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Biopsy prostate cancer perineural invasion and tumour load are associated with positive posterolateral margins at radical prostatectomy: implications for planning of nerve-sparing surgery

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Biopsy prostate cancer perineural invasion and tumour load are associated with positive posterolateral margins at radical prostatectomy: implications for planning of nerve-sparing surgery

Aims: Radical prostatectomy (RP) for prostate cancer is frequently complicated by erectile dysfunction and urinary incontinence. However, sparing of the nerve bundles adjacent to the posterolateral sides of the prostate reduces the number of complications at the risk of positive surgical margins. Preoperative selection of men eligible for safe, nerve-sparing surgery is therefore needed. Our aim was to identify pathological factors associated with positive posterolateral surgical margins in men undergoing bilateral nerve-sparing RP.

Methods and results: Prostate cancer patients undergoing RP with standardised intra-operative surgical margin assessment according to the NeuroSAFE technique were included. Preoperative biopsies were reviewed for grade group (GG), cribriform and/or intraductal carcinoma (CR/IDC), perineural invasion (PNI), cumulative tumour length and extraprostatic extension (EPE). Of 624 included patients, 573 (91.8%) received NeuroSAFE bilaterally and 51 (8.2%) unilaterally, resulting in a total of 1197 intraoperative posterolateral surgical margin assessments. Side-specific biopsy findings were correlated to ipsilateral NeuroSAFE outcome. Higher biopsy GG, CR/IDC, PNI, EPE, number of positive biopsies and cumulative tumour length were all associated with positive posterolateral margins. In multivariable bivariate logistic regression, ipsilateral PNI [odds ratio (OR) = 2.98, 95% confidence interval (CI) = 1.62–5.48; $P < 0.001$] and percentage of positive cores (OR = 1.18, 95% CI = 1.08–1.29; $P < 0.001$) were significant predictors for a positive posterolateral margin, while GG and CR/IDC were not.

Conclusions: Ipsilateral PNI and percentage of positive cores were significant predictors for a positive

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posterolateral surgical margin at RP. Biopsy PNI and tumour volume can therefore support clinical decision-making on the level of nerve-sparing surgery in prostate cancer patients.

Keywords: NeuroSAFE, percentage of positive biopsies, perineural invasion, prostate biopsy, prostate cancer, surgical margin

Introduction

Radical prostatectomy (RP) is complicated by erectile dysfunction and urinary incontinence in 20–90% and 3–16% of prostate cancer patients, respectively.[1,2] Preservation of the neurovascular bundles adjacent to the prostate can reduce these complication rates, but is usually contraindicated in patients with clinical suspicion of extraprostatic extension (EPE).[3–6] Suspicion of EPE is based on clinical stage, magnetic resonance imaging (MRI), nomograms and intraoperative assessment, but its prediction is still inaccurate.[7] This can result in either nerve-sparing surgery with positive surgical margins in non-organ confined tumours or redundant sacrifice of nerve-bundles in localised tumours.[8]

There is a strong clinical need to consider more objective parameters to support clinical decision-making at the level of nerve-sparing during RP. Little is known to what extent pathological factors during preoperative biopsies could contribute to the assessment of eligibility for nerve-sparing surgery. While many studies have revealed factors associated with RP-positive surgical margins in general, such as Gleason score, their relevance for guidance of nerve-sparing surgical approach has not yet been investigated.[9,10] The reason for lack of comprehensive studies regarding this subject is that the level of nerve-sparing surgery is highly heterogeneous and often not explicitly registered or communicated to pathologists in a standardised manner. This variability applies to both side (none, one or both sides) and extent (no, partial, complete) of nerve-sparing surgery (Figure 1).

