routinely implemented during all prostate biopsies. At the same time, it contributes potentially useful spatial information during the interpretation of biopsy specimens. While the decision to pursue NS is multifactorial in nature and cannot be determined solely on the basis of positive core proximity, we propose that such data can be contextualized with and supplement other clinical factors and nomograms in the decision-making and patient counseling process.[6,8] Indeed, further prospective validation of our technique in a larger cohort of patients is warranted.

Conclusion

Determining the proximity of positive biopsy cores to the capsular margin during prostate biopsy may offer useful information in predicting ECE at the time of RP. We present a staining method that is safe, inexpensive, quick, and easy to perform in order to quantify this data. Given the prognostic role of ECE on prostate cancer mortality, routine implementation of this technique at the time of TRUS biopsy can yield information that may facilitate patient counseling and help determine the utility of NS approaches, but our results require validation in a larger cohort. □

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EDITORIAL COMMENT

As diagnostic and treatment strategies for prostate cancer evolve, we often turn to highly technological solutions with significant cost and complexity. The technique described by Singla et al[1] in this article is simple and cheap and creates new information that would otherwise not be available. In so doing, the authors can predict the presence and extent of extra-capsular extension with some consistency, approaching other techniques that rely on imaging that may not be available to all providers. The authors are to be commended on the use of ingenuity and practical technology to provide value without significantly increasing the cost of the procedure.

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1. Singla N, Walker JT, Woldu SL et al. Does proximity of positive prostate biopsy core to capsular margin help predict side-specific extracapsular extension at prostatectomy? *Can J Urol* 2019;26(1): 9634-9643.