Perineural invasion on prostate biopsy does not predict adverse pathological outcome

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Introduction: *The clinical significance of perineural invasion (PNI) on prostate needle biopsy is controversial. The aim of this present study is to determine the role of PNI on prostate biopsy in predicting adverse findings at radical prostatectomy in a recent cohort of screen detected prostate cancer.*

Materials and methods: *We analyzed 470 patients diagnosed with prostate cancer from a prospectively maintained database at Princess Margaret Hospital. Out of the 470 patients diagnosed with prostate cancer, 139 underwent radical prostatectomy. Pathological specimens were examined, and perineural invasion was identified as carcinoma tracking along or around a nerve in the perineural space. We investigated the predictive value of PNI on biopsy with PNI on radical prostatectomy as well as the ability of PNI on prostate biopsy to predict adverse findings at radical prostatectomy.*

Results: *Perineural invasion was present in 124 (26%) of biopsy specimens diagnosed with prostate cancer and 94 (68%) of those who chose radical prostatectomy. Perineural invasion on prostate needle biopsy was not predictive of radical prostatectomy Gleason score ($p = .377$), pathological stage ($p = .852$), extraprostatic extension ($p = .258$), surgical margin ($p = .079$), lymphovascular invasion ($p = .499$), and upgrading ($p = .514$) or downgrading ($p = .208$) at radical prostatectomy. The sensitivity, specificity, positive predictive value, and negative predictive value of PNI on biopsy for PNI on radical prostatectomy were 32%, 82%, 79%, and 37% respectively. The Cohen's Kappa correlation coefficient was .11.*

Conclusions: *Perineural invasion on prostate needle biopsy is not predictive of radical prostatectomy outcome. Furthermore, perineural invasion on biopsy has limited predictive value for perineural invasion at radical prostatectomy.*

Key Words: perineural invasion, prostate biopsy, prostate cancer

Introduction:

Assessing the extent of the disease for patients diagnosed with prostate cancer is critical for guiding effective treatment options. Gleason score, serum prostate-specific antigen (PSA), and clinical stage are widely used preoperative indicators for predicting patient outcome following therapy.[1,2] These diagnostic tools however, are imperfect and would benefit from further exploration of additional preoperative factors in order to determine a more accurate prognosis of disease following treatment.[3,4]

Perineural invasion (PNI) is the spread of invasive tumors in, around, and through the peripheral nerve.[5] PNI has emerged as a key pathologic feature of many

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malignancies, including the pancreas, colon and rectum, and stomach.[5] For many of these malignancies PNI has been a marker for poor outcome and decreased survival.[5] In prostate cancer, several earlier studies have demonstrated that PNI is associated with extraprostatic extension on radical prostatectomy.[6-8] Consequently, PNI is thought to be one of the main mechanisms of extension of tumor from the prostatic parenchyma to the periprostatic soft tissue.[9]

The capacity of PNI on biopsy to predict adverse affects following radical prostatectomy or radiotherapy is uncertain.[10] Some studies have reported that PNI predicts a significantly greater risk for aggressive pathology features as well as a higher risk for biochemical progression after radical prostatectomy or radiotherapy,[11,12] while other studies have found PNI on biopsy to have no predictive value at all.[3,13] In a systematic review[14] concerning the importance of PNI on biopsy as a prognostic indicator Harden et al concluded that the weight of evidence suggested that PNI was a significant prognostic indicator. However, former studies are based on earlier cohorts and some even prior to wide-scale screening. In addition surgical expertise has increased and margin rates are lower even in those with extraprostatic extension.[15] We hypothesize that in a contemporary cohort the association of PNI with pathological outcome in radical prostatectomy may differ.

We aim to explore the predictive value of PNI on biopsy with PNI on radical prostatectomy and to investigate the role of PNI on prostate biopsy in predicting adverse findings at radical prostatectomy in a recent cohort of screen detected prostate cancer.