With standardised intraoperative frozen sections (IFS), according to the NeuroSAFE technique, surgical margins of the prostate adjacent to the neurovascular bundle are assessed during operation.[11,12] Here, RP is performed in a bilateral nerve-sparing fashion, after which prostate tissue adjacent to the neurovascular bundle is removed and submitted for intraoperative pathological evaluation. If the tumour reaches into the surgical margin, a secondary resection of the ipsilateral neurovascular bundle is performed; if the tumour does not reach into the surgical margin, the ipsilateral neurovascular bundle remains intact. Application of the NeuroSAFE procedure results in a significant increase of nerve-bundle preservation without negatively affecting surgical margin status or biochemical recurrence rates.[11–14]

We hypothesise that objective and quantitative assessment of biopsy tumour features can support clinical decision-making regarding nerve-sparing surgery. In a large and well-characterised cohort of prostate cancer patients, whom had all undergone standardised nerve-sparing RP according to the NeuroSAFE technique, we assessed the pathological characteristics of their preoperative biopsy. The aim of this study was to identify pathological factors at biopsy associated with positive posterolateral surgical margins at RP, which could optimise selection of patients for nerve-sparing surgery.

Patients and methods

STUDY POPULATION

Since September 2018, eight medical centres in the Netherlands have collaborated within the Anser Prostate Network. Prostate cancer patients scheduled for RP are referred to the Anser Prostate Operation Clinic, while diagnosis, imaging and multidisciplinary therapeutic decision-making is performed in one of the referral centres. In this study, we included men who had undergone RP with NeuroSAFE in the Anser Prostate Operation Clinic between September 2018 and April 2020, operated by a team of four experienced urological surgeons. NeuroSAFE was omitted uni- or bilaterally in case of clinically established extra-prostatic extension or fibrotic adhesions caused, for instance, by previous operations. Patients without uni- or bilateral NeuroSAFE or without availability of biopsy slides for review were excluded. The study was approved by the institutional Medical Ethical Committee (METC-2019-0352). Informed consent was obtained. Data are only available after receiving project approval by Anser Research Committee due to privacy/ethical restrictions.

