Clinics in Medicine

ISSN: 2688-6731

Research Article

Perineural Invasion in Prostate Biopsy and Radical Prostatectomy Specimens and Their Relation to Biochemical Failure

Hernandez CH[1,2], Perez MS[3], Gonzalez DC[4] and Escobar SH[3]*

[1]Department of Urology, University of Las Palmas de Gran Canaria, Spain

[2]Department of Urology, Hospital Doctor Jose Molina Orosa, Spain

[3]Department of Urology, Doctor Negrín University Hospital, Spain

[4]Sanitas La Moraleja Hospital, Spain

Abstract

Background: The prognostic importance of Perineural Invasion (PNI) in prostate cancer has been under continuous debate. The main goal of this article is to evaluate if the presence of perinerual invasion in a prostate biopsy (bPNI) or in the radical prostatectomy specimen (pPNI) would be as useful as the classic prognostic markers to improve the classification of patients with localized prostate cancer in prognostic groups.

Methods: Retrospective analysis of patients who had undergone radical prostatectomy (June 2004 - December 2015). We excluded patients with a lack of clinical data and those had undergone neoadjuvant or adjuvant treatment. We analyzed the relationship of classical prognostic factors with the presence of bPNI and pPNI, as well as their relationship with Biochemical Failure (BF).

Results: Among 531 patients, 429 met the inclusion criteria. An association between positive bPNI (15% and 2%) and the presence of greater risk of extraprostatic extension in the radical prostatectomy specimen (p=0.007) was observed. The positive pPNI (49%) correlated with the Gleason score for the surgical specimen (p=0.002) and with the presence of positive surgical margins (p=0.006). However, neither bPNI nor pPNI were related to risk for biochemical relapse when correlated with biochemical relapse-free survival at 5years and 10 years.

Conclusion: The presence of bPNI in the biopsy sample may be an independent factor for the presence of extraprostatic extension after radical surgery. Its role as an independent prognostic factor for biochemical relapse, the same as with the pPNI, was not verified in our series.

Keywords: Prostate neoplasms; Disease progression; Prostatectomy; Perineural invasion; Prostate biopsy

Introduction

An important determinant of tumor aggressiveness is the ability to break the basal membranes and extend outside the organ of origin. The classic paradigm of tumor metastasis is the spread of the tumor through blood vessels and lymphatic channels. On the other hand, the path of neural invasion by neoplastic cells, which is well recognized in different tumor lines such as pancreatic cancer and cancer of the head and neck, has a more uncertain role in the case of prostate cancer [1].

The nerve microenvironment is a rich network of cells whose role is to support the surrounding neuronal cells. The main cells that are found in the interior and adjacent to the peripheral nerves are Schwann cells, macrophages and fibroblasts. There is increasing evidence that these support cells interact with the cancer and promote its invasion and spread along the nerves. Recently, molecular determinants of perineural invasion have been identified, such as neurotrophins (a family of proteins that regulate the growth and development of axons, as well as the maintenance of mature neurons), and chemokines (a family of signaling proteins, with the ability to induce chemotaxis in nearby sensitive cells) [1,2].

Prostate cancer has been recognized as a tumor prone to invasion and growth along the periprostatic nerves, hence the interest in the importance of PNI in tumor pathology with a wide range of aggressiveness. In 1993, Bastacky et al. [3] described for the first time the association between the presence of perineural invasion in prostate biopsy with a greater incidence of extraprostatic extension in the study of the radical prostatectomy specimen. Then in 1994, Ravery et al. [4] corroborate in their series, the relationship between the presence of PNI in the prostate biopsy and a greater incidence of extraprostatic extension in the piece of radical prostatectomy, as well as, an increased risk of biochemical progression. Since then, different studies have been published that evaluate the impact of PNI on the long-term oncological results of prostate cancer. Among them, some show an association between PNI (both of the biopsy and the piece of radical prostatectomy) with a higher incidence of BF [5,6], while other authors found no association between the variables described [7,8]. Thus, despite the biological plausibility of PNI being a potential determinant of the behavior of prostate tumors, the association between PNI and progression of prostate cancer in patients with localized stage undergoing radical prostatectomy remains a controversial issue now a days.

