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Perineural invasion is a marker for pathologically advanced disease in localized prostate cancer

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Abstract

Purpose—To determine if PNI should be included in addition to PSA, biopsy Gleason score, and clinical T-stage for risk-stratification of patients with localized prostate cancer.

Methods and Materials—We analyzed prostatectomy findings for 1550 patients, from a prospectively collected institutional database, to determine whether PNI was a significant predictor for upgrading of Gleason score or pathologic T3 disease after patients were stratified into low-, intermediate-, and high-risk groups (on the basis of PSA, biopsy Gleason score, and clinical T-stage).

Results—For the overall population, PNI was associated with a significantly increased frequency of upgrading and of pathologic T3 disease. After stratification, PNI was still associated with significantly increased odds of pathologic T3 disease within each risk group. In particular, for low-risk patients, there was a markedly increased risk of extraprostatic extension (23% vs 7%), comparable to that of intermediate-risk patients. Among high-risk patients, PNI was associated with an increased risk of seminal vesicle invasion and lymph node involvement. Furthermore, over 80% of high-risk patients with PNI were noted to have an indication for post-operative radiation.

Conclusions—PNI may be useful for risk-stratification of prostate cancer. Our data suggest that low-risk patients with PNI on biopsy may benefit from treatment typically reserved for those with intermediate-risk disease. In addition, men with high-risk disease and PNI, who are contemplating surgery, should be informed of the high likelihood of having an indication for postoperative radiation therapy.

Keywords

Perineural invasion; Prostate cancer; Risk stratification; Gleason score; Pathologic stage

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Introduction

Outcomes for patients with localized prostate cancer can vary widely depending on a number of well-established variables, including PSA, Gleason score, T-stage, and others. Those with favorable prognostic factors may have long-term failure-free probability in excess of 90% with either surgery or radiation therapy. On the other hand, patients with adverse prognostic factors fare much worse with the same or even more aggressive therapy, with 5-year relapse-free probability of 40–50%.[1]

Patients undergoing radiation therapy are frequently stratified into low-, intermediate-, and high-risk groups based on 3 widely accepted risk-stratification variables: biopsy Gleason score, pretreatment PSA, and clinical T-stage. One frequently used scheme divides patients as follows: “low-risk” patients are those with PSA < 10, Gleason score 6 or less, and clinical stage T1 or T2a; “high-risk” patients are those with PSA > 20, Gleason score 8–10, or clinical stage T2c or greater; and patients who fall into neither of these categories are regarded as “intermediate-risk”[2]. Similar stratification criteria have been used in multi-institutional studies, and the justification comes in part from nomograms which estimate the risk of extraprostatic extension, seminal vesicle involvement, and lymph node involvement from surgical series. In general, when patients are managed with radiotherapy, those with low-risk factors are well-managed with brachytherapy alone, external beam radiation therapy, or may be considered for an active surveillance program. The management of intermediate-risk patients is more complicated, in part because this group of patients is more heterogeneous. Many different approaches are used, all of which strive to improve outcomes with more aggressive therapy. Possible options include brachytherapy boost with external beam radiation[3], dose-escalated external beam radiation[4], inclusion of pelvic lymph nodes with external beam radiation[5], and/or the addition of androgen deprivation[6]. The optimal combination of these different strategies has yet to be determined. At our institution, we include the proximal seminal vesicles in the target volume (compared to prostate alone in low-risk patients), use a higher total dose, and consider these patients for a six-month course of androgen deprivation. High-risk patients are recommended to undergo treatment with long-term androgen deprivation and treated with radiation to the pelvis in addition to the prostate and seminal vesicles [5, 7, 8]. Thus, patients deemed at higher risk for treatment failure are generally treated more aggressively.

The effectiveness of such combinations of Gleason score, PSA, and clinical stage is surprising when one considers the inconsistent reliability of pretreatment subjective factors such as biopsy Gleason score and clinical T-stage when the pretreatment assessments are compared to pathologically-reviewed outcomes. Several studies have demonstrated a high rate of discordance between biopsy Gleason score and prostatectomy Gleason score. Although the frequency of discrepancy decreases somewhat with an increasing number of biopsies, the frequency of “undergrading” at the time of biopsy remains at 30–40% in most reports[9, 10]. Similarly, it is well-known that pathologic T3 disease may be underappreciated by digital rectal exam[11].

