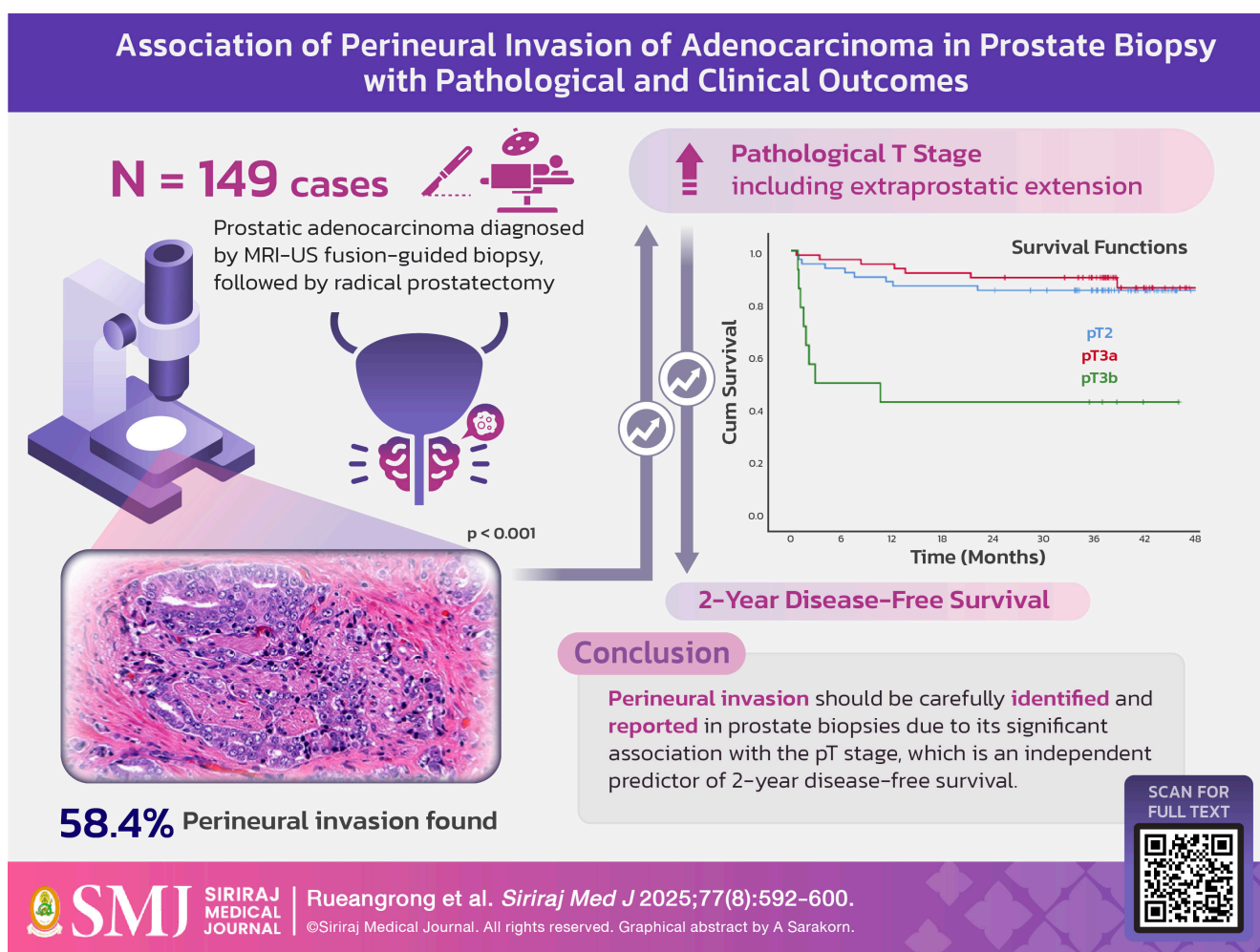


Association of Perineural Invasion of Adenocarcinoma in Prostate Biopsy with Pathological and Clinical Outcomes

Perineural invasion of adenocarcinoma in prostate biopsy

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Received 28 May 2025 Revised 11 July 2025 Accepted 12 July 2025

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<https://doi.org/10.33192/smj.v77i8.275687>



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ABSTRACT

Objective: This study aims to evaluate the association between perineural invasion and pathological stage, including extraprostatic extension, and its impact on prognosis.

Materials and Methods: A total of 149 men diagnosed with prostatic adenocarcinoma by magnetic resonance imaging/ultrasound (MRI-US) fusion-guided biopsy and radical prostatectomy between July 1, 2018 and December 31, 2019 at Siriraj Hospital were identified. Their pathological, clinical, and radiological findings were retrospectively analyzed. Patients with and without perineural invasion were compared using descriptive and inferential statistics.