Citation: Hernandez CH, Perez MS, Gonzalez DC, Escobar SH. Perineural Invasion in Prostate Biopsy and Radical Prostatectomy Specimens and Their Relation to Biochemical Failure. Clin Med. 2019; 1(3): 1015.

Copyright: © 2019 Kemal Tolga Saracoglu

Publisher Name: Medtext Publications LLC

Manuscript compiled: October 26th, 2019

***Corresponding author:** Casandra Hernandez Hernandez, Department of Urology, University of Las Palmas of Gran Canaria, Las Palmas of Gran Canaria, Las Palmas, Spain, Tel: +34-679826667; E-mail: casandrahdezhdez@gmail.com

© 2019 - Medtext Publications. All Rights Reserved.

To study the relation of the perineural invasion in the sample of transrectal biopsy of the prostate and in the in radical prostatectomy specimens with the classical prognostic factors, as well as, its efficiency as a prognostic factor of Biochemical Failure (BF).

Material and Methods

Patients

Patients diagnosed with prostate cancer and undergoing radical prostatectomy between June 2004 and December 2015 in a single center have been retrospectively analyzed. As inclusion criteria for the study, it was considered an adequate clinical diagnosis with digital rectal examination, PSA and transrectal ultrasound, no previous neoadjuvant or adjuvant treatment, and the diagnostic biopsy of prostate cancer been performed in our center. Patients whose biopsies came from a private center or from another public center were excluded if they had not been reviewed in our hospital.

Prostate biopsies were performed under local anesthesia or under sedation. The number of cylinders extracted more frequently was 6 or 12 samples, each one duly documented with its zonal distribution.

For the collection of data on the PNI of the samples, both of the biopsies and of the piece of prostatectomy, in cases in which the presence or absence of PNI was not described, it was considered the absence of perineural invasion.

After an adequate clinical staging by digital rectal examination, PSA and histological diagnosis, patients were classified according to D'Amico clinical risk groups and underwent open or laparoscopic radical prostatectomy.

The follow-up after radical prostatectomy was carried out with the measurement of the PSA level, with a first determination among the first 6 months after surgery, then every six months until the third year of follow-up and annually thereafter. Biochemical relapse was considered when two progressive increases of PSA levels above 0.2 ng/ml ocurred.

Statistical analysis

The degree of concordance between bPNI and pPNI was analyzed by kappa analysis. Through the χ^2 test, we performed the relationship between bPNI and pPNI among the different classical prognostic variables. For the multivariate analysis, a Cox Regression was performed to estimate the relative importance of the different prognostic factors in predicting the risk of BF. To assess the actuarial survival free of BF according to the perineural affectation, Kaplan-Meier and log-rank test were used. Statistical significance was considered with P<0.05.

Results

Between June 2004 and December 2015, 531 radical prostatectomies were performed with a diagnosis of prostate cancer in our center, 429 patients met the inclusion criteria. Perineural invasion was found in 65 patients (15.2%) in the prostate biopsy and in 210 patients (49.0%) in the radical prostatectomy specimen. We observed in the distribution of bPNI between classical clinical and pathological variables, on the one hand, that the presence of bPNI was associated with a greater frequency of extraprostatic extension in pathological staging (p=0.007) and on the other hand that pPNI was associated with the Gleason score (p=0.002) and with the surgical margins (p=0.006) (Table 1). With a median follow-up of 85 months (13 months to 153 months), among the 429 patients, there were a total of 102 (23.8%) cases of FB. We can see the absence of direct relationship in the Kaplan Meier between the BF and the bPNI (p=0.840) (Figure 1) as well as with the pPNI (p=0.613) (Figure 2). We performed a multivariate analysis between BF and classic clinical factors by adding bPNI (Table 2), confirming the absence of significance of bPNI

Table 1: Univariable analysis of prognostic factors for BF in a bIPN and pIPN cohort.

