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Biopsy Perineural Invasion in Prostate Cancer Patients who are Candidates for Active Surveillance by Strict and Expanded Criteria

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Abstract

Objective—To evaluate the association of biopsy perineural invasion (PNI) with adverse pathological findings on radical prostatectomy in patients who would have been candidates for active surveillance (AS).

Methods—Using a prospectively populated database of 3084 men who underwent open radical prostatectomy, candidates for AS by strict (Johns Hopkins) and expanded (University of Toronto) criteria were identified. The presence of adverse pathologic features at radical prostatectomy was compared between those men with and without biopsy PNI.

Results—Of 596 men who met strict criteria for active surveillance, 16 (3%) had biopsy PNI. In the strict AS cohort, there were no differences in adverse pathologic features at radical prostatectomy between those with and without PNI. Of 1197 men who were candidates for AS by expanded criteria, 102 (9%) had biopsy PNI. Men with biopsy PNI in the expanded AS cohort were more likely to have extraprostatic extension ($p < 0.001$) and pathological upgrading ($p = 0.01$) at prostatectomy. In addition, those with PNI had larger dominant nodules ($p < 0.001$), and cancer comprised a greater percentage of their prostate glands ($p < 0.001$). There was no difference in the proportion with a positive margin between the two groups ($p = 0.77$).

Conclusions—Biopsy PNI was rare in patients who met strict criteria for AS. Among those men who met expanded criteria, PNI was associated with adverse pathologic findings upon

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prostatectomy. The presence of biopsy PNI may have a role in further risk stratifying patients who meet expanded criteria for AS.

Keywords

Prostate cancer; Perineural invasion; Active Surveillance; Radical Prostatectomy; Extraprostatic extension; Upgrading

Introduction

Active surveillance has been increasingly adopted in response to the overtreatment of men with low-risk prostate cancer.¹ The strategy of active surveillance programs is to identify patients with clinically indolent tumors and avoid or delay definitive treatment in these men.² Although the rationale for active surveillance is well established, there is no consensus regarding the optimal characteristics of patients who should be managed by this strategy. The varied inclusion criteria in cohorts of men undergoing longitudinal study of active surveillance reflect these varied definitions of insignificant disease, which are usually based on prostate biopsy characteristics and the level of prostate-specific antigen (PSA) and/or its derivatives, such as PSA density.^{3–9}

The role of perineural invasion in the selection of men for active surveillance is unclear. Biopsy perineural invasion has been associated with worse outcomes following definitive therapy.^{10–12} Furthermore, when studied in patients undergoing active surveillance, biopsy perineural invasion was associated with both clinical and pathologic progression, suggesting that men with biopsy perineural invasion may not be good candidates for active surveillance.^{13,14} Despite its lack of consideration in established selection criteria, biopsy perineural invasion has been shown to influence selection of patients for active surveillance in the clinical setting.¹⁵ However, in patients who meet the most conservative criteria for active surveillance, biopsy perineural invasion has not been associated with adverse findings at radical prostatectomy, suggesting that, in highly selected patients, this pathologic finding should not exclude patients from this treatment option.^{16,17}

Due to the uncertainty that remains regarding the role of biopsy perineural invasion in selecting men for active surveillance, we performed a study to evaluate the association of biopsy perineural invasion with adverse pathological findings on radical prostatectomy and biochemical recurrence following radical prostatectomy in patients who would have been candidates for active surveillance. In consideration of the varying selection criteria in patients offered active surveillance, we performed our analyses in two cohorts of men—those who met strict criteria for active surveillance and those who met expanded criteria.

Material and Methods

Study Population

The study population consisted of all 3,084 men who underwent radical prostatectomy by a single surgeon (XXXX) at XXXX between November 1999 and July 2015 and were included in a prospectively populated and continuously maintained database. Those who received neoadjuvant androgen deprivation therapy ($n = 42$), were diagnosed with prostatic

tissue obtained from transurethral resection ($n = 11$), had fewer than 6 biopsy cores ($n = 54$), and were missing data regarding the number of cores ($n = 307$), number of positive cores ($n = 15$), biopsy grade ($n = 1$), and pathological grade ($n = 3$) were excluded from the analysis.