Results: Perineural invasion was identified in 87 of 149 patients (58.4%) and showed no significant association with baseline features ($p > 0.05$). However, perineural invasion was significantly associated with higher pathological T stage (pT2, pT3a, pT3b) ($p < 0.001$), including extraprostatic extension (pT3 disease) in univariate analysis. Multivariate analysis demonstrated a notable correlation between the pathological T stage and 2-year disease-free survival ($p < 0.001$).

Conclusion: Perineural invasion should be carefully identified and reported in prostate biopsy specimens, due to its significant relationship with the pathological T stage, including extraprostatic extension.

Keywords: Prostate cancer; prostatic adenocarcinoma; image-guided biopsy; perineural invasion; pathological stage (Siriraj Med J 2025; 77: 592-600)

INTRODUCTION

In 2020, prostate cancer was the second most diagnosed cancer and the fifth leading cause of cancer-related deaths among men worldwide.¹ Prostatic adenocarcinoma accounts for over 95% of all prostate cancer cases.² Prostate needle biopsy is the gold standard for diagnosing prostatic adenocarcinoma.³

Perineural invasion (PNI), observed in up to 38% of prostate biopsies⁴, is considered one of the pathognomonic features of prostate cancer.² It has been hypothesized that carcinoma cells spreads along nerve bundles in the dorsolateral aspect of the prostate gland, following a path of least resistance — an observation consistent with the known tropism of carcinoma cells for nerves.⁵⁻¹⁰

Several studies employing various research designs have demonstrated associations between perineural invasion (PNI) and adverse pathological features, disease progression, and recurrence in multivariate analyses.^{9,11-16} Two cross-sectional studies similar to ours reported an association between PNI and extraprostatic extension.^{13,14} A randomized controlled trial focusing on patients undergoing active surveillance also confirmed the association between PNI and clinical progression.¹⁵ However, two other cross-sectional studies found no relationship between PNI and extraprostatic extension, pathological stage, or positive surgical margins.^{4,17} Similarly, a case-control study evaluating long-term disease-free survival in patients who underwent radical prostatectomy found no significant association between PNI and biochemical disease-free survival.⁸ Although these studies focus on the relationship between PNI in prostate biopsies and pathological or

clinical outcomes, they differ in several aspects, such as research design, sample size, institutional setting, inclusion criteria, treatment modalities, study periods, and biopsy techniques, which may affect interpretation and contribute to variability in the results.

Harnden *et al.*¹² conducted the first systematic evaluation of PNI's prognostic value in biopsies, analyzing 10 surgical and 11 radiotherapy articles. Their findings support PNI as a prognostic factor for recurrence. However, the authors also highlighted inconsistencies in reporting and incomplete data, which affected the analysis of both positive and negative results. Factors such as biopsy technique, number of cores and sections influence the involvement of nerve detection but are rarely documented. Additionally, the lack of standardized reporting, limited reproducibility, and variability in treatment approaches and patient classification further complicate interpretation.

Two recent systematic reviews also identified perineural invasion (PNI) as an independent prognostic factor for biochemical recurrence, while acknowledging many of the same limitations. One review noted that variability in PNI detection methods may contribute to significant heterogeneity, potentially affecting the validity of study results.¹⁸ Another reported a wide range in PNI frequency, from 6.7% to 33.0%, attributing this variability to differences in reproducibility among pathologists. The paper also highlighted that different biopsy techniques, such as conventional transrectal ultrasound (TRUS) guided and MRI-ultrasound fusion-guided methods, can influence PNI detection rates.¹⁹

These uncertainties have fueled decades of debate regarding the prognostic value of PNI in prostate biopsy. Thus, the objective of our study was to analyze the prognostic value of PNI, as a predictor of TNM classification and 2-year disease-free survival, using well-defined variables and comprehensive data. Ultimately, our goal is to increase awareness of PNI and aid physicians in disease evaluation and treatment planning.

MATERIALS AND METHODS

Patient selection

Following approval by the Siriraj Institutional Review Board (Certificate of Approval No. Si 228/2022), pathological and clinical data of patients diagnosed with prostatic adenocarcinoma were retrieved from the electronic database of the Siriraj Pathology Unit's electronic database (HCLAB). The inclusion criteria were: (1) patients diagnosed with prostatic adenocarcinoma by means of both core biopsy and radical prostatectomy performed at Siriraj Hospital between July 1, 2018, and December 31, 2019; (2) biopsies were conducted using magnetic resonance imaging/ultrasound (MRI-US) as fusion-guided techniques; (3) availability of pathology reports, glass slides, and complete medical records for review.