For those who undergo surgery, the pathologic T-stage and prostatectomy Gleason score appear to be stronger predictors of outcome than clinical T-stage and biopsy Gleason score[12]. However, for patients treated with radiation therapy, pathologic stage and Gleason score are never known. Given the high rates of discrepancy between biopsy and prostatectomy Gleason scores, in addition to the frequency of understaging on clinical exam, it would be helpful to identify additional factors to guide treatment decisions. The purpose of this study was to examine whether the presence of perineural invasion in the biopsy specimen was associated with either higher grade or T-stage in the specimens of men treated with prostatectomy. If so, this would provide a pathologic rationale for the inclusion of PNI as a risk-stratification factor in addition to the three most commonly employed risk-stratification factors.

Methods

Database

At the University of Michigan Health System, pathological outcomes from prostate biopsies and prostatectomies are prospectively and explicitly recorded in an IRB-approved longitudinal database at our institution. Data were analyzed from all patients in this database with clinically localized prostate cancer (cT1–3, N0/x) for whom pathological data on prostatectomy and biopsy specimens were available. Patients treated with hormonal therapy prior to prostatectomy were excluded. The analyzed population is relatively modern and included 1550 men who underwent RP from August 1994 through June 2005. 415 patients had their biopsies performed at the University of Michigan; and patients who were biopsied at other institutions had their specimens reviewed in our Department of Pathology. The database included an indication of whether PNI was noted at the time of biopsy. Data on percent positive cores, however, was incomplete for patients who were biopsied at an outside hospital. The vast majority of patients (1476/1550; 95%) underwent a planned open radical retropubic prostatectomy; 62 (4%) had laparoscopic RP; 6 (0.4%) had perineal prostatectomy; and 6 (0.4%) were converted from laparoscopic to an open procedure. Six patients (of an initial 1556) were excluded from the study due to missing data.

Outcomes

We examined the proportion of patients whose Gleason score was “upgraded” at the time of prostatectomy. Upgrading was defined as the finding of prostatectomy Gleason score of 7 or greater in patients whose biopsy Gleason score was less than 7. We also examined the rate of finding pathologic T3 disease at the time of prostatectomy. Lastly, we determined the proportion of patients found to have positive margins. The data tables also include the odds of having an indication for post-operative radiation therapy, which we defined as having pathologic T3 disease *or* positive margins. Each of these outcomes was compared between patients with and without evidence of PNI in their biopsy specimens.

Analysis

Chi-square tests of association were performed for the entire population and within standard risk-stratification groups to determine whether PNI was significantly associated with each of the adverse features described above. Low-risk (LR) was defined as PSA < 10, biopsy GS < 7, *and* clinical T-stage ≤ T2a. High-risk (HR) was defined as PSA > 20, biopsy GS 8–10, *or* clinical T-stage ≥ T2c. Remaining patients were classified as intermediate-risk (IR). In order to control for other established risk-stratification variables, logistic regression was used for multivariate analysis to determine if PNI had any independent predictive value.

Results

Association between PNI and other pretreatment characteristics

The characteristics of the 1550 men included in this analysis are shown in Table 1. The majority of patients had low- or intermediate-risk disease. Overall, 15% (n=240) were noted to have evidence of PNI in their biopsy specimens. There was a statistically significant association between the presence of PNI and adverse pretreatment risk-features, including higher clinical T-stage, higher biopsy Gleason score, and higher mean PSA. Thus, compared to the PNI-negative patients, a smaller proportion of the PNI-positive patients fell into low-risk category (19% vs 51%). Conversely, among low-risk patients, the frequency of PNI was only 7% (47/712).

Association between PNI and upgrading of Gleason score

For the entire study population, PNI was also significantly associated with a higher rate of each of the adverse pathologic features we considered (Table 2). For patients with biopsy Gleason score < 7, the presence of PNI in the biopsy was associated with an increased frequency of upgrading (54% vs 41%, p = 0.02). After stratifying patients into low-, intermediate-, and high-risk groups (Table 3), there remained a numerical trend toward more frequent upgrading, particularly among low-risk patients. However, these differences were no longer statistically significant. Patients with a biopsy Gleason score of 7 or more were rarely (7%) found to have an even higher prostatectomy Gleason score, regardless of PNI status.