Two cohorts of men who met selection criteria for active surveillance were further identified. The “strict” active surveillance cohort was defined according to the Johns Hopkins experience⁵ based on the Epstein criteria for active surveillance¹⁸, namely clinical stage T1c, biopsy Gleason 3 + 3 or less, PSA less than 10 ng/mL, PSA density less than 0.15 ng/mL/cm³, and 2 or fewer positive biopsy cores with 50% or less involvement of any positive core. The “expanded” active surveillance cohort was defined according to the University of Toronto experience^{4,19}, namely clinical stage less than T3, PSA of 10 ng/mL or less (15 ng/mL or less if age greater than 70), and Gleason 3 + 3 disease or less (Gleason 3 + 4 or less if age greater than 70).

Prostate volumes on transrectal ultrasound were not universally available as referring urologists routinely performed prostate biopsies. Thus, the pathological prostate mass was used as a surrogate for clinical prostate volume in the determination of PSA density, as the two measurements are highly correlated ($r = 0.81$).²⁰ Bilateral extended pelvic lymphadenectomy was routinely performed. All prostate specimens were reviewed by fellowship-trained genitourinary pathologists at XXXX. Postoperatively, patients were monitored with periodic clinical and PSA assessments.

Outcomes

The primary study outcome was adverse pathology at radical prostatectomy. Specifically, the presence of extraprostatic extension, pathologic upgrading, positive surgical margin, and lymph node involvement were considered. Pathologic upgrading was defined as pathologic Gleason 3 + 4 or higher for patients with biopsy Gleason 3 + 3, and pathologic Gleason 4 + 3 or higher for patients with biopsy Gleason 3 + 4. Major upgrading was defined as pathologic Gleason 4+4 or higher. Additionally, the diameter of the dominant tumor nodule and the percentage of the prostate specimen comprised of cancer were considered. A secondary outcome was biochemical recurrence following radical prostatectomy, as defined as two successive postoperative PSA values of 0.2 ng/mL or greater.

The primary predictor was the presence of perineural invasion on prostate needle biopsy. Biopsy perineural invasion was defined as the histopathologic finding of circumferential or longitudinal tracking of prostate cancer cells along a nerve within the perineural space. The presence or absence of biopsy perineural invasion was assessed in all biopsy specimens prior to radical prostatectomy and did not knowingly alter treatment selection or surgical technique. For purpose of comparison, men in each active surveillance cohort were categorized into two groups according to the presence or absence of biopsy perineural invasion.

Statistical Analysis

Demographic, clinical, and pathologic characteristics were compared between groups using *t* tests or Wilcoxon rank sum tests for continuous variables and chi-square or Fisher’s exact tests for categorical variables. To assess for potential confounding, we performed additional

analyses. First, logistic regression was used to assess whether performance of a nonstandard prostate biopsy (6–11 cores) confounded the relationship between biopsy perineural invasion and outcomes. Second, we used logistic regression to assess whether the 2005 adoption of the International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading²¹ confounded the relationship. In both cases, there were no substantial changes in the results, so we only report our primary findings.

Statistical analyses were carried out using R (version 13.2)²² using the packages dplyr²³ for data manipulation and compareGroups²⁴ for descriptive tables. Statistical significance was defined as $p < 0.05$. The XXXX Institutional Review Board approved the study (PRO0304058).

Results

Strict Active Surveillance Cohort

Baseline demographic, clinical, and biopsy characteristics of the study population are summarized in Table 1. A total of 596 men were identified who met strict criteria for active surveillance, of whom 16 (3%) had biopsy perineural invasion. In the strict cohort, men with biopsy perineural invasion had greater comorbidity ($p = 0.04$) and were more likely to have two positive biopsy cores (63% vs. 32%, $p = 0.02$) relative to men without biopsy perineural invasion. No significant differences were identified with respect to patient age, race, body mass index, surgical year, preoperative PSA, PSA density, and the highest maximum percentage of cancer on biopsy.

Pathologic findings at radical prostatectomy are summarized in Table 2. In the strict cohort, there were no significant differences in extraprostatic extension (13% vs. 7%, $p = 0.30$), pathologic upgrading (56% vs. 42%, $p = 0.37$), median tumor volume (5% vs. 5%, $p = 0.86$), or diameter of the dominant nodule (1.0 cm vs. 1.1 cm, $p = 0.24$) between those men without and without biopsy perineural invasion. Major pathologic upgrading, surgical margin involvement, and lymph node invasion were rare and only identified in men without biopsy perineural invasion.