Data collection

All biopsy and radical prostatectomy specimens were submitted for evaluation after routine 10% formalin fixation, paraffin embedding, sectioning at a thickness of 3–5 micrometers, and hematoxylin and eosin staining. Specimens were blinded by masking patient identifiers and diagnostic details, and were reviewed by a genitourinary pathologist and an anatomic pathology resident utilizing light microscopy, following the College of American Pathologists' guidelines. PNI was defined as the presence of cancer cells abutting, indenting nerves, up to and including circumferential involvement¹², and was recorded as either present or absent.

Clinical data were collected and reviewed by a urologist and a research fellow, while radiologic data were collected and reviewed by a radiation oncologist. None of them were informed of the presence or absence of PNI in each patient. Biochemical recurrence was defined as a prostate-specific antigen (PSA) level greater than 0.2 ng/mL after radical prostatectomy.

Sample size calculations

nQuery Advisor was applied to determine the required sample size needed to detect differences with 80% power (2-sided type 1 error; $\alpha = 0.05$). Assuming a 1:1.5 enrollment ratio for patients undergoing MRI-US

fusion-guided biopsy with and without PNI, and based on a previous study¹⁴, reporting rates of extraprostatic extension of 66.7% in a group of patients with PNI and 39.7% in a group without PNI, the required sample size was calculated as 145 cases. Thus, with 149 subjects included, this study was adequately powered to detect significant differences.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics, Version 26. Two-tailed tests were employed, and a p-value of <0.05 was considered statistically significant. Descriptive statistics were used to summarize characteristics of men with and without PNI in prostate biopsies.

For univariate analysis, continuous variables were compared using the Mann-Whitney U test and independent t-test. Categorical variables were evaluated using the chi-squared test. Kaplan-Meier survival curves were used to illustrate 2-year disease-free survival rates in patients stratified by pathological T stage, with comparisons made using the log-rank test.

In multivariable analysis, associations between 2-year disease-free survival and both pathological T stage and initial PSA levels were examined using Cox proportional hazards regression models. Results were summarized as hazard ratios with corresponding 95% confidence intervals.

RESULTS

Of the 149 patients who met the inclusion criteria, PNI was identified in 87 biopsy specimens (58.4%). Patients with and without PNI had similar mean ages at diagnosis. Initial PSA levels were similar between the groups. The number of core biopsies performed did not differ significantly between the two groups. PNI in the prostatectomy specimen was more frequent in the group with PNI in their biopsy (98%) compared to the group without PNI in their biopsy (74%) ($p < 0.001$) (Table 1).

PNI was significantly associated with higher pathological T stage (pT2, pT3a, pT3b), including extraprostatic extension (pT3 disease) ($p < 0.001$). (Table 2).

Furthermore, significant associations were observed between 2-year disease-free survival and pathological T stage in both univariate (Table 3) and multivariate analyses, with the strongest association seen in patients with pT3b (adjusted HR, 6.84; 95% CI, 2.43–19.27; $p < 0.001$) (Table 4).

Kaplan-Meier analysis further confirmed that more advanced pathological T stage was associated with poorer disease-free survival, especially in patients with pT3b tumors (log-rank $p < 0.001$) (Table 5, Fig 1).

TABLE 1. Characteristics of patients with and without PNI.

Variable	PNI in biopsy		p-value
	No (n=62)	Yes (n=87)	
Age (year) ^a	67.7 ± 6.5	67.7 ± 6.6	0.994
iPSA (ng/mL) ^b	8.3 (5.4, 11.4)	8.9 (6.8, 15.0)	0.176
Number of core biopsy ^b	25.0 (21.0, 29.3)	24.0 (20.0, 30.0)	0.633
PNI in prostatectomy ^c	46 (74.2%)	85 (97.7%)	< 0.001

^a Normally distributed data are presented as mean ± standard deviation. Comparisons between groups were analyzed using the independent t-test.

^b Non-normally distributed data are presented as median (interquartile range). Comparisons between groups were analyzed using the Mann-Whitney U test.

^c Data are presented as n (%). Comparisons between groups were analyzed using chi-square tests.

Abbreviations: PNI, perineural invasion; SD, standard deviation; iPSA, initial prostate-specific antigen; ng/mL, nanograms per milliliter

TABLE 2. Association between PNI and pathological and clinical outcomes.