Variable	bIPN		p	bIPN		p
	Negative	Positive		Negative	Positive	
Age, me +/- SD	61,18 (5,92)	61,29 (6,07)	0,884	61,31 (6,14)	61,23 (5,71	0,880
PSA			0,166			0,662
<10	282 (77,5)	51 (78,5)		188 (77,7)	187 (78,9)	
10-20	77 (21,2)	11 (16,9)		51 (21,1)	45 (19,0)	
>20	5 (1,4)	3 (4,6)		3 (1,2)	5 (2,1)	
Pathological stage			0,007			0,124
pT2	253 (69,5)	34 (52,3)		154 (70,3)	133 (63,3)	
pT3	111 (30,5)	31 (47,7)		65 (29,7)	77 (36,7)	
Pathological Gleason score			0,206			0,002
≤ 6	161 (44,2)	20 (30,8)		107 (48,9)	74 (35,2)	
7 (3+4)	155 (42,6)	36 (55,4)		78 (35,6)	113 (53,8)	
7 (4+3)	35 (9,6)	6 (9,2)		24 (11)	17 (8,1)	
≥ 8	13 (3,6)	3 (4,6)		10 (4,6)	6 (2,9)	
Surgical margin			0,088			0,006
Negative	133 (36,5)	31 (47,7)		149 (68,0)	116 (55,2)	
Positive	231 (63,5)	34 (52,3)		70 (32,0)	94 (44,8)	

bIPN: Perineural Invasión at Biopsy; pIPN: Pathological Perineural Invasion

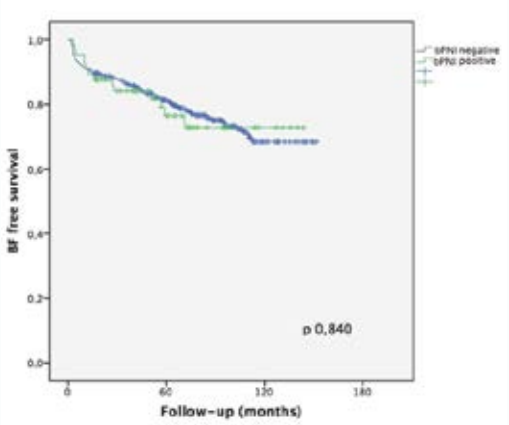

Figure 1: Kaplan-Meier BF-free survival curves stratified by bPNI on univariable analysis.

Table 2: Multivariate analyses of clinical factors associated with disease control.

Variable	BF		
	HR	(IC 95%)	p
Age	0,989	0,950-1,029	0,575
PSA			
<10	1.000		ref
10-20	2218	1,310-3,754	0,003
>20	2193	0,480-10,008	0,311
Clinical stage			
T1c-T2a	1.000		ref
T2b	1332	0,760-2,336	0,317
≥ T2c	1115	0,518-2,398	0,780
Gleason score at biopsy			
≤ 6	1.000		ref
7 (3+4)	2313	1,312-4,080	0,004
7 (4+3)	2429	1,138-5,182	0,022
≥ 8	3776	0,870-16,401	0,076
bPNI	0,687	0,343-1,376	0,289

PSA: Prostate-Specific Antigen; HR Hazard Ratio; CI: Confidence Interval; bPNI: Perineural Invasión at Biopsy

© 2019 - Medtext Publications. All Rights Reserved.

in the Kaplan Meier between the BF and the bPNI (p=0.840) (Figure 1) as well as with the pPNI (p=0.613) (Figure 2). We performed a multivariate analysis between BF and classic clinical factors by adding bPNI (Table 2), confirming the absence of significance of bPNI (p=0.295) as an independent prognostic factor of BF. In the same way, a multivariate analysis was carried out between the BF and the classical pathological prognostic factors extracted from the analysis of the radical prostatectomy specimen, in addition with the pPNI. In this analysis, pPNI was not considered an independent prognostic factor of BF (p=0.613) (Table 3).