In the strict cohort, 12 men (2%) experienced biochemical recurrence at a median follow up of 78 months (IQR 42–113 months). All men who recurred had no evidence of biopsy perineural invasion.

Expanded Active Surveillance Cohort

A total of 1197 men were identified who met expanded criteria for active surveillance, of whom 102 (9%) had biopsy perineural invasion. In the expanded cohort, men with biopsy perineural invasion had higher clinical stage ($p < 0.001$), a greater number of positive cores ($p < 0.001$), higher maximum percentage of cancer in a single biopsy core ($p < 0.001$), and a larger proportion with biopsy Gleason 3+4 (5% vs. 1%, $p = 0.01$) relative to men without biopsy PNI. PSA density was also higher in those patients with biopsy perineural invasion (0.10 ng/mL/cm³ vs. 0.09 ng/mL/cm³, $p = 0.01$). No significant differences were identified with respect to patient age, race, body mass index, comorbidity, preoperative PSA, or surgical year.

At prostatectomy, men with biopsy perineural invasion in the expanded cohort were more likely to have extraprostatic extension (24% vs. 10%, $p < 0.001$) and pathological upgrading (63% vs. 49%, $p = 0.01$). In addition, men with biopsy perineural invasion had greater median tumor volume (10% vs. 5%, $p < 0.001$) and a greater diameter of the dominant nodule (1.1 cm vs. 1.5 cm, $p < 0.001$). There were no differences in major upgrading (5% vs. 5%, $p = 0.81$) or surgical margin involvement (4% vs. 3%, $p = 0.77$) between groups. Lymph node invasion was rare and only identified in men without biopsy perineural invasion.

In the expanded cohort, 50 men (4%) experienced biochemical recurrence at a median follow up of 81 months (IQR 46–118 months). There was no difference in biochemical recurrence between those men who did and did not have biopsy perineural invasion (7% vs. 4%, $p = 0.19$).

Comment

Men who underwent radical prostatectomy yet met strict criteria for active surveillance rarely had perineural invasion identified on prostate biopsy. In these highly selected men, there was no association between the presence of biopsy perineural invasion and adverse pathologic findings at prostatectomy. However, men who met expanded criteria for active surveillance had a much higher rate of perineural invasion on prostate biopsy. In these patients, biopsy perineural invasion was associated with adverse pathologic features, including extraprostatic extension, pathologic upgrading, and a higher volume of disease.

It is not surprising that perineural invasion on prostate biopsy was not associated with adverse pathologic features in men who met strict criteria for active surveillance, as others have corroborated these findings.^{16,17} In a study of 313 men who met Epstein biopsy criteria for active surveillance (Gleason score 6 or less, 2 or fewer positive cores, and 50% or less involvement of any core), 52 (17%) had evidence of biopsy perineural invasion.¹⁷ In that cohort, men with and without perineural invasion had no difference in surgical margin involvement (6.7% vs 7.3%) or organ-confined disease (84.3% vs. 91.6%). These findings were recently validated in a larger cohort, in which biopsy perineural invasion was identified in 63 of 845 patients (7%) who met Epstein criteria for active surveillance but underwent radical prostatectomy.¹⁶ Those men with perineural invasion had a greater extent of disease on biopsy than those without; however, there was no difference in extraprostatic extension, positive margins, tumor volume, or prostatectomy Gleason score. These findings—as well as the findings of the current study—largely support the conclusion that biopsy perineural invasion has little prognostic value in highly selected candidates for active surveillance.

There has been increasing enthusiasm, however, for expanding the criteria for surveillance beyond these conservative parameters²⁶, and biopsy perineural invasion may have prognostic value in this setting. As selection criteria are expanded—for example, to include patients with higher volume or Gleason 3+4 disease—the added sensitivity comes at the expense of including more men with pathologically significant disease.²⁵ These expanded criteria may be particularly relevant in older men or those with competing risks. In the University of Toronto experience, which incorporates expanded surveillance criteria including some older men with intermediate-risk disease, 30 of 980 patients (3%) developed metastasis at a

median follow up of 6.3 years despite reclassification and treatment.²⁷ These data highlight the heterogeneity of risk in patients who meet expanded surveillance criteria, which is significant as the opportunity for cure is lost upon metastatic progression. In the current study, the presence of biopsy perineural invasion in men who met expanded criteria for active surveillance was associated with a 2-fold increase in the likelihood of extracapsular extension at prostatectomy, and 63% of these men had pathological upgrading. These findings suggest a potential role for biopsy perineural invasion in identifying those men at highest risk for progression on active surveillance if expanded inclusion criteria are used.