PNI is a predictor of higher pathologic stage and positive margins

Among all patients with PNI, there was about a two-fold increase in the rate of pathologic T3 disease (36% vs 16%) and positive margins (36% vs 19%, Table 2). This difference remained statistically significant within each risk group on both univariate and multivariate analysis, adjusting for PSA, clinical T-stage, and biopsy GS (Table 4). In low- and intermediate-risk patients, the difference was due almost entirely to pathologic evidence of extraprostatic extension (EPE) and was most pronounced in the low-risk group. Specifically, the absolute frequency of EPE among low-risk patients with PNI was 23%, which is comparable to the risk of EPE in the intermediate-risk group (21–30%). Among high-risk patients, in addition to a high proportion of patients with EPE, a substantial number were found to have seminal vesicle invasion (SVI) and/or nodal involvement. On multivariate analysis, PNI was associated with significantly higher risk of SVI in high-risk patients with an odds ratio of 2.6. As a result of the higher frequency of pT3 disease, patients with PNI were also more likely to have an indication for adjuvant radiation therapy, defined as either pathologic T3 disease or positive margins. Among high-risk patients, the frequency of having at least one of these indications was greater than 80%.

Discussion

The relevance of PNI to risk-stratification in localized prostate cancer is controversial. Previous studies examining prostatectomy results have been inconsistent although some show that PNI is associated with higher Gleason scores and/or EPE at the time of prostatectomy [13, 14]. However, even the studies that suggest PNI is important have generally included smaller numbers of patients and have not stratified patients according to criteria most commonly used for patients considering radiation therapy. Thus, from the currently available literature, it is not clear whether there is pathological evidence to justify inclusion of PNI for risk-stratification.

Similarly, the data on clinical outcomes following radiation therapy (brachytherapy or external-beam radiation) are mixed with regard to the importance of PNI as a prognostic factor. Recent studies on brachytherapy outcomes suggest no difference in biochemical outcomes for patients with or without PNI[15, 16]. On the other hand, it has been reported that low-risk patients with PNI are at higher risk for biochemical failure after external beam radiation[17], and there is now also early evidence suggesting decreased survival in low-risk patients with PNI when compared to other low-risk patients[18].

Our data for the overall population are consistent with those of previous reports. Because our database included only patients selected to undergo prostatectomy, the majority of patients had relatively favorable disease. Nevertheless, we found that approximately 40% of patients with Gleason score less than 7 were upgraded at the time of prostatectomy to a Gleason score of 7 or more. This high rate of upgrading is occurs despite otherwise favorable factors, such as low PSA and minimal or undetectable disease on digital rectal exam. It has been proposed that PNI

may be a marker for occult high-grade disease. Consistent with this, we found a significantly higher rate of upgrading among patients with evidence of PNI at biopsy. After standard stratification, among low-risk patients, there remained an absolute increase in the frequency of upgrading of 10% in patients with PNI. However, the difference was no longer statistically significant. Given the relatively small number of low-risk patients with PNI, we cannot exclude the possibility that PNI is a marker for higher-grade disease.

On the other hand, these data clearly demonstrate that PNI is a marker for more advanced (i.e., higher stage) disease. In particular, among low-risk patients, the risk of pathologic T3 disease was nearly 3-fold higher when PNI was present. This difference was due almost entirely to EPE. In absolute terms, the risk of EPE in a low-risk patient with PNI was comparable to that found in the intermediate-risk group. Furthermore, the predictive value of PNI for pT3 disease remained significant on multivariate analysis, adjusting for clinical T-stage, biopsy Gleason score, and PSA. However, for intermediate- and high-risk patients, in whom the underlying risk of EPE is much higher compared with low-risk patients, the higher frequency of pT3 was only marginally significant, and the odds of EPE were not significantly associated with PNI.

