Pathology (■ 2018) ■(■), pp. 1–7

ANATOMICAL PATHOLOGY

Quantitative perineural invasion is a prognostic marker in prostate cancer

Sabine Lubig[1], Thore Thiesler[1], Stefan Müller[2], Roland Vorreuther[3], Norbert Leipner[4], Glen Kristiansen[1]

[1]*Institute of Pathology of the University Hospital Bonn, Bonn, Germany;* [2]*Department of Urology of the University Hospital Bonn, Bonn, Germany;* [3]*Department of Urology, Evangelische Kliniken Bonn, Bonn, Germany;* [4]*Practice of Radiotherapy Bonn-Rhein-Sieg, Bonn, Germany*

Summary

This study aimed to investigate the prognostic value of a quantitative, detailed, yet practical analysis of perineural invasion in radical prostatectomy specimens in a high-risk prostate cancer cohort.

A total of 114 patients with prostate cancer who underwent radical prostatectomy between 2000 and 2013 were analysed. Using S100 protein immunohistochemistry assisted in the detection of nerves. In the area of closest proximity of the tumour to the dorso-lateral margins, nerves were counted and the infiltration of nerves was categorised (0–3). Category 0 was nerves without immediate tumour-cell-contact. All nerves being fully surrounded by tumour (classical perineural carcinosis) were categorised group 3. Two further categories discriminated between nerves that were touched either by carcinoma cells below 50% of the circumference (category 1) or above (category 2).

Perineural carcinosis (Pn1) was seen in 61.4% of cases and correlated positively with ISUP grades, pT categories and presence of intraductal carcinoma but failed significance on Kaplan–Meier analysis. A more quantitative analysis of percentual perineural involvement did demonstrate significant survival differences: cases with less than one Pn1-positive nerve in 5 high power fields had longer survival times. Incomplete perineural involvement (category 1–2) did not have a prognostic value, endorsing the current definition of perineural carcinosis as full circumferential encasement of a nerve by tumour cells.

A quantitative analysis of the percentage of nerves positive for perineural invasion has a higher prognostic value than the classical dichotomous statement on the mere presence of perineural invasion.

Key words: Prostate cancer; perineural invasion; perineural carcinosis; prognostic factor.

Received 22 July, revised 22 August, accepted 31 August 2017
Available online: xxx

INTRODUCTION

Perineural invasion (PNI), defined as a tumour cell invasion in, around, and through the nerves,[1] is highly prevalent in prostate cancer. If carefully analysed, it is found in 75% of radical prostatectomy specimens and in up to 25% of needle biopsies from patients without lymph node metastasis.[2–4] PNI is meanwhile an established diagnostic category of the UICC TNM system. The existence of PNI is a sign of impending metastatic tumour spread just like lymphatic or vascular invasion; hence, it is a mechanism of tumour progression, especially in prostate cancer. De la Taille *et al.* suggested positive PNI findings should be reported as an important preoperative predictor of pathological stage.[5] The importance of this route of tumour extension is already known for other neurotropic neoplasms such as pancreas, rectal and gastric cancer.[6–8] Villers *et al.* have proven the ability of PNI positive cancers to grow along intraprostatic nerve tissue and penetrate the prostatic capsule.[9] Perineural invasion appears as a symbiotic interaction between nerves and neurotopic cancer cells, resulting in increased tumour growth.[10] However, it may also induce nerve growth, as Ayala *et al.* were able to show directional outgrowth of neurites toward cancer colonies as well as tumour cell migration along those nerves *in vitro*. This indicates functional signalling between nerve fibres and infiltrating neoplastic cells, which gained the ability to respond to proinvasive signals within the nerves.[4,11] This leads to a significantly increased nerve count and capsular nerve surface area in comparison to cancer free areas.[12] Hirai *et al.* demonstrated that there is a prognostic value to PNI at least for pancreatic cancer.[13] Findings of perineural invasion in those types of cancer were associated with poor outcome. Law *et al.* recognised a lowered cancer-specific 5-year survival in patients with PNI in pancreatic cancer and found an increased recurrence rate.[6] Even though these results indicate that perineural cancer spread generally worsens patient outcome, its prognostic significance and diagnostic relevance in prostate cancer is still controversial. Some studies show no significant differences, others prove the relation between perineural infiltration and worse outcome.[14] There is a higher risk of prostatic capsule invasion at radical prostatectomy for patients with perineural invasion.[15] These findings have been associated with an increased risk of clinical failure.[5,16–21] In patients with high Gleason scores, the PNI positivity suggests an increased risk of metastasis and prostate cancer death.[22,23] Lee *et al.* examined a large sample of prostate specimens observing that perineural infiltration in biopsies predicts higher pathological T-stage and positive margins at radical prostatectomy.[24,25] However, Maru *et al.* reported that PNI