Materials and methods

Subjects

Our institution maintains an ethics-approved prospective database of continuous patients with no previous diagnosis of prostate cancer undergoing transrectal ultrasound (TRUS) guided prostate biopsy. From September 2008 to January 2010, 1041 consecutive patients were available from our database for analysis. All patients were referred from general practitioners for concerns related to prostate specific antigen (PSA), abnormal prostate examination, voiding symptoms, a strong family history of prostate cancer, or at the request of the patient. Indications for TRUS guided prostate biopsy followed the American Urological Association best practice statement using PSA kinetics, absolute PSA, DRE, family history, ethnicity and patient anxiety.[16] Based on these recommendations, biopsies were performed at the discretion of five urologists at the Princess Margaret Hospital in Toronto, Canada.

Prostate biopsies

All patients who had a first-time biopsy had a standardized 11-core technique taking two cores from each lateral portion, three cores from each medial portion, and one from the middle of the prostate performed by one of three uroradiologists. Those who had a repeat biopsy had a standardized 15-core technique performed with the addition of two cores taken from each transition zone.[17]

Pathology

Prostate biopsy: All biopsy specimens were histologically graded according to the ISUP 2005 update Gleason grading system by consensus of two experienced uropathologists who had regular consensus meetings to decide on the final report for any challenging cases.[18] Perineural invasion was defined as carcinoma tracking along or around a nerve within the perineural space. Pathologists at out institution recorded the presence or absence of this finding in the prostate biopsy and radical prostatectomy specimens in all cases.

Radical prostatectomy: All radical prostatectomy were reviewed by expert uropathologists. Gleason score on radical prostatectomy was determined by the pathologist using the protocol outlined by the Gleason grading system.[18] Pathological stage was determined using the TNM grading system, following the protocol outlined by the seventh edition of the American Joint Cancer Committee Cancer Staging Manuel.[19] Extraprostatic extension was classified according to the Epstein classification system as focal if a few tumor cells were present outside the prostate gland and as established if more extensive extraprostatic spread was present.[20] Surgical margins were considered to be positive when the tumor showed histological extension to the surface.

Statistical analysis

For the purpose of analysis we stratified the cohort in two groups according to PNI results on biopsy and radical prostatectomy. We performed a univariate analysis to examine the association of PNI on biopsy for outcome on radical prostatectomy using Wilcoxon-Mann-Whitney (since both PSA and age are not normally distributed) for continuous variables and chi square test for categorical variables.

To examine the predictive value of PNI on biopsy for PNI on radical prostatectomy the sensitivity, specificity, positive predictive value, negative predictive value, and Cohen's Kappa were calculated along with their 95% confidence intervals.

All statistical analysis was performed using SPSS (IBM, New York, NY, USA) version 17.0.1. For all tests a p value < 0.05 was considered statistically significant.

TABLE 1. **Patient characteristics**

Covariate	PNI on biopsy (n = 470)		p value	PBI on radical prostatectomy (n = 139)		p value
	PNI (+) (n = 124)	PNI (-) (n = 346)		PNI (+) (n = 94)	PNI (-) (n = 45)	
Age years (interquartile range)	69 (62-75)	66 (61-72)	0.3	63 (58-68)	63 (57-68)	0.1
PSA ng/mL (interquartile range)	6.55 (5-12.1)	5.81 (4.4-8.1)	0.09	5.7 (.4.2-8.4)	5.5 (4.5-7.9)	0.2
Number of prior biopsy (median range)	0 (0-2)	0 (0-3)	0.5	0 (0-1)	0 (0-2)	0.4
DRE (% positive)	54.8% (68)	28.9% (100)	.001	37.2% (35)	31% (14)	.480
Family history (% positive)	20.8% (25)	19.8% (66)	.812	25.5% (24)	18.1% (8)	.340
Mean number of biopsy cores (SD)	12.1 (2.0)	11.8 (1.9)	.051	11.4 (1.3)	11.9 (2.1)	.161
Mean number of biopsy cores positive (SD)	5.8 (2.9)	2.8 (2.0)	.0001	4.6 (2.5)	3.2 (2.4)	.003