There is some evidence to suggest a prognostic value of biopsy perineural invasion in men undergoing active surveillance. For example, in a recent study of 165 active surveillance patients^{13, 14} (8.5%) had evidence of biopsy perineural invasion. Selection criteria did not consider PSA density and included men with 3 positive cores. The presence of perineural invasion on the initial biopsy was found to be an independent predictor of disease progression (i.e., pathologic upgrading or ≥ 3 positive cores) on initial confirmatory biopsy. Furthermore, a retrospective review of the REduction by Dutasteride of clinical progression Events in Expectant Management (REEDDEM) study identified 302 men on active surveillance.¹⁴ These men had a PSA of 11 ng/mL or less, clinical stage T2a or less, Gleason score 6 or less, 3 or fewer positive cores, and less than 50% maximum involvement in any core. Biopsy perineural invasion was identified in 11 men (4%) and was found to be an independent predictor of clinical progression (HR 2.39). While these data suggest that patients with biopsy perineural invasion on initial biopsy may not be good candidates for active surveillance, future study is required to assess prognostic value of this pathologic finding in the setting of other means of risk stratification, including genomic profiling and magnetic resonance imaging.

These findings should be considered in the context of several limitations. First, this is a single-institution retrospective analysis with risk of unmeasured bias and potential confounding; however, the study is strengthened by the use of a large prospectively collected and longitudinally maintained dataset. Second, biopsy technique was not standardized because many of the patients were referred to our institution for prostatectomy. Nearly a third of men in the expanded cohort had less than a standard 12-core biopsy; however, the number of biopsy cores (6–11 vs. ≥ 12) was not associated with presence of biopsy perineural invasion (Table 1), extraprostatic extension (Supplemental Table 1a), or pathologic upgrading (Supplemental Table 1b). Thus, we found no evidence that suboptimal sampling due to nonstandard biopsy technique confounded the relationship between biopsy perineural invasion and adverse pathology at prostatectomy. Lastly, the study period spanned the introduction of the 2005 ISUP Consensus Conference on Gleason grading²¹, whereby cribriform, glomeruloid, and poorly formed glands were reclassified from pattern 3 to pattern 4, resulting in stage migration. While pathological upgrading was more common in patients treated after adoption of the updated grading system, the relationship between biopsy perineural invasion and pathologic upgrading in the expanded cohort persisted after adjusting for year of treatment (Supplemental Table 1b).

Conclusion

Among men who meet strict criteria for active surveillance, biopsy perineural invasion is rare and is unlikely to have a role in excluding men from active surveillance. However, among those men who meet expanded criteria, biopsy perineural invasion is associated with adverse pathologic findings at prostatectomy, suggesting that these men may not be good candidates for active surveillance. Further study is needed to evaluate the role of biopsy perineural invasion in identifying those men at greatest risk of metastatic progression or cancer-specific death while on active surveillance protocols.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Demographic, clinical, and prostate biopsy characteristics in men with and without biopsy perineural invasion who met strict and expanded criteria for active surveillance.

Table 1

Characteristics	Strict Criteria			Expanded Criteria		
	PNI N = 16	No PNI N = 580	P Value *	PNI N = 102	No PNI N = 1095	P Value *
<i>Age, years, mean (SD)</i>	57.8 (7.2)	59.3 (6.2)	0.43	58.9 (7.3)	59.2 (6.4)	0.69
<i>Race (%)</i>			0.11			0.99
White	14 (88)	560 (97)		98 (96)	1053 (96)	
Non-white	2 (13)	20 (3)		4 (4)	42 (4)	
<i>BMI, kg/m², mean (SD)</i>	27.8 (4.9)	27.9 (3.9)	0.97	28.0 (4.1)	27.7 (3.8)	0.52
<i>Charlson comorbidity index (%)</i>			0.04			0.74
0	10 (63)	489 (84)		86 (84)	922 (84)	
1	4 (25)	69 (12)		11 (11)	132 (12)	
2+	2 (13)	22 (4)		5 (5)	41 (4)	
<i>Year (%)</i>			0.24			0.77
1999–2004	3 (19)	211 (36)		39 (38)	397 (36)	
2005–2015	13 (81)	369 (64)		63 (62)	698 (64)	
<i>Clinical stage (%)</i>			–			<0.001
T1c	16 (100)	580 (100)		58 (57)	870 (80)	
T2a	–	–		23 (23)	166 (15)	
T2b	–	–		12 (12)	38 (3)	
T2c	–	–		9 (9)	21 (2)	
<i>Preoperative PSA, ng/mL, mean (SD)</i>	4.0 (1.8)	4.7 (1.8)	0.17	4.9 (2.0)	4.8 (2.0)	0.50
<i>PSA density, ng/mL/cm³, mean (SD)</i>	0.07 (0.04)	0.08 (0.03)	0.69	0.10 (0.04)	0.09 (0.04)	0.01
<i>Number of biopsy cores (%)</i>			0.41			0.86
6–11	3 (19)	183 (32)		34 (33)	350 (32)	
12+	13 (81)	397 (68)		68 (67)	745 (68)	
<i>Number of positive cores (%)</i>			0.02			<0.001
1	6 (38)	394 (68)		11 (11)	497 (45)	