Print ISSN 0031-3025/Online ISSN 1465-3931 © 2018 Royal College of Pathologists of Australasia. Published by Elsevier B.V. All rights reserved.
DOI: https://doi.org/10.1016/j.pathol.2017.09.013

Please cite this article in press as: Lubig S, et al., Quantitative perineural invasion is a prognostic marker in prostate cancer, Pathology (2018), https://doi.org/10.1016/j.pathol.2017.09.013

positivity in radical prostatectomy specimens has no value as a predictor of prognosis in adenocarcinoma.[3] The significant positive correlation between higher Gleason scores and the existence of Pn1 found in needle biopsies suggests that PNI is unlikely to represent an independent prognostic parameter in prostate cancer.[8,26] Higher Gleason scores, positive margins and preoperative prostate specific antigen (PSA) levels are independently associated with biochemical recurrence following radical prostatectomy. In this setting, perineural invasion does not appear to be an independent prognostic parameter.[25,27–32] These largely negative findings merit a closer look at the technical conduction of Pn1 recognition, which may have potential for improvement. Kurtz *et al.* demonstrated that the detection of nerves, and therefore the accurate detection of perineural cancer spread, is increased from 30% to 82% if S100 replaces or is performed in addition to the standard haematoxylin and eosin (H&E) staining techniques for specimens.[33] Therefore, the first step to an improved diagnostic process could be immunohistochemistry to assist in detection of perineural invasion. Also, the question of extent of Pn1 has not been addressed yet, as the standard procedure simply dichotomises whether PNI is present or not. Another feature not yet systematically analysed is the influence of the applied diagnostic criteria to define perineural invasion, which may be more relevant than generally perceived. As the name suggests, PNI is described as the infiltration of tumour cells into the nerve sheath that surrounds the nerve fibres. Most pathologists require complete circumferential embedding of the nerve fibre as a mandatory diagnostic criterion of perineural invasion. But what about cases where tumour cells lack complete circumferential infiltration, or just peripherally impede adjacent nerves? These cancer cells that already touch nerve tissue may just commence infiltrating those nerve sheaths.

These questions prompted us to provide a more detailed, yet practical approach to analyse PNI in prostate cancer, that allows for a detailed analysis of the correlations of perineural invasion with other clinico-pathological parameters including patient outcome.

MATERIALS AND METHODS

Patient selection

All histological specimens were obtained from 114 patients undergoing radical prostatectomy between 2000 and 2013, who were diagnosed in the Institute of Pathology, University Bonn, the vast majority ($n = 100$) of whom subsequently underwent radiation therapy. The patient data, needle-biopsy results if available, postoperative histopathological and radiation therapy reports were collected and reviewed. For 106 patients follow up data were available. Thirty-seven percent of cases received androgen-deprivation therapy after surgery.

The median age of the patients at the time of diagnosis was 64.24 years (range 45–81 years). The median overall survival for the entire population was 94 months (range 5–205 months). During follow up 16 patients died after a median of 80.5 months (range 29–148 months).