Fishers Exact or Chi Square test was used for categorical variable comparisons and the Wilcox Rank Sum Test was used for continuous variable comparisons.
PNI = perineural invasion; PSA = prostate-specific antigen; DRE = digital rectal examination

TABLE 2. **The association between PNI on biopsy and radical prostatectomy outcome (n = 138)**

Characteristic	PNI (+) biopsy	PNI (-) biopsy	p value
Radical prostatectomy Gleason score			.377
Gleason 6	14.3% (5)	24.7% (24)	
Gleason 7	77.1% (27)	70.1% (68)	
Gleason 8 or above	8.6% (3)	5.2% (5)	
Pathological stage			.852
pT2a	14.3% (5)	12.8% (12)	
pT2c	45.7 (16)	54.3 (51)	
pT3a	31.4% (11)	26.6% (25)	
pT3b	8.6% (3)	6.3% (6)	
Surgical margin	34.3% (12)	19.6% (19)	.079
Extraprostatic extension	40% (14)	29.6% (29)	.258
Lymphovascular invasion	6.25% (2)	3.4% (3)	.499
Upgrade at radical prostatectomy			.09
GL6 to GL7 (%)	22.8% (8)	14.5% (14)	
GL7 to GL8 (%)	2.9% (1)	1% (1)	
GL 6 to GL 8 (%)	0	1% (1)	
Downgrade at radical prostatectomy	8.6% (3)	11.3% (11)	.1

*Fishers exact test and Chi Square was used for all categorical variable comparisons.
PNI = perineural invasion; GL = Gleason score

Results

Overall 470 (48%) of patients in our cohort were diagnosed with prostate cancer. Radical prostatectomy was performed in 139 (30%) of these patients. Perineural invasion was present in 124 (26%) of biopsy specimens diagnosed with prostate cancer and 94 (68%) of those who chose radical prostatectomy.

Table 1 shows patient characteristics. The median age for patients with PNI on biopsy and radical prostatectomy is 69 and 63 years respectively. There were no significant differences in patient age, family history, number of previous biopsies, number of cores on biopsy, and serum PSA values among cases with and without PNI on both biopsy and radical prostatectomy. Patients with PNI on biopsy had a greater proportion of positive DRE (54.8%) than those without PNI on biopsy (28.9%) (p = .001). Patients with PNI on biopsy had a higher percentage of cores positive for cancer (5.8 ± 2.9 versus 2.8 ± 2.0, p = .0001).

Table 2 shows the association between PNI on biopsy and radical prostatectomy outcome. PNI on biopsy was not associated with any adverse outcome on radical prostatectomy (extraprostatic extension, surgical margin or upgrading). PNI on biopsy was also not predictive of Gleason score on radical prostatectomy (p =. 377) or pathological stage at radical prostatectomy (p = .852).

Table 3 is a contingency table demonstrating the accuracy of PNI on biopsy to predict PNI on radical prostatectomy specimen. The sensitivity, specificity, positive predictive value, and negative predictive value of PNI on biopsy for PNI on radical prostatectomy were 32% (95% CI 21%-45%), 82% (95% CI 69%-89%), 79% (95% CI 66%-91%), and 37% (95% CI 24%-48%) respectively. The Cohen's Kappa correlation coefficient was .11.

TABLE 3. **PNI on biopsy versus PNI on radical prostatectomy (n = 138)**

Correlation between PNI biopsy and PNI on radical prostatectomy	
Cohen's Kappa	.11
Sensitivity	32% (95% CI 21%-45%)
Specificity	82% (95% CI 69%-89%)
Positive predictive value	79% (95% CI 66%-91%)
Negative predictive value	37% (95% CI 24%-48%)

	PNI (+) radical prostatectomy	**PNI (-) radical prostatectomy**
PNI (+) biopsy	30	8
PNI (-) biopsy	63	37