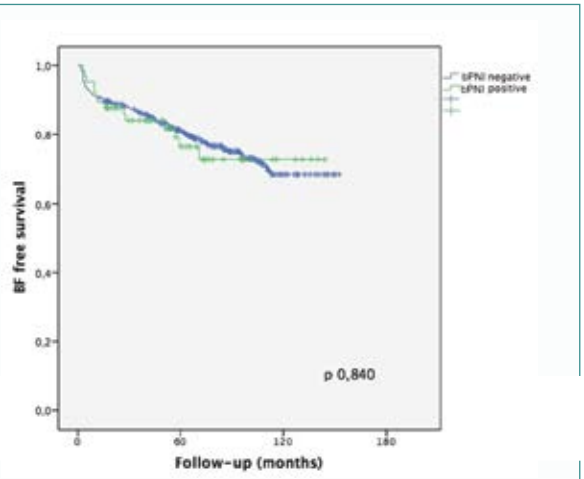

Figure 2: Kaplan–Meier BF-free survival curves stratified by pPNI on univariable analysis.

Table 3: Multivariate analyses of pathological factors associated with disease control.

Variables		HR	(IC 95%)	p
Pathological stage	pT2vs pT3	1637	0,994-2,694	0,053
RP Gleason score	≤ 6			ref
	7 (3+4)	1202	0,759-2,238	0,337
	7 (4+3)	2878	1,319-6,281	0,008
	≥ 8	3599	1,174-11,029	0,025
Surgical margin	Positive - negative	3139	1,911-5,155	<0,0001
pPNI	Positive - negative	0,883	0,545-1,431	0,613

Discussion

Tumor dissemination, in addition to being carried out through classical routes (blood and lymphatic) can occur through tumoral perineural invasion, so that tumor cells invade both the epineurium (the outermost layer of a nerve that is made up of loose connective tissue cells) as the perineurium (dense connective tissue that surrounds a nervous beam), and can reach the endoneurium (loose connective tissue) associating intimately with Schwann cells and nerve axons [1,2].

Despite the high incidence of PNI in many types of tumors, such as head and neck, bladder, prostate, stomach, colon and rectum, etc., its true prognostic significance remains difficult to recognize. Pancreatic cancer is a reference in the study of perineural invasion due to its high incidence, being considered a histopathological hallmark in this entity. A meta-analysis published in 2017 concludes that the presence of neural invasion in pancreatic adenocarcinoma is an independent factor of disease-free survival, progression-free survival and overall survival [9].

In localized prostate cancer, the presence of PNI presents a wide variability in its incidence. In prostate biopsy, the incidence of PNI in the published series ranges from 7% to 72% [4,10], being the most frequent finding digits of around 20% [7,11,12]. In our case of 429 patients, 15.2% had a positive bPNI. Regarding the frequency of PNI in the piece of radical prostatectomy, in the published studies they present even more variability with numbers ranging from 12% to 90%, being in our series of 49.5% [13,14].

To elucidate about the pathogenesis of PNI, there are several studies carried out on cultures with human prostate cancer cell lines with different degrees of aggressiveness, concluding that there is the presence of a mutual tropism and a paracrine interaction between neurons and prostatic tumoral cells, which provide the nerves with a prosperous environment for tumor growth, and that the interaction between both generates beneficial effects on the growth of both the nerves and the tumor [15].

In the clinical field, in prostate cancer we can find several studies that correlate the perineural invasion, both in the prostate biopsy and in the histological study of the radical prostatectomy specimen, with the classic clinical and anatomopathological prognostic variables. In this way, there are those who associate bPNI with a higher rate of positive surgical margins [16,17], with a greater incidence of extraprostatic extension [18], or with a higher risk of BF [5,19]. In 2014 Mathhew et al. [20] demonstrated the association of both bPNI, Ki-67 expression and Gleason score of the biopsy with increased risk of local and systemic progression, as well as worse cancer-specific survival. On the other hand, other studies did not find a relationship between the presence of bPNI and worse anatomopathological findings or long-term oncological results [7,21]. In our study, we observed a relationship between bPNI and the presence of extraprostatic extension (p=0.002) and close to significance in relation to surgical margins (p=0.088), without subsequently linking the bPNI with an increased risk of BF (p=0.840).

