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Predicting the Risk of Non–organ-confined Prostate Cancer When Perineural Invasion Is Found on Biopsy

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Abstract

OBJECTIVE—To more precisely define the risk of non–organ-confined (non-OC) prostate cancer among men with perineural invasion (PNI) identified on prostate biopsy.

MATERIALS AND METHODS—The Johns Hopkins radical prostatectomy database was queried for men with PNI reported on prostate biopsy. Patients with and without non-OC disease were compared for differences in preoperative clinical and pathologic characteristics, including three biopsy-based measures of tumor volume (number of cores with cancer, percentage of cores with cancer, and maximum percent core involvement with cancer). After evaluating the different preoperative variables in univariate analyses, a multivariable logistic regression model was generated, and bootstrap estimates of the risk of non-OC disease were calculated.

RESULTS—In total, 556 patients with PNI were analyzed, 279 (50.2%) of whom were found to have non-OC prostate cancer. In univariate analyses, preoperative prostate-specific antigen, clinical T stage, biopsy Gleason sum, and the three biopsy-based measures of tumor volume were significantly associated with non-OC disease. Of the three measures of tumor volume, the best fit to the data and highest degree of model discrimination were obtained using maximum percent core involvement with cancer. Incorporating this variable, preoperative prostate-specific antigen, clinical T stage, and biopsy Gleason sum into a multivariable model, the estimated risk of non-OC disease was found to range from 13.8% to 94.4% (bootstrap corrected c-index = 0.735).

CONCLUSION—Men with PNI on prostate biopsy are at a wide range of risk for non-OC disease. Preoperative estimation of this risk is improved by considering readily available biopsy estimates of tumor volume.

Perineural invasion (PNI) is defined as the tracking of tumors cells along or around nerve fibers and is a well-established mechanism of tumor spread.¹ The presence of PNI is associated with adverse outcomes for a number of malignancies, including cancers of the skin, pancreas, colon, prostate, and head and neck.^{2–6} Looking specifically at prostate cancer, a recent meta-analysis found that approximately 50% of men with PNI on prostate

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biopsy will be diagnosed with extraprostatic cancer at radical prostatectomy—a number nearly twice that of patients without PNI.⁷ In contrast to this finding, a study from our institution found that the subset of men with PNI and very-low-risk prostate cancer had only a 15% risk of non-organ-confined (non-OC) disease.⁸ Given the wide published variability in the risk of non-OC disease associated with PNI, we sought to develop a clinical tool analogous to the Partin Tables⁹ to more precisely risk stratify men with PNI detected on prostate biopsy.

PATIENTS AND METHODS

Following institutional review board approval, we retrospectively queried the Johns Hopkins radical prostatectomy database for patients found to have PNI on preoperative prostate biopsy and who underwent surgery from January 2008 to December 2011. Men with non-OC disease (defined as the presence of extracapsular extension, seminal vesicle invasion, and/or positive lymph nodes) were compared with the remainder of the cohort for differences in preoperative characteristics, including age, race, prostate-specific antigen (PSA), clinical T stage, biopsy Gleason sum, and risk group as defined by D'Amico et al¹⁰. In addition, because previous studies have shown that the relationship between PNI and extraprostatic extension is attenuated by differences in tumor volume,^{11,12} we also compared groups for differences in three biopsy-based surrogate measurements of tumor volume: (1) number of cores with cancer, (2) percentage of cores with cancer (defined as number of cores with cancer/total number of sampled cores $\times$ 100), and (3) maximum percent core involvement with cancer. Of note, cases were excluded from the final analysis if any of the three biopsy-based measures of tumor volume were missing or ambiguously reported in the pathology report.

Volume Data Collection

The pathology reports of men with PNI on prostate biopsy were reviewed, and data were collected regarding the total number of sampled cores, total number of cores with cancer, and percent involvement of each positive core. Because biopsy cores are frequently fragmented during prostate biopsy, in these cases, we conservatively estimated percent core involvement by averaging the reported percent involvement of each fragmented segment. Along these same lines, in cases in which multiple fragmented cores were submitted in a single specimen container (almost always two cores) and fragmentation prohibited attributing percent involvement to a single core, both cores were considered positive and averaging was used. In total, 18.9% of cases required some form of averaging.