CI = confidence interval, PNI = perineural invasion

Discussion

The search for better markers to risk stratify patients with prostate cancer is ongoing. PNI in earlier studies demonstrated promise in predicting both extraprostatic extension and positive surgical margins.[7,10] Therefore it became standard practice to report PNI findings in all biopsy specimens in many academic centers. In the present study, 470 patients (48%) were diagnosed with prostate cancer, 139 (30%) of which elected to undergo radical prostatectomy. This high positive biopsy rate reflects the nature of our cohort, where all the patients were referred from general practitioners due to concerns related to PSA, abnormal prostate examination, voiding symptoms, a strong family history of prostate cancer, or at the request of the patient. In our contemporary cohort PNI on prostate biopsy was unrelated to adverse pathological outcome. It was not predictive of radical prostatectomy Gleason score, pathological stage, extraprostatic extension, surgical margin, lymphovascular invasion, and upgrading or downgrading on radical prostatectomy. In addition, PNI on biopsy was also found to have limited predictive value for PNI on radical prostatectomy.

The clinical significance of PNI on prostate needle biopsy is controversial. Bastacky et al was the first to address the significance of PNI on prostate needle biopsy in the pre PSA era from 1986 to 1989.[21] In this study PNI was found to be a significant predictor of extraprostatic extension at radical prostatectomy. Further studies have concluded similar findings, demonstrating PNI on biopsy as having a significant predictive value for adverse findings on radical prostatectomy and biochemical recurrence,[6] while an almost equal amount of studies have found PNI on biopsy to have no predictive value at all.[3]

Our findings differ from these studies due to the contemporary nature of our cohort, as it represents a more current population undergoing prostate cancer treatment. In a cohort of patients from 2002 to 2007, Loeb et al found that although the relationship between PNI on biopsy and adverse findings at radical prostatectomy exists, the associated risk for EPE is lower then in the pre-PSA era.[12] Our study cohort differs from the one described by Loeb et al, because of the wide scale use of active surveillance

at our institution. While the aforementioned study includes mainly low risk patients (77% of patients with a Gleason score on biopsy ≤ 6) the majority of our cohort is intermediate risk (60% met D'Amico criteria for intermediate risk). The prevalence of PNI among low risk patients is low, with only 15% of patients in the above study having PNI on biopsy specimen. We therefore believe that our findings that PNI on biopsy has a limited predictive value even in an intermediate risk group may better capture current treatment trends. Furthermore, in a cohort of patients who meet the criteria for active surveillance, Al-Hussain et al found PNI to have no significance in predicting adverse findings at radical prostatectomy.[13]

A limitation of our study is that we only assessed PNI and its outcome at radical prostatectomy, and as a result, we were unable to assess the role that PNI on biopsy can have in other forms of treatment including active surveillance or radiotherapy. Furthermore, although we recorded the presence or absence of PNI in all cases, we did not quantify the extent or laterality of PNI on biopsy or radical prostatectomy. In addition, our results are limited by the number of patients in our cohort, which ultimately limits the power of our conclusions. Despite these potential limitations, our studies strengths include an institution database were all patient parameters were obtained prospectively by expert urologists and uropathologists. Another strength of our study is the large and contemporary patient population with PNI status on both biopsy and radical prostatectomy.

Our findings that PNI on biopsy is not able to predict adverse findings at radical prostatectomy indicate that PNI on biopsy has limited clinical relevance. If our results are confirmed in a larger multicenter study, we suggest that PNI on biopsy should be removed from inclusion on biopsy reports as it time consuming for pathologists to report, has a potential to influence a surgeon's decisions, and can create more anxiety for patients.