Variable	PNI in biopsy		OR (95% CI)	p-value
	No (n=62)	Yes (n=87)		
EPE	19 (23.2%)	63 (76.8%)	5.94 (2.90; 12.20)	< 0.001
Pathological T stage				< 0.001
pT2	43 (63.2%)	25 (36.8%)		
pT3a	18 (27.7%)	47 (72.3%)	4.49 (2.16; 9.35)	
pT3b	1 (6.3%)	15 (93.8%)	25.80 (3.21; 207.22)	
Pathological N stage				0.240
pN0	61 (43.0%)	81 (57.0%)		
pN1	1 (14.3%)	6 (85.7%)	4.52 (0.53; 38.52)	
Clinical M stage				1.000
cM0	62 (41.9%)	86 (58.1%)		
cM1	0 (0.0%)	1 (100.0%)	N/A	
2-year disease-free survival				0.697
No	46 (41.8%)	64 (58.2%)		
Yes	9 (37.5%)	15 (62.5%)	0.84 (0.34; 2.07)	

All data are presented as n (%). Comparisons between groups were analyzed using Chi-square tests.

Abbreviations: PNI, perineural invasion; OR, odds ratio; CI, confidence interval; EPE, extraprostatic extension; pT, pathological primary tumor; pN, pathological node; cM, clinical metastasis.

TABLE 3. Association between 2-year disease-free survival and patient characteristics and pathological outcomes.

Factors associated with DFS	2-year disease-free survival		p-value
	DSF (n=110)	Non-DSF (n=24)	
Pathological T stage^a			< 0.001
pT2	51 (85.0%)	9 (15.0%)	
pT3a	53 (88.3%)	7 (11.7%)	
pT3b	6 (42.9%)	8 (57.1%)	
iPSA (ng/mL)^b	8.3 (6.2, 11.4)	12.8 (7.3, 22.7)	0.013
Age (year)^c	67.8 ± 6.7	68.4 ± 5.7	0.702

^a Data are presented as n (%). Comparisons between groups were analyzed using chi-square tests.

^b Non-normally distributed data are presented as median (interquartile range). Comparisons between groups were analyzed using the Mann-Whitney U test.

^c Normally distributed data are presented as mean ± standard deviation. Comparisons between groups were analyzed using the independent t-test.

Abbreviations: DFS, disease-free survival; pT, pathological primary tumor; iPSA, initial prostate-specific antigen; ng/mL, nanograms per milliliter; SD, standard deviation

TABLE 4. Multivariate Cox regression analysis of the relationship between 2-year disease-free survival and patient characteristics and pathological outcomes.

Factors associated with DFS	Multivariate	
	Adjusted HR (95%CI)	p-value
Pathological T stage		
pT2	1	
pT3a	0.78 (0.29-2.10)	0.627
pT3b	6.84 (2.43-19.27)	< 0.001
iPSA	0.99 (0.97-1.01)	0.525

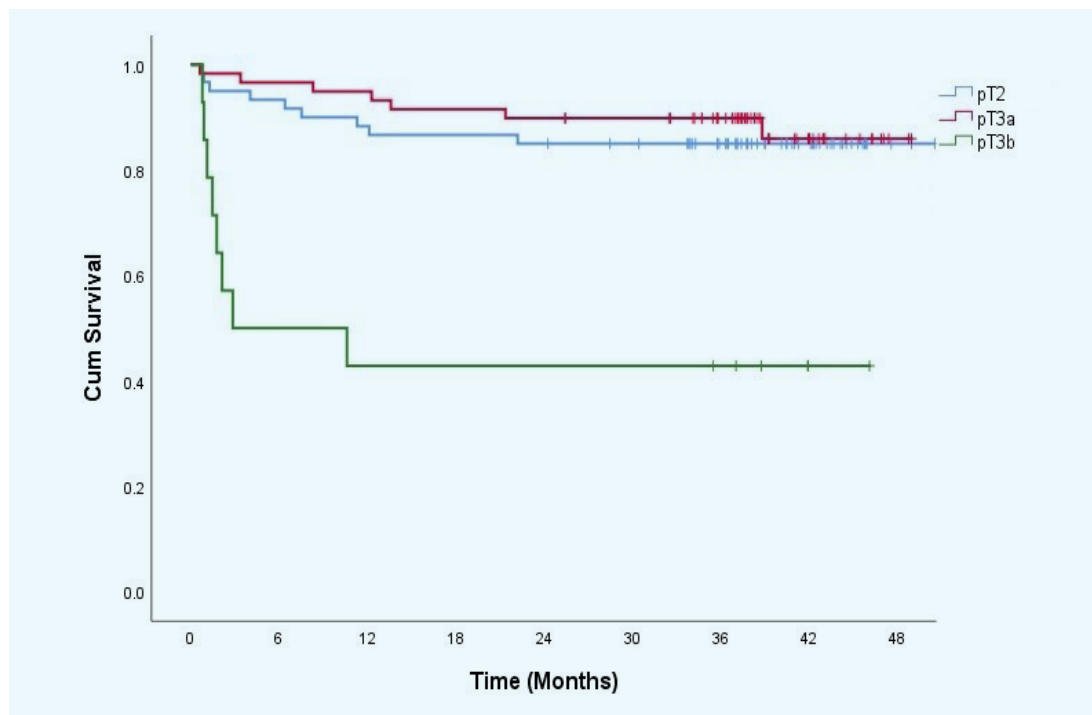
Abbreviations: DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; pT, pathological primary tumor; iPSA, initial prostate-specific antigen

TABLE 5. Association between pathological T stage and disease-free survival.