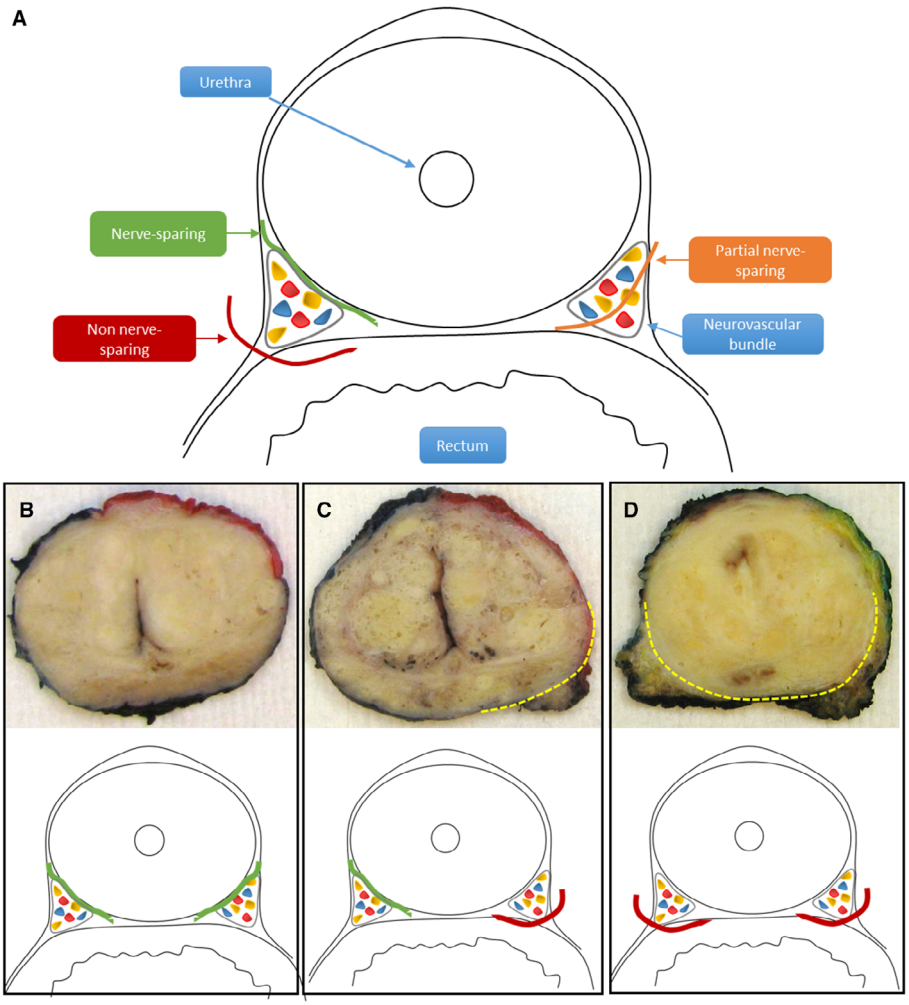

Figure 1. Schematic overview of levels of nerve-sparing radical prostatectomy. **A,** Levels of nerve-sparing surgery at the posterolateral sides of the prostate. At complete nerve-sparing surgery (green) the dissection plane is immediately adjacent to the prostate, leaving the bundle intact. At complete non-nerve sparing surgery (red) the neurovascular bundle is entirely dissected. At partial nerve-sparing surgery (orange) a part of the bundle is dissected. Different levels of nerve-sparing surgery can be performed on either side of the prostate. Gross picture and schematic representation of (**B**) bilateral complete nerve-sparing surgery, (**C**) one-sided nerve-sparing and one-sided non-nerve-sparing surgery and (**D**) bilateral non-nerve-sparing surgery. The yellow dashed line in **C** and **D** represents prostate capsule.

NEUROSAFE PROCEDURE

The NeuroSAFE procedure was performed as described previously.[12,15] Briefly, RP was initially performed in a bilateral nerve-sparing manner, after which the prostate tissue adjacent to the neurovascular bundle was dissected from apex to base. The dissected posterolateral prostate tissues were inked for orientation and submitted for IFS assessment to the pathology department. If IFS evaluation showed tumour in the surgical margin, a secondary resection of the ipsilateral neurovascular bundle was performed, otherwise the neurovascular bundle remained intact.

PATHOLOGICAL EVALUATION

The IFS and pathological evaluation of RP specimens has been reported in detail previously.[15] In brief, the dissected posterolateral prostate tissues were cut into 5-mm sections, resulting in a total of seven to 10 sections per side. The sections were snap-frozen and stained with haematoxylin and eosin. The pathologist evaluated the IFS and reported the cumulative length, Gleason pattern at the margin and number of slides in the case of a positive surgical margin, which was defined as at least one malignant gland reaching into the ink. RP specimens and eventual secondary

resections were entirely embedded for diagnostic purposes.

Preoperative biopsies were retrospectively reviewed by one genitourinary pathologist (G.v.L.) for study purposes. Grade group (GG), cumulative tumour length, perineural invasion (PNI), cribriform and/or intraductal carcinoma (CR/IDC) and EPE were monitored for each side and target lesion separately, according to the 2014 International Society of Urological Pathology (ISUP) recommendations.[16] The side-specific biopsy findings were correlated with an ipsilateral NeuroSAFE outcome. When a patient had undergone target and systematic biopsy at one side, the highest GG was taken. If the target lesion was located in the midline of the prostate, the pathological parameters were taken into account for both sides. In this case, the number of biopsies and cumulative tumour length were divided by two for the right and left side of the midline lesion.