Statistical Analysis

Univariate comparisons between groups were performed with the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. In addition, univariate logistic regression models were used to determine whether any of the measures of tumor volume were significantly associated with risk of non-OC disease. To facilitate clinical prediction, the volume measures in each model were categorized into quartiles defined by the distribution in the OC patients. The adequacy of model fit to the data was compared among the different volume measures using the likelihood ratio chi-square test,

and model discrimination was compared with the concordance index (c-index). Once the optimal volume metric for predicting non-OC disease was identified from the univariate analyses, a multivariable logistic regression model was generated, including other preoperative predictor variables previously validated by our group.⁹ This final multivariable model was used with 1000 bootstrapped samples to generate predicted probabilities of non-OC disease for each combination of the volume metric and other predictor variables.¹³ All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC), and a *P* value of <.05 was considered statistically significant.

RESULTS

During the study period, 4189 patients underwent a radical prostatectomy at either Johns Hopkins Hospital or Johns Hopkins Bayview Medical Center. Of these patients, 820 (19.6%) were noted to have PNI on preoperative biopsy, 560 (68.3%) of whom had complete analyzable biopsy data, including the 3 biopsy-based measures of tumor volume. An additional 4 (0.5%) patients from this group were excluded because of incomplete final surgical pathology data. After performing these exclusions, a total of 556 patients formed the final study cohort.

Among the 556 patients studied, the median number of sampled cores was 12 (range, 6–20; interquartile range 12–12), with 523 (94.1%) of patients undergoing a minimum 12-core biopsy. At radical prostatectomy, 279 (50.2%) of men were found to have non-OC prostate cancer. Of those patients, 277 (99.3%) had extracapsular tumor extension, 62 (22.2%) seminal vesicle invasion, and 26 (9.3%) lymph node involvement. Table 1 compares the characteristics of patients with and without non-OC prostate cancer.

Univariate logistic regression models demonstrated that each of the three surrogate measures of tumor volume was significantly associated with the risk of non-OC disease: total number of cores with cancer (c-index = 0.608, *P* <.001), percentage of cores with cancer (c-index = 0.604, *P* <.001), and maximum percent core involvement with cancer (c-index = 0.663, *P* <.001). Because maximum percent core involvement yielded the best fit to the data, the remainder of our analysis focused on this variable.

In our multivariable model, preoperative PSA (<10 vs >10 ng/mL), clinical T stage (T1c, T2a, and >T2a), and biopsy Gleason sum (6, 3+4, 4+3, 8–10) were statistically significant predictors of non-OC disease. Adding maximum percent core involvement with cancer to this model significantly improved the fit to the data (Table 2; likelihood ratio test *P* = .0002) and the bootstrap corrected c-index increased from 0.716 to 0.735, supporting improved risk discrimination after accounting for biopsy tumor volume.

Using this multivariable model, we generated tables to describe the bootstrapped predicted probabilities and 95% confidence intervals of non-OC prostate cancer for each quartile of maximum percent core involvement with cancer stratified by preoperative PSA, clinical T stage, and biopsy Gleason sum (Table 3). In brief, the risk of non-OC disease ranged from 13.8% to 94.4% and correlated directly with increasing volume quartile.

COMMENT

Consistent with the meta-analysis by Cozzi et al,⁷ we found that half of all men in our PNI cohort were diagnosed with non-OC disease at radical prostatectomy. Furthermore, we observed that preoperative PSA, biopsy Gleason sum, clinical T stage, and maximum percent core involvement with cancer were independently associated with the risk of non-OC disease (Table 1). Incorporating these variables into a multivariable predictive model, we constructed risk tables with estimated probabilities of non-OC prostate cancer ranging from 13.8% to 94.4%. In sum, the results of our analysis demonstrate that the finding of PNI on prostate biopsy is not universally associated with non-OC disease. Rather, this finding must be viewed within the context of these other preoperative factors. Novel to our work, we show that biopsy tumor volume is a strong predictor of non-OC cancer in PNI patients, even after accounting for PSA, clinical stage, and biopsy Gleason score.