It is likely that the increased frequency of EPE reflects both greater tumor volume and more aggressive disease. Nearly all cases of EPE occur at least in part by extension of cancer along the perineural space[19], and more recent work suggests that, at least *in vitro*, cells in the perineural space may have an increased capacity for proliferation[20]. There is also evidence that PNI is a marker for a greater volume of disease, including an association with higher percent positive cores (PPC), which is also increasingly used for risk-stratification[21]. Unfortunately, the information on percent positive cores is incomplete in our database, in part because some patients whose biopsies were performed at outside hospitals had only the positive biopsy slides reviewed in our department of pathology. We did examine whether there was a correlation between PPC and PNI for the subset of patients in whom the PPC was known but found no significant correlation (data not shown). Thus, we can neither exclude nor confirm the possibility that PNI and PPC may carry some redundant information with regard to risk-stratification.

An important limitation of our study is that we have only analyzed pathological endpoints. However, other studies have shown that EPE is associated with an increased risk of disease progression[22]. Thus, our results fit well with recent reports that PNI is associated with adverse clinical outcome, particularly in low-risk patients, after treatment with standard-dose (70 Gy) external beam radiation[18]. Given our finding that PNI is associated with a markedly increased risk of EPE in low-risk patients, it is essential, at a minimum, during radiation planning to provide adequate margins on the prostate. It is likely with modern radiotherapy techniques that coverage would be sufficient, and certainly coverage would be sufficient if pelvic fields were used. In addition, it seems likely that the increased rate of pathologic T3 disease reflects a larger tumor burden. As a result, patients treated with only modest doses of radiation, such as those frequently prescribed for low-risk patients, may be more prone to treatment failure. On the other hand, PNI-positive patients who receive higher doses may be expected to have excellent control rates, comparable to their PNI-negative counterparts. The lack of difference in clinical outcomes in brachytherapy series may be attributable to the higher-doses received by all patients in those series. In summary, our study provides strong pathological corroboration for previously published studies showing that PNI is associated with poorer clinical outcomes following standard-dose external beam radiation.

Our results are somewhat equivocal with regard to the importance of PNI as a marker for occult high-grade disease. Given the clear association between PNI and higher Gleason score, it seems likely that with sufficient numbers, one would be able to demonstrate a statistically significant association between PNI and upgrading of Gleason score at the time of prostatectomy.

However, our data suggest that a substantial number of patients with PNI and low Gleason score will, in fact, be confirmed to be have a low Gleason score at the time of prostatectomy. Thus, low-risk patients with PNI cannot be assumed to have occult Gleason pattern 4. However, the association between grade and PNI may be explored further in the future if treatment recommendations are substantially different for patients who are deemed intermediate-risk on basis of Gleason score, as opposed to more advanced stage.

Finally, these data suggest that among high-risk patients, PNI may also be a marker for exceptionally high-risk disease. Because the underlying frequency of EPE was already quite high in the high-risk group, there not a significant increase in the risk of EPE when PNI was present. However, there *was* a significant increase in the risk of seminal vesicle invasion (15% vs 5%) and lymph node involvement, findings that are generally associated with extremely poor long-term disease control. Since we recommend long-term hormonal therapy, as well as pelvic radiation (in addition to a high-dose to the prostate), to all high-risk patients, these findings are unlikely to alter our management of high-risk patients at this time. However, for patients considering surgery, our data suggest that they are extremely likely (80%) to have an indication for post-operative radiation based on the two recently reported randomized trials supporting adjuvant radiation when patients are found to have either positive margins or pathologic T3 disease[23, 24].

Conclusions

We found that patients with PNI identified at biopsy were much more likely to have evidence of EPE at the time of prostatectomy. This finding was most pronounced among low-risk patients. Although no clinical endpoints were analyzed in this study, our results provide a pathologic rationale for treating low-risk, PNI-positive patients similarly to patients with intermediate-risk disease. At our institution, we would recommend that high-dose radiation be delivered to the prostate with adequate margins to account for EPE. In addition, pelvic radiation and/or a course of androgen deprivation could be considered. Furthermore, high-risk patients with PNI should be advised that their odds of avoiding radiation by undergoing surgery are extremely small.

