

# The impact of nerve sparing on incidence and location of positive surgical margins in radical prostatectomy

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## What's known on the subject? and What does the study add?

Nerve sparing radical prostatectomy has been associated with increased risk of positive surgical margins due to the close anatomical relationship of the neurovascular bundle to the posterolateral aspect of the prostatic fascia.

Our study of 945 men who underwent radical prostatectomy by one experienced surgeon found no increased risk of positive surgical margins, whether the cancer was organ confined or extracapsular extension was present.

## OBJECTIVE

- To examine whether nerve-sparing surgery (NSS) is a risk factor for positive surgical margins (PSMs) in patients with either organ-confined prostate cancer or extracapsular extension (ECE).

## PATIENTS AND METHODS

- Clinicopathological outcome data on 945 consecutive patients treated with radical prostatectomy (RP) were prospectively collected.
- All patients underwent RP (bilateral, unilateral or non-NSS) by one surgeon between 2002 and 2007.
- Risk of PSMs and their locations with respect to NSS was determined by multivariate logistic regression analysis adjusting for preoperative risk factors for PSMs within pT2, pT3a and pT3b tumours.

## RESULTS

- Overall a PSM was identified in 19.6% of patients in an unscreened population with

mean prostate-specific antigen (PSA) level of 8.1 ng/mL.

- There was no significant difference in rates of PSMs between NSS groups on multivariate analysis ( $P = 0.147$ ).
- There was no significant difference in pT2 ( $P = 0.880$ ), pT3a ( $P = 0.175$ ) or pT3b ( $P = 0.354$ ) tumours.
- The only significant predictor of PSMs was preoperative PSA level (risk ratio 1.289,  $P = 0.006$ ).
- There was no significant difference in the location of PSMs except for the pT3a group, where the patients that had bilateral NSS were at higher risk of a posterolateral PSM ( $P = 0.028$ ).

## CONCLUSIONS

- With appropriate selection of patients, NSS does not increase the risk of PSMs, whether the cancer is organ confined or ECE is present.
- The adverse impact of the NSS procedure in the hands of an experienced surgeon is minimal and is a realistic compromise to obtain the increase in health-related quality of life offered by NSS.

## KEYWORDS

nerve sparing, positive surgical margins, radical prostatectomy

## INTRODUCTION

A positive surgical margin (PSM) in radical prostatectomy (RP) is defined as cancer at the inked surface of the specimen [1,2]. This can either result from surgical incision

into the capsule of organ-confined prostate cancer (OCC PSM) or be associated with extracapsular extension (ECE PSM) beyond the limits of surgical resection [3,4]. PSMs have been reported in 5–46% of cases [5].

Due to the close anatomical relationship of the neurovascular bundle to the posterolateral aspect of the prostatic fascia, nerve-sparing surgery (NSS) has often been suggested as a possible risk factor for PSMs [6,7]. Walsh and Donker [8] first described

the technique of NSS RP in which the neurovascular bundles are spared, increasing the chance of recovering erectile function and preserving urinary continence. Although the apex has been reported as the most common site of PSMs overall [9], Palisaar *et al.* [10] reported that lateral sites were the most common in the NSS group.

Several single-surgeon [11,12] and multicenter [13] studies have found no significant association between NSS and PSM after adjusting for other risk factors such as age, PSA level, Gleason grade, P stage and year of surgery. Billis *et al.* [4] did not find an increased risk of PSM with NSS in OCC or in the presence of ECE. However, NSS on the side of ECE has been implicated as a risk factor for PSMs by others [6,7].

In a large cohort of patients who underwent retropubic RP, we studied the effect of NSS (bilateral, unilateral and non-NSS) on the rates of PSMs, to determine the safety of the NSS procedure. Location and extent of PSMs were reviewed within pT2, pT3a and pT3b tumour subgroups.