Conclusion

PNI on biopsy is not predictive of adverse findings at radical prostatectomy. Furthermore PNI on biopsy is not able to predict PNI found at radical prostatectomy. Our results suggest that PNI is not clinically useful and should thus be removed from biopsy reports. □

References

1. Partin AW, Kattan MW, Subong EN et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: a multi-institutional update. *JAMA* 1997;277(18):1445-1451.
2. Cooperberg MR, Lubeck DP, Mehta SS, Carrol PR. Time trends in clinical risk stratification for prostate cancer: implications for outcomes (data from CaPSURE). *J Urol* 2003; 170(6 Pt 2):S21-S25.
3. Freedland SJ, Csathy GS, Dorey F, Aronson WJ. Percent prostate needle biopsy tissue with cancer is more predictive of biochemical failure or adverse pathology after radical prostatectomy than prostate specific antigen or Gleason score. *J Urol* 2002;167(2 Pt 1):516-520.
4. Draisma G, Boer R, Otto SJ et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 2003;95(12):868-878.
5. Liebig C, Ayala G, Wilks JA, Berger DH, Albo D. Perineural invasion in cancer: a review of the literature. *Cancer* 2009;115(15):3379-3391.
6. Lee IH, Roberts R, Shah RB, Wojno KJ, Wei JT, Sandler HM. Perineural invasion is a marker for pathologically advanced disease in localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;68(4):1059-1064.
7. Vargas SO, Jiroutek M, Welch WR, Nucci MR, D'Amico AV, Renshaw AA. Perineural invasion in prostate needle biopsy specimens: correlation with EPE at resection. *Am J Clin Pathol* 1999;111(2):223-228.
8. Holmes GF, Walsh PC, Pound CR, Epstein JI. Excision of the neurovascular bundle at radical prostectomy in cases with perineural invasion on needle biopsy. *J Urol* 1999;53(4):752-756.
9. Villers A, McNeal JE, Redwine EA, Freiha FS, Stamey TA. The role of perineural space invasion in the local spread of prostatic adenocarcinoma. *J Urol* 1989;142(3):763-768.
10. Bismar TA, Lewis JS Jr, Vollmer RT, Humphrey PA. Multiple measures of carcinoma extent versus perineural invasion in prostate needle biopsy tissue in prediction of pathologic stage in a screening population. *Am J Surg Pathol* 2003;27(4):432-440.
11. Lee JT, Lee S, Yun CJ et al. Prediction of perineural invasion and its prognostic value in patients with prostate cancer. *Korean J Urol* 2010;51(11):745-751.
12. Loeb S, Epstein JI, Humphreys EB, Walsh PC. Does perineural invasion of prostate biopsy predict adverse prostatectomy outcomes? *BJU Int* 2010;105(11):1510-1513.
13. Al-Hussain T, Carter B, Epstein J. Significance of prostate adenocarcinoma pernineural invasion on biopsy in patients who are otherwise candidates for active surveillance. *J Urol* 2011;186(2): 470-473.
14. Harden P, Shelly MD, Clements H et al. The prognostic significance of perineural invasion in prostatic cancer biopsies: a systematic review. *Cancer* 2007;109(1):13-24.
15. Han M, Partin AW, Chan DY, Walsh PC. An evaluation of the decreasing incidence of positive surgical margin in a large retropubic prostatectomy series. *J Urol* 2004;171(1):23-26.
16. Greene KL, Albertsen PC, Babaian RJ et al. Prostate specific antigen best practice statement: 2009 update. *J Urol* 2009;182(5): 2232-2241.
17. Babaian RJ, Toi A, Kamoi K et al. A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy. *J Urol* 2000;163(1):152-157.
18. Montironi R, Cheng L, Lopez-Beltran A et al. Original Gleason system versus 2005 ISUP modified Gleason system: the importance of indicating which system. *Eur Urol* 2010;58(3):369-373.
19. Edge SB, Byrd DR, Compton CC, Frtiz AG, Greene FL, Trotti A. AJCC Cancer staging manual: seventh edition. American Joint Cancer Committee 2010.

20. Epstein JI, Carmichael MJ, Pizov G, Walsh PC. Influence of capsular penetration on progression following radical prostatectomy: a study of 196 cases with long-term follow up. *J Urol* 1993;150(1): 135-141.
21. Bastacky SI, Walsh PC, Epstein JI. Relationship between perineural tumor invasion on needle biopsy and radical prostatectomy capsular penetration in clinical stage B adenocarcinoma of the prostate. *Am J Surg Pathol* 1993;17(4):336-341.