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TABLE 1

Patient characteristics

Patient Characteristics	Overall (n=1550)		
	PNI +	PNI −	p-value
Number of Patients (% of total)	241 (15%)	1309 (84%)	
Surgery Date			0.73
1994–1997	44%	42%	
1998–2001	32%	35%	
2002–2005	24%	23%	
Mean Age (SD)	61 (7.6)	60 (7.5)	0.07
Clinical T-stage			<.0001
< T2b	73%	90%	
T2b	18%	7%	
> T2b	9%	3%	
Biopsy GS			<.0001
bGS 2–6	31%	63%	
bGS 7	63%	34%	
bGS 8–10	6%	3%	
Mean Pre-tx PSA	8.7 (9.4)	7.5 (6.6)	0.05
Risk Group			<.0001
Low	19%	51%	
Intermediate	63%	41%	
High	18%	8%	

TABLE 2

Outcomes for entire patient population

Outcomes	Overall (n=1550) PNI +	PNI −	p-value
Pathologic GS			<.0001
pGS 2–6	18%	42%	
pGS 7	71%	54%	
pGS 8–10	11%	4%	
Number of Patients with Biopsy GS < 7	74	822	
Upgraded GS (≥ 7)	54%	41%	0.02
Path. T-stage ≥ T3	36%	16%	<.0001
EPE	33%	15%	<.0001
SVI	10%	4%	0.0001
Positive Margin	36%	19%	<.0001
Node positive	4%	1%	0.0001
Indication for Post-op Radiation	51%	29%	<.0001

TABLE 3

Outcomes within each risk group. Frequencies for which the odds ratio was significantly greater than 1 (PNI+ vs PNI−) on univariate analysis are shown in bold.

	Low Risk (n=712)		Intermediate Risk (n=686)		High Risk (n=152)	
	PNI +	**PNI −**	**PNI +**	**PNI −**	**PNI +**	**PNI −**
Number of Patients	47	665	151	535	43	109
Pathologic GS						
pGS 2–6	51%	62%	12%	23%	2%	16%
pGS 7	49%	37%	83%	73%	54%	56%
pGS 8–10	0%	1%	5%	3%	44%	28%
Number of Patients with Biopsy GS < 7	47	665	20	131	7	26
Upgraded GS (≥ 7)	49%	38%	55%	50%	86%	50%
Path. T-stage ≥ T3	**23%**	**8%**	**30%**	**21%**	**70%**	**44%**
EPE	**23%**	**8%**	**27%**	**18%**	**65%**	**40%**
Focal	17%	5%	14%	12%	19%	19%
Established	6%	3%	13%	6%	46%	21%
SVI	2%	1%	5%	5%	**37%**	**18%**
Positive Margin	**27%**	**15%**	**31%**	**19%**	**63%**	**37%**
Focal	21%	13%	27%	16%	37%	27%
Established	6%	2%	4%	3%	26%	10%
Node positive	0%	<1%	2%	1%	16%	6%
Indication for Post-Op Radiation	**43%**	**20%**	**46%**	**33%**	**81%**	**61%**

TABLE 4

Adjusted odds ratios (with 95% confidence intervals) from multivariate analysis within each risk group, adjusting for PSA, clinical T-stage, biopsy Gleason score. Odd ratios associated with a p-value < 0.05 are shown in bold.

	Low Risk	Intermediate Risk	High Risk
Upgraded GS	1.5 (0.8–2.7)	1.6 (0.6–4.6)	5.3 (0.5–63)
Pathologic T3	**2.6** (1.2–5.6)	**1.5** (1.0–2.3)	**2.3** (1.0–5.2)
EPE	**2.8** (1.3–6.0)	1.5 (0.9–2.3)	2.1 (0.9–4.8)
SVI	1.5 (0.2–13)	0.9 (0.4–2.3)	**2.5** (1.0–5.9)
Positive Margin	**2.1** (1.2–5.1)	**2.5** (1.3–3.1)	**2.9** (1.1–5.4)
Node positive	--	1.9 (0.4–8.3)	4.1 (0.8–22)
Indication for Post-op Radiation	**2.9** (1.6–5.5)	**1.7** (1.2–2.5)	2.0 (0.8–5.0)