## PATIENTS AND METHODS

Between 2002 and 2007, RP was performed by one surgeon (P.S.) at St Vincent's Hospital, Sydney, NSW, Australia on a consecutive series of 945 men with biopsy confirmed prostate cancer who had not received neoadjuvant hormonal or radiation therapy (Human Research Ethics Committee approval H00/088). Bilateral NSS (BNSS) was performed on 704 patients, unilateral NSS (UNSS) on 171 and non-NSS (NNSS) on 70. Clinical and pathological outcome data were collected prospectively and entered on our database. Preoperative PSA level was missing in 60 patients (6.3%). Clinical and pathological staging was defined using the 2002 American Joint Committee on Cancer guidelines.

### OPERATIVE TECHNIQUE

The neurovascular bundle was released in a retrograde manner and dependent on the circumstances incorporated an intrafascial dissection with or without a high fascial release. An interfascial technique was used if there were concerns about ECE. A NNSS approach was defined as a wide resection to

the pararectal fat from apex to bladder neck, after incising the levator fascia and prostatic fascia laterally. In patients where the nerve bundle underwent incremental excision in an interfascial plane, such that >50% of the bundle was considered to be preserved as assessed by the surgeon, it was defined as a NSS. UNSS was defined as wide resection of the nerve bundle on one side. All NSS data was recorded at the time of operation.

The decision of whether or not to perform NSS was based on several factors including age, clinical stage, biopsy characteristics, preoperative PSA level and potency status as well as patient preference. In each case the final decision for NSS was made intraoperatively by the surgeon.

All specimens were assessed by one pathologist at Douglass Hanly Moir Pathology, Sydney (W.D.) using a non-whole mount technique. Basal and apical sections were sliced in the postero-antero plane with an average of eight blocks. The remainder of the prostate was cut in transverse sections at 3–5-mm intervals. The prostate slices were subdivided and labelled into four quadrants (two anterior and two posterior) resulting in a mean of 32 blocks.

ECE was defined as tumour cells outside the contour of the prostatic capsule. A PSM was defined as any neoplastic cells at the inked margin, with focal being one small site and extensive being multiple sites. Mapping of PSMs was based on classification in apex, posterolateral, posterior, lateral, anterior and base locations.

Clinical and pathological characteristics in BNSS, UNSS and NNSS groups were defined by frequencies and the mean. Differences were assessed by anova for continuous variables and Pearson's chi-squared test for categorical variables. The risk ratios of PSMs were calculated using a binary logistic regression model adjusting for age, clinical stage, preoperative PSA level, Gleason biopsy score and percentage of positive biopsy cores both for the entire cohort and within each pathological stage. Risk ratios for PSMs with BNSS and UNSS were compared with NNSS as the referent group. Differences in location of PSMs were assessed by Pearson's chi squared test, with  $P < 0.05$  considered to indicate statistical significance.

## RESULTS

BNSS was performed in 704 patients (74.5%), UNSS in 171 (18.1%) and NNSS in 70 (7.4%). The mean (sd) PSA level was 8.1 (6.9) ng/mL. Preoperative and pathological patient characteristics are listed in Table 1. Patients who underwent BNSS were significantly younger and had lower clinical stages, Gleason biopsy scores, percentage of positive biopsy cores and preoperative PSA levels (all  $P < 0.001$ ) than those who underwent UNSS or NNSS. On pathology, BNSS patients had significantly lower pathological stage, ECE, seminal vesical invasion, Gleason RP score (all  $P < 0.001$ ) and lymph node invasion (LNI;  $P = 0.002$ ).