The relationship between pPNI and the risk of BF in patients with localized prostate cancer presents a lower number of published studies with respect to its homonym in the biopsy, but they coincide in the heterogeneity of the results. On the one hand, different authors have demonstrated the association between both described variables, such as the case of Ozcan et al. [6] who correlated the presence of pPNI with the pathological stage, the surgical margins and the pathologica Gleason grade, resulting in pPNI an independent prognostic factor of BF in the multivariate analysis (p=0.0003). In the same way, Jeon et al. [22] associated the presence of pPNI independently with the classic prognostic variables of the prostatectomy piece and later with the risk of BF (p=0.001). Andersen et al. [23] found that patients with pPNI had no association with BF, but it was associated with an increased risk of clinical relapse (p=0.012) together with the Gleason score (p=0.019) and positive surgical margins (p=0.002); in addition, both the pPNI and the Gleason score in radical prostatectomy specimens were associated with a higher specific cancer mortality.

On the other hand, Somford et al. [8] did not relate the presence of pPNI with a higher risk of BF in the multivariate analysis, as well as other studies with similar characteristics [14,24,25]. In our case, pPNI was associated with a worse degree of definitive Gleason score (p=0.003) and a higher risk of positive surgical margins (p=0.010). However, there was no relationship between the presence of pPNI and the risk of BF (p=0.519).

Among the limitations of this series we find first, the type of study design, a retrospective study with low level of scientific evidence and

© 2019 - Medtext Publications. All Rights Reserved.

with data deficit secondary to the a posteriori collection of them. Second, the high number of pathologists who evaluate the samples and the low rates of PNI detection both in the biopsy and in the piece of prostatectomy justifies the need to have a pathologist specialized in uro-oncology to bring our detection closer to the rates described in the most recent literature.

In conclusion, in localized stage prostate cancer, the comparison between the different studies published to date on the importance of perineural invasion is complex given the heterogeneity of the them, so that both in the prostate biopsy at diagnosis as in radical prostatectomy specimens, the PNI continues to be a subject of much controversy without, in our case, being an independent prognostic factor of worse long-term oncological results.