Histopathological analysis

Following careful central review of all cases, two representative blocks were chosen from each prostatectomy specimen for further analysis. For identification of nerves, S100 protein was detected by immunohistochemistry (polyclonal antibody Cat. no. Z031; 1:2000; Dako, Germany). Slides were reviewed with a Leica DM500 microscope (Leica, Germany) at 10×/0.22 by a single examiner (SL) under supervision of a genitourinary pathologist (GK). First, areas of interest, defined by a close proximity of invasive carcinoma to the pseudocapsule of the prostate, where the density of nerves is highest, were identified. In each high power field (HPF) nerves were counted and classified using four categories (0–3). Category 0 denotes nerves without immediate epithelial tumour cell contact (Fig. 1A,B). All nerves being fully surrounded by tumour cells defining classical perineural infiltration were categorised as group 3 (Fig. 1G,H). We decided on two more categories to discriminate between nerve fibres that were touched by tumour cells either below (category 1, Fig. 1C,D) or above (category 2, Fig. 1E,F) 50% of the circumference of the nerve. All cases were centrally reviewed (GK) and Gleason scores and presence of intraductal carcinoma were recorded according to current World Health Organization (WHO) criteria.[34]

Statistical analysis

The influences of parameters like Gleason score, pathological T stage, margins, PNI, HPF and the total number of nerves on disease free survival and overall survival among patients were estimated using the Kaplan–Meier procedure. Univariate Cox regression was performed to calculate the hazard ratios.

The association of PNI or the intensity of nerve-tumour contact with regards to the reasoned categories described above with various clinico-pathological characteristics was assessed using the non-parametric Spearman correlation test. Chi-squared test was computed to assess the effects of PNI positive versus negative groups as well as lower grade and higher grade nerve-tumour association on histopathological parameters.

All analysis was performed using SPSS version 24 (SPSS, USA). All results were considered significant at p values <0.05.

RESULTS

General descriptive statistics

The mean patient age was 73.35 years (range 55–87 years). The mean preoperative PSA level was 11.78 ng/mL (range 1.10–166 ng/mL). Pathological stages were pT2 (43%), pT3 (55.2%) and pT4 (1.8%). International Society of Urological Pathology (ISUP) grades of the tumours after central review were as follows: two cases were ISUP grade 1, 39 cases ISUP grade 2, 18 cases ISUP grade 3, 19 cases ISUP grade 4, and 36 ISUP grade 5. Surgical margins were positive in 50.5% of cases. Intraductal carcinoma (IDC-P) was found in 38.6% of cases.

Evaluation of perineural involvement

Of both blocks evaluated, the results of the block with the higher rate of classical perineural invasion was chosen for further statistical analysis. The mean number of HPFs evaluated was 7.23 (median 7, range 2–16). The mean total number of nerves was 80.51 (median 77, range 5–222). The average number of nerves without immediate contact to tumour epithelia (category 0) was 62.38 (median 56.5, range 3–188; mean 79.7% of all nerves), category 1 was 7.54 (median 5, range 0–37; mean 9.8%), category 2 was 4.89 (median 2, range 0–34; mean 5.2%), and category 3 was 5.61 (median 1, range 0–58; mean 5.1%). Perineural carcinosis (category 3) was seen in 70 cases (61.4%). For further statistics, only the percentages of nerve involvement for each category were considered. The medians of the percentages for the four categories (over all cases) were 81.59% (category 0), 6.89% (category 1), 2.88% (category 2) and 1.79% (category 3).

Associations of perineural involvement with clinicopathological parameters

Spearman correlation analysis of the categories with increasing degrees (category 0–3) of perineural involvement revealed that only categories 2 and 3 showed a positive and significant correlation with ISUP grade, pT categories and

Please cite this article in press as: Lubig S, et al., Quantitative perineural invasion is a prognostic marker in prostate cancer, Pathology (2018), https://doi.org/10.1016/j.pathol.2017.09.013

Download English Version:

https://daneshyari.com/en/article/6555511

Download Persian Version:

https://daneshyari.com/article/6555511

Daneshyari.com