PSMs were identified in 185 patients (19.6%). PSMs were found in 128 (18.2%) of the BNSS, 36 (21.1%) of the UNSS and 21 (30.0%) of the NNSS groups. BNSS and UNSS both had a decreased risk of PSM compared with NNSS on univariate analysis, which trended towards significance ( $P = 0.051$ ). Multivariate logistic regression was done adjusting for known preoperative risk factors (Table 2). This revealed no significant difference in risk of PSM with BNSS or UNSS compared with NNSS (risk ratio [RR] 0.583,  $P = 0.112$  for UNSS and RR 0.639,  $P = 0.147$  for BNSS). The only significant risk factor for PSM was preoperative PSA level (RR 1.289 per one unit increase in sd,  $P = 0.006$ ), with the percentage of positive biopsy cores being of modest significance on univariate analysis ( $P = 0.049$ ).

In pT2 tumours, PSMs were recorded in 61 BNSS (11.4%), eight UNSS (12.5%) and four NNSS (14.3%) patients, in pT3a tumours there were PSMs in 51 BNSS (42.1%), 17 UNSS (29.3%) and six NNSS (28.6%) patients and in pT3b tumours PSMs were present in 16 BNSS (35.6%), 11 UNSS (28.2%) and nine NNSS (47.4%) patients. There was no significant difference in risk of PSM with NSS in pT2, pT3a or pT3b tumours on multivariate analysis after adjusting for confounding variables.

Mapping of surgical margins showed no significant difference in location of PSMs between the NSS groups ( $P = 0.092$ ). The observed sites from most to least common were apex occurring in 47.4%, posterolateral 28.4%, anterior 7.6%, base 7.6%, lateral 5.7% and posterior 3.3%. Within pathological stages, there was no significant

TABLE 1 Preoperative and pathological characteristics of patients stratified by NSS technique

Variable	NSS procedure, n (%)			P*
	BNSS	UNSS	NNSS	
Total no. patients	704	171	70	
Age at RP, years:				<0.001†
<50	55 (7.8)	3 (1.8)	0 (0.0)	
50–<60	317 (45.0)	55 (32.2)	18 (25.7)	
60–<70	297 (42.2)	100 (58.5)	40 (57.1)	
≥70	35 (5.0)	13 (7.6)	12 (17.1)	
Mean	59.6	62.3	64.2	
Preoperative PSA level, ng/mL:				<0.001†
<4.0	96 (13.6)	15 (8.9)	3 (4.3)	
4.0–9.9	436 (61.9)	92 (53.8)	39 (55.7)	
10.0–19.9	118 (16.8)	41 (24.0)	22 (31.4)	
>20.0	8 (1.1)	10 (5.8)	5 (7.1)	
unknown	46 (6.5)	13 (7.6)	1 (1.4)	
Mean	7.5	9.6	10.8	
Clinical stage:				<0.001
T1	406 (57.8)	57 (33.3)	25 (35.7)	
T2	295 (41.9)	111 (64.9)	45 (64.3)	
T3	3 (0.4)	3 (1.8)	0 (0.0)	
Gleason biopsy score:				<0.001
2–6	316 (44.9)	18 (10.5)	5 (7.1)	
7	354 (50.3)	126 (73.7)	55 (78.6)	
8–10	30 (4.3)	26 (15.2)	10 (14.3)	
% positive biopsy cores	36.4	48	52.3	<0.001†
Pathological stage:				<0.001
pT2	537 (76.3)	74 (43.3)	28 (40.0)	
pT3a	121 (17.2)	58 (33.9)	21 (30.0)	
pT3b	45 (6.4)	39 (22.8)	19 (27.1)	
pT4	1 (0.1)	0 (0.0)	2 (2.9)	
Gleason RP score:				<0.001
2–6	200 (28.4)	13 (7.6)	1 (1.4)	
7	470 (66.8)	118 (69.0)	53 (75.7)	
8–10	34 (4.8)	40 (23.4)	16 (22.9)	
LN status:				0.002
Positive	6 (0.9)	5 (2.9)	4 (5.7)	
Negative	350 (49.7)	147 (86.0)	53 (75.7)	
No LN dissection	348 (49.4)	19 (11.1)	13 (18.6)	

\*chi-squared test except where noted; †significance calculated by ANOVA.

difference in location of PSM for pT2 or pT3b tumours; however, patients with pT3a who underwent BNSS had a significantly higher incidence of posterolaterally located PSMs ( $P = 0.028$ ; Table 3).