References

1. Marchesi F, Piemonti L, Mantovani A, Allavena P. Molecular mechanisms of perineural invasion, a forgotten pathway of dissemination and metastasis. Cytokine Growth Factor Rev. 2010;21(1):77-82.
2. Bakst RL, Wong RJ. Mechanisms of Perineural Invasion. J Neurol Surg B Skull Base. 2016;77(2):96-106.
3. 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):336-41.
4. Ravery V, Boccon-Gibod LA, Dauge-Geffroy MC, Billebaud T, Delmas V, Meulemans A, et al. Systematic biopsies accurately predict extracapsular extension of prostate cancer and persistent/recurrent detectable PSA after radical prostatectomy. Urology. 1994;44(3):371-6.
5. Quinn DI, Henshall SM, Brenner PC, Kooner R, Golovsky D, O'Neill GF, et al. Prognostic significance of preoperative factors in localized prostate carcinoma treated with radical prostatectomy. Cancer. 2003;97(8):1884-93.
6. Ozcan F. Correlation of perineural invasion on radical prostatectomy specimens with other pathologic prognostic factors and PSA failure. Eur Urool. 2001;40(3):308-12.
7. Nelson CP, Dunn RL, TWei J, Rubin MA, Montie JE, Sanda MG. Contemporary preoperative parameters predict cancer-free survival after radical prostatectomy: a tool to facilitate treatment decisions. Urol Oncol. 2003;21(3):213-18.
8. Somford DM, Van Oort IM, Cosyns JP, Witjes JA, Kiemeney LA, Tombal B. Prognostic relevance of number and bilaterality of positive surgical margins after radical prostatectomy. World J Urol. 2012;30(1):105-10.
9. Schorn S, Demir IE, Haller B, Scheufele F, Reyes CM, Tieftrunk E, et al. The influence of neural invasion on survival and tumor recurrence in pancreatic ductal adenocarcinoma - A systematic review and meta-analysis. Surg Oncol. 2017;26(1):105-15.
10. 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. 2001;165(1):126-9.
11. Ristau BT, Tomaszewski JJ, Chen YF, Bertolet M, Woldemichael E, Nelson JB. Prostate biopsy perineural invasion is not independently associated with positive surgical margins following radical retropubic prostatectomy. World J Uro. 2015;33(9):1269-74.
12. Niroomand H, Nowroozi M, Ayati M, Jamshidian H, Arbab A, Momeni SA, et al. Relationship Between Perineural Invasion in Prostate Needle Biopsy Specimens and Pathologic Staging After Radical Prostatectomy. Nephrourol Mon. 2016;8(3):e36022.
13. Kang M, Oh JJ, Lee S, Hong SK, Lee SE, Byun SS. Perineural Invasion and Lymphovascular Invasion are Associated with Increased Risk of Biochemical Recurrence in Patients Undergoing Radical Prostatectomy. Ann Surg Oncol. 2016;23(8):2699-706.
14. Merrilees AD, Bethwaite PB, Russell GL, Robinson RG, Delahunt B. Parameters of perineural invasion in radical prostatectomy specimens lack prognostic significance. Mod Pathol. 2008;21(9):1095-100.
15. 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. 2001;49(3):213-23.
16. Haki Yuksel O, Urkmez A, Verit A. Can perineural invasion detected in prostate needle biopsy specimens predict surgical margin positivity in D'Amico low risk patients? Arch Ital Urol Androl. 2016;88(2):89-92.
17. Yang R, Cao K, Han T, Zhang YF, Zhang GT, Xu LF, et al. Perineural invasion status, Gleason score and number of positive cores in biopsy pathology are predictors of positive surgical margin following laparoscopic radical prostatectomy. Asian J Androl. 2017;19(4):468-72.
18. Cannon GM Jr, Pound CR, Landsittel DP, Bastacky SI, Dhir R, Becich MJ, et al. Perineural invasion in prostate cancer biopsies is not associated with higher rates of positive surgical margins. Prostate. 2005;63(4):336-40.
19. de la Taille A, Rubin MA, Bagiella E, Olsson CA, Buttyan R, Burchardt T, et al. Can perineural invasion on prostate needle biopsy predict prostate specific antigen recurrence after radical prostatectomy?. J Urol. 1999;162(1):103-6.
20. Tollefson MK, Karnes RJ, Kwon ED, Lohse CM, Rangel LJ, Mynderse LA, et al. Prostate Cancer Ki-67 (MIB-1) Expression, Perineural Invasion, and Gleason Score as Biopsy-Based Predictors of Prostate Cancer Mortality: The Mayo Model. Mayo Clin Proc. 2014;89(3):308-18.
21. 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. 2002;59(1):85-90.
22. Jeon HG, Bae J, Jun-Seok Yi, Hwang IS, Lee SE, Eunsik Lee. Perineural invasion is a prognostic factor for biochemical failure after radical prostatectomy. Int J Urol. 2009;16:682-6.
23. Andersen S, Richardsen E, Nordby Y, Ness N, Størkersen O, Al-Shibli K, et al. Disease-specific outcomes of radical prostatectomies in Northern Norway; a case for the impact of perineural infiltration and postoperative PSA-doubling time. BMC Urol. 2014;14:49.
24. Ng JC, Koch MO, Daggy JK, Cheng L. Perineural invasion in radical prostatectomy specimens: lack of prognostic significance. J Urol. 2004;172(6 pt 1):2249-51.
25. Gazel E, Tastemur S, Acikgoz O, Yigman M, Olcucuoglu E, Camtosun A, et al. Importance of Neutrophil/Lymphocyte Ratio in Prediction of PSA Recurrence after Radical Prostatectomy. Asian Pac J Cancer Prev. 2015;16(5):1813-16.

© 2019 - Medtext Publications. All Rights Reserved.