STATISTICAL ANALYSIS

Biopsy GG, CR/IDC, EPE, PNI and different biopsy methods (systematic and target) were compared using the χ^2 test. The cumulative tumour length and number of biopsies were compared using the Mann–Whitney test. To predict a positive posterolateral surgical margin at NeuroSAFE on the left and right sides, we included the presence of clinically significant prostate cancer (defined as GG2 with CR/IDC or higher than GG2) on the left and right biopsy sides, the presence of PNI on the left and right biopsy sides, the percentage of positive cores on the left and right biopsy sides and preoperative prostate-specific antigen (PSA) level. To evaluate the association of clinicopathological biopsy variables with posterolateral NeuroSAFE margin outcome, we performed bivariate logistic regression. Using this methodology, we estimated bivariate outcome (left and right NeuroSAFE) based on several predictors that have a coefficient on both outcomes. For example, the presence of clinically significant prostate cancer detected on the left side of the prostate will have a coefficient for the left NeuroSAFE, but also for the right posterolateral surgical margin status. In this analysis, we only evaluated patients who had biopsies on both sides and underwent bilateral NeuroSAFE. The discriminative ability of the model was assessed using the area under the receiver operating characteristic curve (AUC) and we assessed the optimism corrected AUC for internal validation. All statistical analyses were performed using R version 4.1.0, completed by R-package package VGAM,[17] rmda[18] and pROC.[19]

Results

PATIENT CHARACTERISTICS

The median age of the 624 patients was 68 years [interquartile range (IQR) = 64–71] and the median preoperative PSA level was 9.2 ng/ml (IQR = 6.3–13.4) (Table 1). The biopsy worst tumour grade at revision was GG1 in 103 (16.5%), GG2 in 271 (43.4%), GG3 in 177 (28.4%) and GG4 or GG5 in 73 (11.7%) men. One hundred and seventy (27.2%) patients had undergone systematic and target biopsies, 323 (51.8%) systematic biopsies only and 131 (21.0%) target biopsies only. At RP, 50 (8.0%) men had GG1, 319 (51.1%) GG2, 185 (29.6%) GG3 and 70 (11.2%) GG4 or GG5, whereas 359 (57.5%) had pT2, 180 (28.8%) pT3a and 85 (13.6%) pT3b.

POSTEROLATERAL SURGICAL MARGIN STATUS

Intraoperative posterolateral surgical margin assessment according to the NeuroSAFE technique was applied bilaterally in 573 (91.8%) and unilaterally in 51 (8.2%) patients, resulting in a total of 1197 NeuroSAFE analyses. Of these, 170 (14.2%) had a positive and 1027 (85.8%) a negative surgical margin. In 96 of 1197 (8.0%) NeuroSAFE assessments, no biopsies had been performed on the ipsilateral side (Table 2). A positive posterolateral margin at NeuroSAFE was associated with higher ipsilateral biopsy tumour grade. Twenty-eight of 267 (10.5%) ipsilateral biopsy GG1 had a positive posterolateral NeuroSAFE margin compared to 69 of 338 (20.4%) GG2 and 60 of 261 (23.0%) GG ≥ 3 ($P < 0.001$). In addition, seven of 235 (3.0%) men without cancerous tissue at preceding ipsilateral biopsies and six of 96 (6.3%) men without ipsilateral biopsy had positive NeuroSAFE. CR/IDC was found in 262 of 1101 (23.8%) side-specific biopsies. NeuroSAFE was positive in 65 of 262 (24.8%) patients with CR/IDC and 99 of 839 (11.8%) without ($P < 0.001$). In total, 15 men had side-specific biopsies with EPE, 10 of whom (66.7%) had a positive surgical margin compared to 154 of 1086 (14.2%) without EPE at biopsy ($P < 0.001$). A similar relation was found for biopsy PNI, where 83 of 255 (32.5%) men with PNI had positive IFS compared to 81 (9.6%) without ($P < 0.001$). Furthermore, men with positive posterolateral NeuroSAFE margin had a higher median cumulative tumour length (17.2 versus 4.5 mm; $P < 0.001$) and a higher percentage of side-specific positive biopsies (80 versus 40%; $P < 0.001$) compared to those with a negative margin.