There were 34 patients who had a PSM in the UNSS group (21.1%). Six of these had a PSM in the region of the neurovascular bundle (posterolateral) in the presence of pT3 disease. All six posterolateral PSMs in the UNSS group with pT3 disease were on the same side as the wide nerve resection. There were no PSMs on the ipsilateral side to the nerve preservation.

### DISCUSSION

The importance of patient selection for NSS is highlighted by the reduced incidence of PSMs in the BNSS group. This is probably accounted for by the more favourable preoperative characteristics of this group as a result of the selection process for the NSS procedure. The only significant predictor of PSMs amongst the preoperative characteristics was PSA level (RR 1.289,  $P = 0.006$ ), a well-recognised predictor of margin status [14]. The percentage of positive biopsy cores was of modest significance on univariate analysis ( $P = 0.049$ ), although this did not persist in the multivariate analysis. Several other studies have also failed to show a correlation of Gleason grade, clinical stage or age with margin status [14,15]. The present series of 945 consecutive patients commences at the 1750th open RP for the single surgeon involved. This is well into the plateau phase of the learning curve (>250 patients) as established by Vickers *et al.* [16] and clinicopathological outcomes should not be affected by the surgeon's case numbers.

In the present study, the association between NSS technique and margin status trended towards significance on univariate analysis ( $P = 0.051$ ), with those patients undergoing BNSS at decreased risk of PSM. However, on multivariate logistic regression, adjusting for age, clinical stage, PSA level, Gleason biopsy score and percentage of positive biopsy cores there was no significant difference in risk of PSM in the UNSS and BNSS groups compared with the NNSS group (RR 0.583,  $P = 0.112$  for UNSS and RR 0.639,  $P = 0.147$  for

	RR	95% CI	P	TABLE 2 Risk ratios for PSMs in multivariate binary logistic regression
Age at RP	0.997	0.869–1.145	0.971	
PSA level	1.289	1.076–1.545	0.006	
Gleason 2–6	1.000		Referent	
Gleason 7	0.891	0.602–1.318	0.563	
Gleason 8–10	1.224	0.611–2.450	0.569	
% positive biopsy cores	1.117	0.943–1.322	0.199	
Clinical stage T1	1.000		Referent	
Clinical stage T2	1.112	0.781–1.584	0.556	
NNSS	1.000		Referent	
UNSS	0.583	0.300–1.135	0.112	
BNSS	0.639	0.349–1.170	0.147	

TABLE 3 Location of PSMs in relation to pathological stage and NSS technique

	pT2				pT3a				pT3b			
	BNSS	UNSS	NNSS	P	BNSS	UNSS	NNSS	P	BNSS	UNSS	NNSS	P
Location PSM, n (%)												
Apex	41 (61.2)	6 (60.0)	3 (50.0)	0.871	20 (36.4)	9 (52.9)	4 (50.0)	0.028	6 (28.6)	3 (23.1)	6 (46.2)	0.515
Posterolateral	12 (17.9)	1 (10.0)	1 (16.7)		23 (41.8)	1 (5.9)	1 (12.5)		7 (33.3)	5 (38.5)	5 (38.5)	
Posterior	0	1 (10.0)	0		2 (3.6)	1 (5.9)	0		1 (4.8)	1 (7.7)	0	
Anterolateral	11 (16.4)	2 (20.0)	1 (16.7)		0	3 (17.6)	1 (12.5)		2 (9.5)	3 (23.1)	0	
Lateral	1 (1.5)	0	0		6 (10.9)	1 (5.9)	0		1 (4.8)	1 (7.7)	0	
Base	2 (3.0)	0	1 (16.7)		4 (7.3)	2 (11.8)	2 (25.0)		4 (19.0)	0	2 (15.4)	
Extent of PSM, n (%)												
Focal	52 (9.7)	7 (10.9)	4 (14.3)		41 (33.9)	13 (22.4)	5 (23.8)		10 (22.2)	8 (20.5)	5 (26.3)	
Extensive	9 (1.8)	1 (1.6)	0		10 (8.3)	4 (6.9)	1 (4.8)		6 (13.3)	3 (7.7)	4 (21.1)	