DFS (%)	Time			
	1 year	2 year	3 year	4 year
pT2	88.3	85.0	85.0	85.0
pT3a	94.9	89.8	89.8	85.9
pT3b	42.9	42.9	42.9	42.9

All data are presented as percentage (%).

Abbreviations: DFS, disease-free survival; pT, pathological primary tumor



	0 month	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
pT2	60	56	53	52	51	49	40	20	2
pT3a	59	57	56	54	53	51	41	16	2
pT3b	14	7	6	6	6	6	5	1	0

Fig 1. Kaplan-Meier analysis illustrating the relationship between pathological T stage (pT2, pT3a, pT3b) and disease-free survival. The study revealed a significant association, with more advanced pathological T stage linked to poorer disease-free survival outcomes ($p < 0.001$).

Abbreviation: pT, pathological primary tumor

DISCUSSION

PNI, a neoplastic process involving nerves²⁰, is a common yet clinically significant feature of prostatic adenocarcinoma.⁷ Although substantial evidence supports PNI as a potential route for carcinoma spread^{5–10}, its prognostic value in prostate biopsies remains controversial due to conflicting pathological and clinical associations.^{4,8–9,11–17,21}

Our study demonstrates a strong association between PNI in biopsy specimens and advanced pathological T stage, including extraprostatic extension. A systematic review indicates that patients at high risk of extraprostatic extension should avoid nerve-sparing surgery, which is associated with the preservation of erectile function and continence.²² Given that the pathological T stage is a well-established independent predictor of survival in prostate cancer, as supported by previous research and our own findings^{2,23–24}, these findings underscore

the clinical importance of recognizing PNI in patient management.

However, no significant association was observed between PNI and lymph node metastasis (N stage) or distant metastasis (M stage). Consistent with prior reports, including those by *O'Malley et al.*⁸ and *Ahmad et al.*²⁵, our findings do not support PNI as a predictor of 2-year disease-free survival. A possible explanation is the relatively favorable prognosis of our cohort: all patients underwent radical prostatectomy, a treatment typically reserved for localized disease²⁶, and only a small proportion presented with lymph node metastases (N1 stage) or distant metastases (M1 stage).

A key strength of our study is the use of MRI-US fusion-guided biopsy, a technique that has been shown to enhance prostate cancer detection, improve tumor grading accuracy, and increase the detection of clinically significant prostate cancer and PNI.^{14,27–31} In our study,

the detection rate of PNI was 58.4%, which is higher than previously reported rates, generally ranging from 7% to 43%¹², and 28.4% in a prior study that also employed MRI-US fusion-guided biopsy.¹⁴ This elevated detection rate likely reflects the enhanced sampling precision of this technique. Although the number of biopsy cores can influence the sampled surface area and, consequently, the likelihood of detecting PNI, our statistical analysis found no significant difference in core numbers between PNI positive and negative cases, thereby reinforcing the validity of our results. These findings underscore the critical role of biopsy acquisition methods in evaluating PNI and highlight the need for standardized biopsy techniques in future studies to enhance data consistency.

Our study included only patients who underwent radical prostatectomy to obtain more comprehensive information on the relationship between PNI and pathological classification. By limiting the cohort to surgically treated patients, we were able to accurately determine the pathological stage, including the status of the primary tumor (pT) and lymph node metastasis (pN).³²

Moreover, given that patients who remain free of biochemical relapse for two years after surgery have been reported to achieve a 90% recurrence-free survival rate,³³ our study incorporated a minimum two-year follow-up period to reduce the likelihood of false negative results. We also compared initial prostate-specific antigen levels, an established prognostic indicator in prostate cancer³⁴, between patients with and without PNI and found no significant difference between the groups. The sample size was determined through power calculation to ensure adequate statistical power.

Systematic reviews, such as that by *Harnden et al.*¹² have suggested that PNI in prostate biopsies is a significant prognostic indicator, supporting immediate treatment over watchful waiting. Similarly, *Cozzi et al.*²¹, in line with our findings, support PNI as a predictor of extraprostatic extension. This has important clinical implications, which influence decisions regarding the preservation of the neurovascular bundle and seminal vesicles.³⁵ Therefore, these findings emphasize the importance of recognizing the prognostic value of PNI in patient management.