Similar to the Partin Tables,⁹ which have been widely adopted because of their validated accuracy and ease of use with readily available preoperative data,^{14–17} we believe that our derived risk tables may prove useful in the prognostication and pretreatment counseling of patients found to have PNI. For example, in the case of a man with PNI and a high biopsy tumor volume, the urologist may advocate for sacrificing the neurovascular bundle(s) and/or performing an extended lymphadenectomy in an attempt to perform the most oncologically advantageous operation. Similarly, this information may be used to counsel men deciding between surgery, radiation, or potentially even active surveillance or ablative therapy. On the basis of our data, the latter two treatment options would be most appropriate for men with PNI and low biopsy tumor volume disease such as the active surveillance population studied by Al-Hussain et al⁸

The concept of biopsy tumor volume as a marker of aggressive disease is not new to the field of prostate cancer research.^{18–21} To date, a number of reports have looked at various biopsy-based surrogate measurements for tumor volume.^{22–25} This literature reflects that a handful of metrics reasonably predict tumor volume without a clear benefit of any one approach. In our study, we evaluated three commonly used biopsy-based surrogates for tumor volume and found that maximum percent core involvement with cancer offered the best clinical discernment.

The present work is not without limitations. As a retrospective study, we cannot exclude the possibility of selection bias. A related limitation is that only 68.1% of men with PNI had complete biopsy data for analysis, raising the question of the representativeness of our sample. However, compared with the group of men excluded from analysis, we found no significant differences with respect to age, race, year of surgery, PSA, clinical stage, biopsy or prostatectomy Gleason score, D'Amico risk group, and surgical margin status (data not shown). This would suggest little if any bias was introduced by excluding men with incomplete biopsy data. A third limitation is our relatively small sample size of 556 patients. Despite this small sample size, we were able to generate robust risk estimates with narrow confidence intervals. Finally, approximately 20% of patients required averaging of data for percentage core involvement because of core fragmentation. As such, it is possible that our risk estimates are affected by this practice. However, by including data from these

specimens, our tables are applicable to real world pathology reporting practices, which often include data from fragmented cores.

CONCLUSION

Controlling for preoperative PSA, clinical stage, biopsy Gleason sum, and maximum percent core involvement, the estimated risk of non-OC among men with PNI ranged from 13.8% to 94.4%, with the highest estimates in the top quartile of tumor volume. The presented risk estimates may aid clinicians and patients weigh the relative risks and benefits of different treatment approaches when faced with a biopsy positive for PNI.

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Table 1

Study cohort characteristics

Variable	Organ-confined (n = 277)	Non-organ-confined (n = 279)	P Value
Age, median (IQR)	59 (54–63)	61 (55–65)	.017
PSA, median (IQR)	5.0 (4.1–6.3)	5.7 (4.1–8.5)	.0005
Race, n (%)	211 (76.2)	225 (80.6)	.438
Caucasian	46 (16.6)	38 (13.6)	
African American/other	20 (7.2)	16 (5.7)	
Clinical T stage, n (%)			<.0001
T1c	195 (72.8)	146 (54.1)	
T2a	48 (17.9)	58 (21.5)	
T2b	25 (9.4)	66 (24.4)	
Biopsy Gleason sum, n (%)			<.0001
6	128 (46.2)	46 (16.5)	
3+4	99 (35.7)	109 (39.1)	
4+3	32 (11.6)	70 (25.1)	
8–10	18 (6.5)	54 (19.3)	
D'Amico risk group, n (%)			<.0001
Low	108 (39.7)	34 (12.2)	
Intermediate	137 (50.4)	173 (62.2)	
High	27 (9.9)	71 (25.5)	
No. positive cores, median (IQR)	5 (3–6)	6 (4–7)	<.0001
% of positive cores, median (IQR)	42 (25–50)	50 (33–67)	<.0001
Max % core involvement, median (IQR)	60 (25–80)	80 (60–90)	<.0001

IQR, interquartile range; PSA, prostate-specific antigen.

Table 2

Logistic regression models evaluating the association between maximum percent core involvement and non-organ-confined disease

Variable	Univariate	
	OR (95% CI)	<i>P</i> Value *
Max % involved with cancer		
35.0	Ref	<.0001
35.1–60.0	2.44 (1.36, 4.38)	
60.1–80.0	3.12 (1.79, 5.46)	
>80.0	6.48 (3.72, 11.29)	
Variable	Multivariable [†]	
	OR (95% CI)	<i>P</i> Value *
Max % involved with cancer		
35.0	Ref	.0002
35.1–60	1.71 (0.90, 3.26)	
60.1–80	2.16 (1.17, 4.01)	
>80.0	3.61 (1.95, 6.66)	

CI, confidence interval; OR, odds ratio.

* *P* value for likelihood ratio test (3 degrees of freedom) for adding maximum percentage involved with cancer to the model.

[†] Adjusted for prostate-specific antigen (continuous), biopsy Gleason (6, 3+4, 4+3, 8–10), and clinical stage—all of which were statistically significant.