Table 1. Pre- and postoperative patient characteristics

Parameters	
Number of patients	624
Preoperative characteristics	
Median age (years, IQR)	68 (64–71)
Median PSA (ng/ml, IQR)	9.2 (6.3–13.4)
Clinical stage	
cT1	282 (45.2%)
cT2	246 (39.4%)
cT3	96 (15.4%)
Highest biopsy grade group	
1	103 (16.5%)
2	271 (43.4%)
3	177 (28.4%)
4	32 (5.1%)
5	41 (6.6%)
D'Amico classification	
Low	55 (8.8%)
Intermediate	347 (55.6%)
High	222 (35.6%)
Biopsy	
Systematic + target	170 (27.2%)
Only systematic	323 (51.8%)
Only target	131 (21.0%)
Median cumulative tumour length (mm) (IQR)	20.0 (10.5–35.8)
Median number of biopsies (IQR)	10.0 (8.0–12.0)
Median number of positive biopsies (IQR)	4.0 (3.0–6.0)
Median percentage of positive biopsies (IQR)	50.0% (36.2%–77.1%)
Postoperative characteristics	
Pathological stage	
pT2	359 (57.5%)
pT3	265 (42.5%)
pT3a	180 (28.8%)
pT3b	85 (13.6%)
Grade group (RP)	
1	50 (8.0%)
2	319 (51.1%)
3	185 (29.6%)
4	34 (5.4%)
5	36 (5.8%)
PLND	
pN0	326 (52.2%)
pN1	56 (9.0%)
pNx	242 (38.8%)

IQR, interquartile range; RP, radical prostatectomy.

PREDICTION OF POSITIVE POSTEROLATERAL NEUROSAFE MARGIN

In total, 480 men had undergone bilateral NeuroSAFE with preoperative biopsies on both sides resulting in 960 intraoperative margin analyses, 140 of which were positive. Bivariate logistic regression was performed to identify parameters associated with a positive posterolateral surgical margin (Table 3). Due to the limited number of events, EPE was omitted from analysis and GG was dichotomised as clinically significant (GG2 with CR/IDC or ≥ GG3 with or without CR/IDC) or insignificant (GG2 without CR/IDC or GG1). Predictive parameters for a positive NeuroSAFE margin at the left side included left-side biopsy PNI (OR = 2.98, 95% CI = 1.62–5.48; $P < 0.001$) and a left-side percentage of positive cores [odds ratio (OR) = 1.18, 95% confidence interval (CI) = 1.08–1.29; $P < 0.001$] (Table 3). Similarly, a positive NeuroSAFE margin at the right side was predicted by biopsy PNI and percentage of positive cores on the right side. PSA and presence of clinically significant prostate cancer at biopsy were not related to a positive NeuroSAFE. The AUC for prediction of a positive intraoperative posterolateral surgical margin was 0.76 (95% CI = 0.71–0.80) and the optimism-corrected AUC was 0.74.

Discussion

Nerve-sparing surgery is offered to prostate cancer patients to decrease the rate of urinary incontinence

Table 2. Preoperative side-specific characteristics of posterolateral NeuroSAFE surgical margins