Although our findings confirm the association between PNI and adverse pathological outcomes, they also highlight the longstanding challenges in assessing its prognostic significance, which are issues that have persisted unresolved over three decades of research.¹² Given the heterogeneity in study designs, variations in biopsy techniques, and differences in patient selection, additional large-scale prospective studies are needed.

These should incorporate diverse treatment strategies, detailed documentation of biopsy parameters, subgroup analyses, and extended follow-up periods to better define the role of PNI in guiding therapeutic decisions.

CONCLUSION

PNI in biopsy specimens is a predictor of advanced pathological T stage, including extraprostatic extension. As pathological T stage is an independent predictor of 2-year disease-free survival, the identification and documentation of PNI in prostate biopsy specimens are essential for accurate risk stratification and treatment planning.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon request due to confidentiality concerns.

ACKNOWLEDGEMENT

The authors would like to thank Nerisa Thornsri, M.Sc., for her assistance with the statistical analysis.

DECLARATIONS

Grants and Funding Information

This research received no external funding.

Conflict of Interest

The authors declare no conflicts of interest.

Registration Number of Clinical Trial

None.

Author Contributions

Conceptualization, N.T.; data curation, R.R.; Formal analysis, R.R.; investigation, R.R., A.T., K.M. and N.T.; methodology, N.T.; project administration, N.T.; resources, C.S., A.T. and N.T.; supervision, N.T.; validation, C.S., A.T. and N.T.; visualization, R.R.; writing—original draft, R.R. and N.T.; writing—review & editing, R.R. and N.T. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

None.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA A Cancer J Clinicians* [Internet]. 2021 [cited 2025 Mar 9];71(3):209–49. Available from: <https://>

2. acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21660
Srigley JR, Tsuzuki T, Amin MB, Rubin MA. Prostatic acinar adenocarcinoma. In: WHO Classification of Tumours Editorial Board Urinary and male genital tumours. 5th ed. International Agency for Research on Cancer: Lyon, France; 2022. p. 203–19.
3. Magi-Galluzzi C. Prostate cancer: diagnostic criteria and role of immunohistochemistry. *Modern Pathology* [Internet]. 2018 [cited 2025 Mar 9];31:12–21. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0893395222011206>
4. Trpkov C, Yilmaz A, Trpkov K. Perineural invasion in prostate cancer patients who are potential candidates for active surveillance: validation study. *Urology* [Internet]. 2014 Jul [cited 2025 Mar 9];84(1):149–52. Available from: [https://www.goldjournal.net/article/S0090-4295\(14\)00375-6/abstract](https://www.goldjournal.net/article/S0090-4295(14)00375-6/abstract)
5. Ayala GE, Wheeler TM, Shine HD, Schmelz M, Frolov A, Chakraborty S, et al. In vitro dorsal root ganglia and human prostate cell line interaction: redefining perineural invasion in prostate cancer. *Prostate* [Internet]. 2001 Nov 1 [cited 2025 Mar 9];49(3):213–23. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/pros.1137>
6. Hassan MO, Maksem J. The prostatic perineural space and its relation to tumor spread: an ultrastructural study. *Am J Surg Pathol* [Internet]. 1980 Apr [cited 2025 Mar 9];4(2):143–8. Available from: https://journals.lww.com/ajsp/abstract/1980/04000/the_prostatic_perineural_space_and_its_relation_to.6.aspx
7. Paner GP, Magi-Galluzzi C, Amin MB, Srigley JR. Adenocarcinoma of the Prostate. In: Amin MB, Grignon DJ, Srigley JR, Eble JN, eds. *Urological Pathology*. 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2014. p. 559–673.
8. O'Malley KJ, Pound CR, Walsh PC, Epstein JI, Partin AW. Influence of biopsy perineural invasion on long-term biochemical disease-free survival after radical prostatectomy. *Urology* [Internet]. 2002 Jan [cited 2025 Mar 9];59(1):85–90. Available from: [https://www.goldjournal.net/article/S0090-4295\(14\)00375-6/abstract](https://www.goldjournal.net/article/S0090-4295(14)00375-6/abstract)
9. Zareba P, Flavin R, Isikbay M, Rider JR, Gerke TA, Finn S, et al. Perineural Invasion and Risk of Lethal Prostate Cancer. *Cancer Epidemiol Biomarkers Prev* [Internet]. 2017 May [cited 2025 Mar 9];26(5):719–26. Available from: <https://aacrjournals.org/cebip/article/26/5/719/71340/Perineural-Invasion-and-Risk-of-Lethal-Prostate>
10. Fromont G, Godet J, Pires C, Yacoub M, Dore B, Irani J. Biological significance of perineural invasion (PNI) in prostate cancer. *Prostate* [Internet]. 2012 Apr [cited 2025 Mar 9];72(5):542–8. Available from: <https://onlinelibrary.wiley.com/doi/10.1002/pros.21456>
11. D'Amico AV, Wu Y, Chen MH, Nash M, Renshaw AA, Richie JP. Perineural invasion as a predictor of biochemical outcome following radical prostatectomy for select men with clinically localized prostate cancer. *J Urol* [Internet]. 2001 Jan [cited 2025 Mar 9];165(1):126–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/11125380/>
12. Harnden P, Shelley MD, Clements H, Coles B, Tyndale-Biscoe RS, Naylor B, et al. The prognostic significance of perineural invasion in prostatic cancer biopsies: a systematic review. *Cancer* [Internet]. 2007 Jan 1 [cited 2025 Mar 9];109(1):13–24. Available from: <https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.22388>
13. Loeb S, Epstein JI, Humphreys EB, Walsh PC. Does perineural invasion on prostate biopsy predict adverse prostatectomy outcomes? *BJU Int* [Internet]. 2010 Jun [cited 2025 Mar 9];105(11):1510–3. Available from: <https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2009.08845.x>
14. Truong M, Rais-Bahrami S, Nix JW, Messing EM, Miyamoto H, Gordetsky JB. Perineural invasion by prostate cancer on MR/US fusion targeted biopsy is associated with extraprostatic extension and early biochemical recurrence after radical prostatectomy. *Hum Pathol* [Internet]. 2017 Aug [cited 2025 Mar 9];66:206–11. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0046817717302393?via%3Dihub>
15. Moreira DM, Fleshner NE, Freedland SJ. Baseline Perineural Invasion is Associated with Shorter Time to Progression in Men with Prostate Cancer Undergoing Active Surveillance: Results from the REDEEM Study. *J Urol* [Internet]. 2015 Nov [cited 2025 Mar 9];194(5):1258–63. Available from: <https://www.auajournals.org/doi/10.1016/j.juro.2015.04.113>
16. Ström P, Nordström T, Delahunt B, Samaratunga H, Grönberg H, Egevad L, et al. Prognostic value of perineural invasion in prostate needle biopsies: a population-based study of patients treated by radical prostatectomy. *J Clin Pathol* [Internet]. 2020 Oct [cited 2025 Mar 9];73(10):630–5. Available from: <https://jcp.bmj.com/content/73/10/630>
17. Bismar TA, Lewis JS, 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* [Internet]. 2003 Apr [cited 2025 Mar 9];27(4):432–40. Available from: https://journals.lww.com/ajsp/abstract/2003/04000/multiple_measures_of_carcinoma_extent_versus.2.aspx
18. Zhang LJ, Wu B, Zha ZL, Qu W, Zhao H, Yuan J, et al. Perineural invasion as an independent predictor of biochemical recurrence in prostate cancer following radical prostatectomy or radiotherapy: a systematic review and meta-analysis. *BMC Urol* [Internet]. 2018 Feb 1 [cited 2025 Jul 10];18(1):5. Available from: <https://bmculol.biomedcentral.com/articles/10.1186/s12894-018-0319-6>
19. Wu S, Lin X, Lin SX, Lu M, Deng T, Wang Z, et al. Impact of biopsy perineural invasion on the outcomes of patients who underwent radical prostatectomy: a systematic review and meta-analysis. *Scand J Urol* [Internet]. 2019 Oct [cited 2025 Jul 10];53(5):287–94. Available from: <https://pubmed.ncbi.nlm.nih.gov/31401922/>
20. Liebig C, Ayala G, Wilks JA, Berger DH, Albo D. Perineural invasion in cancer: a review of the literature. *Cancer* [Internet]. 2009 Aug 1 [cited 2025 Mar 9];115(15):3379–91. Available from: <https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.24396>
21. Cozzi G, Rocco BM, Grasso A, Rosso M, Abed El Rahman D, Oliva I, et al. Perineural invasion as a predictor of extraprostatic extension of prostate cancer: a systematic review and meta-analysis. *Scand J Urol* [Internet]. 2013 Dec [cited 2025 Mar 9];47(6):443–8. Available from: <https://www.tandfonline.com/doi/full/10.3109/21681805.2013.776106>
22. Vis AN, Van Den Bergh RCN, Van Der Poel HG, Motttrie A, Stricker PD, Graefen M, et al. Selection of patients for nerve sparing surgery in robot-assisted radical prostatectomy. *BJUI Compass* [Internet]. 2022 Jan [cited 2025 Jul 11];3(1):6–18. Available from: <https://bjui-journals.onlinelibrary.wiley.com/doi/10.1002/bco2.115>
23. Chalfin HJ, Dinizo M, Trock BJ, Feng Z, Partin AW, Walsh