Table 3

Bootstrapped probability estimates of non-organ-confined prostate cancer among men with perineural invasion on prostate biopsy

Biopsy Gleason Sum					
PSA	Max % Involved with Cancer	3+3	3+4	4+3	8-10
Clinical stage T1c (n = 341)					
10	35	13.8 (7.9–20.8)	26.6 (16.1–39.0)	41.0 (26.1–57.0)	42.3 (26.3–60.0)
	35.1–60	21.3 (12.8–32.0)	38.5 (27.1–50.0)	52.6 (37.8–67.4)	55.7 (40.6–72.7)
	60.1–80	25.5 (17.1–35.2)	43.8 (33.1–54.1)	59.1 (46.0–71.9)	61.9 (46.8–77.4)
	>80	36.6 (25.4–48.9)	56.9 (45.1–67.6)	71.0 (58.9–81.8)	74.3 (60.9–85.6)
>10	35	29.5 (15.6–48.2)	50.2 (31.7–71.9)	63.1 (39.9–82.0)	66.2 (43.2–85.5)
	35.1–60	40.7 (24.3–59.4)	61.9 (44.9–79.9)	75.4 (59.3–87.8)	77.7 (61.6–89.8)
	60.1–80	44.6 (28.4–64.1)	65.5 (48.8–81.0)	78.4 (64.3–89.0)	80.2 (65.3–91.1)
	>80	59.8 (42.5–75.6)	76.7 (63.2–87.4)	86.3 (74.5–93.5)	88.2 (77.8–94.8)
Clinical stage T2a (n = 106)					
10	35	16.3 (8.8–28.5)	31.9 (18.8–47.8)	45.7 (28.7–64.6)	47.5 (30.8–66.7)
	35.1–60	26.5 (14.4–41.5)	43.7 (29.3–58.4)	58.9 (41.7–74.0)	61.5 (44.7–79.0)
	60.1–80	30.6 (17.2–44.8)	49.5 (36.0–63.7)	64.8 (48.8–77.9)	67.5 (50.2–82.4)
	>80	42.5 (27.1–58.0)	62.5 (49.9–74.9)	74.7 (61.7–86.0)	78.4 (64.7–88.6)
>10	35	33.8 (16.5–57.3)	53.4 (32.4–75.7)	68.4 (44.8–86.2)	71.5 (47.3–88.2)
	35.1–60	46.7 (26.2–69.2)	66.4 (46.4–83.2)	79.5 (63.6–91.1)	80.8 (63.9–92.6)
	60.1–80	52.8 (30.6–73.4)	71.5 (53.1–86.3)	79.6 (64.2–90.5)	84.6 (68.7–93.9)
	>80	65.2 (44.8–82.7)	81.0 (66.3–91.2)	88.9 (78.0–95.2)	90.2 (79.8–96.3)
Clinical stage >T2a (n = 91)					
10	35	25.8 (13.6–42.8)	44.1 (25.3–63.8)	57.8 (38.8–75.4)	65.3 (46.8–82.3)
	35.1–60	36.8 (22.3–52.8)	58.6 (42.4–71.9)	71.0 (54.6–83.8)	76.2 (60.8–86.9)
	60.1–80	44.6 (28.7–60.7)	63.5 (50.0–76.7)	76.5 (61.5–87.4)	79.0 (64.2–89.3)
	>80	57.0 (40.3–71.6)	75.3 (63.8–85.1)	84.6 (74.6–92.5)	86.8 (78.0–93.1)
>10	35	47.7 (25.5–73.5)	67.7 (43.2–86.8)	79.8 (58.3–92.6)	81.8 (62.1–93.6)
	35.1–60	61.3 (38.5–80.5)	78.5 (60.8–90.5)	87.6 (75.6–94.5)	88.9 (76.6–95.5)
	60.1–80	66.5 (45.0–84.0)	82.3 (67.5–92.5)	89.6 (77.2–95.4)	90.5 (79.2–96.5)

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Biopsy Gleason Sum					
PSA	Max % Involved with Cancer	3+3	3+4	4+3	8–10
	>80	77.2 (59.0–89.7)	87.0 (75.2–93.5)	93.6 (85.9–97.3)	94.4 (88.2–97.8)

Abbreviation as in Table 1.
Data presented as probability estimates with 95% confidence intervals.
Bootstrap corrected c-index = 0.735.