Characteristics	Strict Criteria		Expanded Criteria	
	PNI N = 16	No PNI N = 580	PNI N = 102	No PNI N = 1095
2	10 (63)	186 (32)	20 (20)	266 (24)
3	–	–	10 (10)	120 (11)
4	–	–	14 (14)	92 (8)
5	–	–	15 (15)	40 (4)
6 or more	–	–	32 (31)	80 (7)
Percentage of cores positive, %, median [IQR]	17 [14–17]	10 [8–17]	39 [17–55]	17 [8–25]
Maximum percentage of cancer in a single core (%)				
< 5%	2 (13)	219 (38)	2 (2)	286 (27)
5–25%	13 (81)	307 (54)	41 (40)	587 (55)
25–50%	1 (6)	47 (8)	29 (28)	159 (15)
>50%	–	–	30 (29)	45 (4)
Biopsy Gleason score (%)				
3+3=6	16 (100)	580 (100)	97 (95)	1082 (99)
3+4=7	–	–	5 (5)	13 (1)

Abbreviations: PNI, perineural invasion; SD, standard deviation; BMI, body mass index; IQR, interquartile range; PSA, prostate-specific antigen;

* *P* values for continuous and categorical variables generated from *t* tests (or Wilcoxon Rank Sum) and chi-square (or Fisher exact) tests, respectively.

Table 2

Radical prostatectomy findings and outcomes in patients with and without perineural invasion who met strict and expanded criteria for active surveillance.

Characteristics	Strict Criteria			Expanded Criteria		
	PNI N = 16	No PNI N = 581	P Value *	PNI N = 102	No PNI N = 1095	P Value *
<i>Extraprostatic extension (%)</i>	2 (13)	39 (7)	0.30	24 (23)	108 (10)	<0.001
<i>Pathologic Gleason Score (%)</i>			0.48			0.01
6 or less	7 (44)	337 (58)		34 (33)	550 (50)	
3+4=7	9 (56)	228 (39)		63 (62)	493 (45)	
4+3=7	0 (0)	13 (2)		3 (3)	37 (3)	
8–10	0 (0)	2 (0.3)		2 (2)	15 (1)	
<i>Upgrading (%)</i>	9 (56)	243 (42)	0.37	64 (63)	535 (49)	0.01
<i>Major upgrading (%)</i>	0 (0)	15 (3)	0.99	5 (5)	52 (5)	0.81
<i>Tumor volume, gland, %, median [IQR]</i>	5 [5–5]	5 [5–10]	0.86	10 [5–15]	5 [5–10]	<0.001
<i>Diameter of dominant nodule, cm, mean (SD)</i>	1.1 (0.4)	1.0 (0.6)	0.24	1.5 (0.5)	1.1 (0.6)	<0.001
<i>Positive margin (%)</i>	0 (0)	12 (2)	0.99	4 (4)	37 (3)	0.77
<i>Lymph node invasion (%)</i>	0 (0)	1 (<1)	0.99	0 (0)	2 (<1)	0.99
<i>Biochemical recurrence (%)</i>	0 (0)	12 (2)	0.99	7 (7)	43 (4)	0.19

Abbreviations: PNI, perineural invasion; SD, standard deviation; BMI, body mass index; IQR, interquartile range; PSA, prostate-specific antigen

* P-values for continuous and categorical variables generated from *t* tests (or Wilcoxon Rank Sum) and chi-square (or Fisher exact) tests, respectively.