- PC, et al. Impact of surgical margin status on prostate-cancer-specific mortality. *BJU Int* [Internet]. 2012 Dec [cited 2025 Mar 9];110(11):1684–9. Available from: <https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2012.11371.x>
24. Milonas D, Ruzgas T, Venclovas Z, Jonusaite D, Matijosaitis AJ, Trumbeckas D, et al. Effect of Clinical Parameters on Risk of Death from Cancer after Radical Prostatectomy in Men with Localized and Locally Advanced Prostate Cancer. *Cancers (Basel)* [Internet]. 2022 Apr 18 [cited 2025 Mar 9];14(8):2032. Available from: <https://www.mdpi.com/2072-6694/14/8/2032>
25. Ahmad AS, Parameshwaran V, Beltran L, Fisher G, North BV, Greenberg D, et al. Should reporting of peri-neural invasion and extra prostatic extension be mandatory in prostate cancer biopsies? correlation with outcome in biopsy cases treated conservatively. *Oncotarget* [Internet]. 2018 Apr 17 [cited 2025 Mar 9];9(29):20555–62. Available from: <https://www.oncotarget.com/article/24994/text/>
26. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* [Internet]. 2017 Apr [cited 2025 Mar 9];71(4):618–29. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0302283816304705?via%3Dihub>
27. Siddiqui MM, Rais-Bahrami S, Truong H, Stamatakis L, Vourganti S, Nix J, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. *Eur Urol* [Internet]. 2013 Nov [cited 2025 Mar 9];64(5):713–9. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0302283813005988?via%3Dihub>
28. Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA* [Internet]. 2015 Jan 27 [cited 2025 Mar 9];313(4):390–7. Available from: <https://jamanetwork.com/journals/jama/fullarticle/2091987>
29. Tran GN, Leapman MS, Nguyen HG, Cowan JE, Shinohara K, Westphalen AC, et al. Magnetic Resonance Imaging-Ultrasound Fusion Biopsy During Prostate Cancer Active Surveillance. *Eur Urol* [Internet]. 2017 Aug [cited 2025 Mar 9];72(2):275–81. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0302283816304900?via%3Dihub>
30. Gordetsky JB, Nix JW, Rais-Bahrami S. Perineural Invasion in Prostate Cancer Is More Frequently Detected by Multiparametric MRI Targeted Biopsy Compared With Standard Biopsy. *Am J Surg Pathol* [Internet]. 2016 Apr [cited 2025 Mar 9];40(4):490–4. Available from: https://journals.lww.com/ajsp/abstract/2016/04000/perineural_invasion_in_prostate_cancer_is_more.9.aspx
31. Choomark S, Aussavavirojekul P, Woranisarakul V, Srinualnad S. Cancer Detection Rate of MRI Ultrasound Fusion Prostate Biopsy in 1,039 Patients and Number Needed to Biopsy in Targeted Lesion. *Siriraj Med J* [Internet]. 2023 Nov 1 [cited 2025 Jul 11];75(11):770–7. Available from: <https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/265361>
32. Paner GP, Srigley JR, Harik LR, Amin MB, Eggner SE, Huang J, et al. College of American Pathologists. 2023. Protocol for the Examination of Radical Prostatectomy Specimens From Patients With Carcinoma of the Prostate Gland. Available from: https://documents.cap.org/protocols/Prostate_4.3.0.0.REL_CAPCP.pdf?_gl=1*17sruex*_ga*NTAxMzc0NzUuMTcyNDU5MzU4NQ.*_ga_97ZFJSQQ0X*czE3NTA2MDkxMzEkbzU1JGcwJHQxNzUwNjA5MTM0JGo1NyRsMCRoMA
33. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* [Internet]. 1999 May 5 [cited 2025 Mar 9];281(17):1591–7. Available from: <https://jamanetwork.com/journals/jama/fullarticle/189741>
34. Vazquez Martinez MA, Correa E, Jeurkar C, Shikdar S, Jain MR, Topolsky DL, et al. The prognostic significance of PSA as an indicator of age standardized relative survival: An analysis of the SEER database 2004-2014. *JCO* [Internet]. 2018 May 20 [cited 2025 Mar 9];36(15_suppl):e18768–e18768. Available from: http://ascopubs.org/doi/10.1200/JCO.2018.36.15_suppl.e18768
35. Sankin A, Tareen B, Lepor H. Side-specific factors associated with extracapsular extension and seminal vesicular invasion in men undergoing open radical retropubic prostatectomy. *Prostate Cancer Prostatic Dis* [Internet]. 2009 [cited 2025 Mar 9];12(2):204–8. Available from: <https://www.nature.com/articles/pcan20092>