	Negative NeuroSAFE n = 1027	Positive NeuroSAFE (incl. < 1 mm, GS3) n = 170	P-value
GG			
No biopsy	90 (8.8%)	6 (3.5%)	< 0.001
No PCA	228 (22.2%)	7 (4.1%)	
GG1	239 (23.3%)	28 (16.5%)	
GG2	269 (26.2%)	69 (40.6%)	
GG3	148 (14.4%)	43 (25.3%)	
GG4	24 (2.3%)	7 (4.1%)	
GG5	29 (2.3%)	10 (5.9%)	
CR/IDC			
CR/IDC−	740 (72.1%)	99 (58.2%)	< 0.001
CR/IDC+	197 (19.2%)	65 (38.2%)	
No biopsy	90 (8.8%)	6 (3.5%)	
EPE			
EPE−	932 (90.7%)	154 (90.6%)	< 0.001
EPE+	5 (0.5%)	10 (5.9%)	
No biopsy	90 (8.8%)	6 (3.5%)	
Perineural			
Perineural−	765 (74.5%)	81 (47.6%)	< 0.001
Perineural+	172 (16.7%)	83 (48.8%)	
No biopsy	90 (8.8%)	6 (3.5%)	
Biopsy			
No	90 (8.8%)	6 (3.5%)	0.010
Systematic	634 (61.7%)	97 (57.1%)	
Systematic + target	169 (16.5%)	33 (19.4%)	
Target	134 (13.0%)	34 (20.0%)	
Median cumulative tumour length (mm) (IQR)	4.5 (0–15.7)	17.2 (9.5–28.8)	< 0.001
Median number of biopsies (IQR)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	< 0.001
Median number of positive biopsies (IQR)	2.0 (0.0–3.0)	4.0 (2.0–5.0)	< 0.001
Median percentage of positive biopsies (IQR)	40.0% (12.5–80.0%)	80.0% (54.2–100.0%)	< 0.001
PSA	9.2 (6.3–13.0)	9.1 (6.1–14.5)	0.498
Clinical stage			
cT1	502 (48.9%)	60 (35.3%)	< 0.001
cT2	393 (38.3%)	91 (53.5%)	
cT3	132 (12.9%)	19 (11.2%)	

IQR, interquartile range; PSA, prostate-specific antigen; GG, grade group; CR/IDC, cribriform and/or intraductal carcinoma; EPE, extraprostatic extension.

Table 3. Bivariate logistic regression for prediction a positive posterolateral surgical margin at a left and right NeuroSAFE side

	NeuroSAFE left		NeuroSAFE right	
Variable	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
csPCa (left)				
No	Reference		Reference	
Yes	1.41 (0.80–2.45)	0.2	1.04 (0.57–1.91)	0.9
csPCa (right)				
No	Reference		Reference	
Yes	0.90 (0.50–1.61)	0.7	0.68 (0.38–1.21)	0.19
Perineural growth (left)				
No	Reference		Reference	
Yes	2.98 (1.62–5.48)	< 0.001	1.03 (0.45–2.37)	0.9
Perineural growth (right)				
No	Reference		Reference	
Yes	0.52 (0.23–1.19)	0.12	2.39 (1.26–4.52)	0.007
Percentage positive cores per 10% (left)	1.18 (1.08–1.29)	< 0.001	0.96 (0.87–1.06)	0.4
Percentage positive cores per 10% (right)	1.01 (0.93–1.10)	0.8	1.18 (1.07–1.30)	0.001
Preoperative PSA per doubling	1.02 (0.74–1.39)	0.9	1.10 (0.78–1.53)	0.6

OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen.

and erectile dysfunction after RP, but increases the risk of posterolateral positive surgical margins and biochemical recurrence.[1–4,8] Identification of predictive parameters for posterolateral surgical margin status could guide decision-making at the level of nerve-sparing surgery. In the current study, posterolateral surgical margins were positive in 170 of 1197 (14.2%) side-specific evaluations. Posterolateral surgical margins were more often positive in men with higher GG, CR/IDC, PNI and EPE at biopsy. At bivariate logistic regression, side-specific presence of PNI and increasing percentage of positive biopsies were independent predictors for a positive ipsilateral posterolateral margin, while biopsy GG, CR/IDC and PSA had no independent value. If validated, these findings could have added value in clinical decision-making on nerve-sparing surgery in individual patients.

In this study we included prostate cancer patients who had all undergone bilateral nerve-sparing surgery according to the NeuroSAFE technique, which resulted in standardisation of the initial nerve-sparing procedure. A few studies have shown that intraoperative NeuroSAFE results in a significant increase of nerve-sparing surgery at RP for prostate cancer.[12–14,20] Preisser *et al.* and Van der Slot *et al.* introduced NeuroSAFE as standard of care being offered to the vast majority of patients.[13,14] To our knowledge, no studies have yet investigated whether preoperative factors are associated with positive posterolateral surgical margin status using a standardised cohort that could be used for risk-based patient selection.

In general, suspicion of EPE is a relative contraindication for nerve-sparing surgery, because it could increase the risk of positive surgical margins. Preoperative risk assessment of EPE is based on clinical stage, MRI and nomograms, but its prediction is still inaccurate.[7] Most EPE nomograms provide an overall risk estimate of EPE regardless of its location, while adjacent posterolateral prostate sides are most relevant for preservation of nerve-bundles.[21,22] Other nomograms provide risk of side-specific EPE to guide patient selection for nerve-sparing.[23–25] Sayyid *et al.* showed that age, PSA, percentage of positive cores, highest core involvement and Gleason score were significant predictors of side-specific EPE.[25] Soeterik *et al.* found PSA density, clinical stage, MRI staging, GG3-5

and percentage of positive cores as significant predictors of EPE.[23] In our study, only ipsilateral PNI and percentage of positive biopsies were significant predictors of a positive posterolateral margin, while clinically significant prostate cancer, clinical stage and PSA did not have independent value. Discordances with previous studies can be explained by the fact that they investigated predictors for side-specific EPE, while our aim was to specifically analyse posterolateral margins adjacent to the nerve-bundles.

Biopsy PNI has been investigated extensively as a prognostic marker with variable outcomes. Two systemic reviews concluded that biopsy PNI is associated with positive surgical margins at RP as well as biochemical recurrence after operation and radiotherapy.[26,27] In a large multicentre study, Celik *et al.* showed that biopsy PNI was also significantly associated with a posterolateral margin status and nerve-sparing surgery, although surgical procedures were not standardised as in the current study.[28] It is not clear whether the risk of positive surgical margins is increasing when PNI is observed in more biopsies. This question is not easily solved, due to the large heterogeneity in the total number of systematic and/target biopsies taken in current practice and the confounding of positive biopsy extent. Biopsy tumour volume was also associated with a positive posterolateral surgical margin, but due to the significant variability in number of systematic and/or target biopsies taken it is difficult to implement tumour volume values in clinical practice. Taken together, we recommend that the presence or absence of PNI at biopsy should be included routinely in pathology reports, not only as a prognostic marker but also to support potentially clinical decisions at the level of nerve-sparing surgery.

To our knowledge, this is the first study investigating parameters being predictive for positive posterolateral margins adjacent to the periprostatic nerve bundles. Our findings can impact clinical decision-making regarding nerve-sparing surgery in general or application of intra-operative margin assessment with NeuroSAFE or fluorescence confocal microscopy.[29,30] The strengths of this study are the use of a large RP cohort initially undergoing standardised bilateral nerve-sparing surgery and detailed pathological biopsy review. A disadvantage is the variability of biopsy procedures between the different centres and the lack of MRI features in our analysis. Radiological findings were read by various radiologists in different referral centres and not reported in a structural manner. We postulate that inclusion of MRI features may further improve our model for preoperative selection of men for nerve-sparing surgery. Finally, our model was developed using data obtained by one prostate cancer network, and needs external validation.

Conclusion

In this study, 14.2% of prostate cancer patients undergoing bilateral nerve-sparing surgery had a positive posterolateral surgical margin adjacent to the periprostatic nerve-bundles. Ipsilateral PNI and percentage of positive biopsies were independent predictors of a positive posterolateral margin and could support decision-making regarding the level of nerve-sparing surgery. We recommend that the presence of PNI in biopsies is reported routinely and should be considered in decision-making regarding the level of nerve-sparing surgery.

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Conflicts of interest

The authors have no conflicts of interest.

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