BNSS). This suggests that preoperative clinicopathological features predict margin status more accurately than NSS technique. Several other single-institutional [10–12,17] and multi-institutional [13] studies have also reported that NSS technique is not a risk factor for PSMs. Nelles *et al.* [13] found in 1018 men from five institutions that neither UNSS (odds ratio 0.99,  $P = 0.97$ ) nor BNSS (odds ratio 0.95,  $P = 0.82$ ) increased risk of PSM compared with NNSS, after adjusting for known preoperative risk factors.

While some studies have controlled for RP pathological features together with known preoperative risk factors in logistic regression [11,17], Palisaar *et al.* [10] performed a similar analysis to the present study, stratifying risk within pathological stages. They compared a retrospective cohort that would have been suitable for NSS with a current cohort, adjusting for stage migration and selection bias. In agreement with the present findings, they observed no significantly increased risk of PSM within pT2, pT3a or pT3b tumour subgroups. This confirms the safety of the NSS procedure, as with appropriate selection of patients there is no increased risk of PSMs with NSS whether the cancer is organ confined or ECE is present.

The reported range of PSMs in the contemporary literature is 11–38% [18], with the apex frequently noted as the most common location [9]. The present overall PSM rate of 19.6% compares favourably to published data particularly given the relatively high mean PSA level of the cohort. Karakiewicz *et al.* [19] in a large multi-institutional study of 5831 patients

reported a PSM rate of 26.7%. In the present study, the apex was the most common site (47.4%), followed by posterolateral (28.4%), a similar finding to Salomon *et al.* [9] and Sofer *et al.* [11] but in contrast to Billis *et al.* [4], who noted posterolateral as the most common site. The pT2 positive rate of 11.4% compared published ranges of 0–61% [12,19,20]. Most these pT2 PSM patients had a focally positive margin (52/61, 85%), with multiple studies finding a pT2 PSM had minimal effect on outcome [2,22] or a significantly better outcome than ECE PSM [21,23–27], particularly if focal rather than extensive [22,25].

Our OCC PSMs were most commonly seen at the apex, with no significant difference in location between NSS groups ( $P = 0.871$ ), a finding in keeping with previous studies [20,21,28]. Although patients with pT3a tumours were not at increased risk of a PSM overall, when a PSM did occur it was more likely to be posterolateral ( $P = 0.028$ ), a similar finding to Palisaar *et al.* [10]. The risk of a posterolateral PSM occurring in a pT3 tumour may be decreased in some studies, which have classified pT2 apical PSMs as pT3 [5], due to the difficulty in identifying the prostatic capsule at the apex. The prognosis of PSMs according to location is still disputed [5,29]. Although a higher risk of relapse has been reported with posterolateral PSMs [30], a recent multicentre study of 7160 patients found no significant difference in risk of biochemical recurrence with location of PSM [27]. Nevertheless, these findings reinforce the particular care that should be taken in dissecting the posterolateral aspect of the prostate if there is any suspicion of ECE.

When looking specifically at the safety of incremental vs wide resection of the neurovascular bundle, the present results suggest that an incremental approach is safe based on there being no significant difference in risk of PSMs with the NSS technique. This is further supported by examining the patients who had unilateral wide resection of the neurovascular bundle, where all six PSMs in the region of the neurovascular bundle (posterolateral) occurred on the side of the wide nerve resection. Similarly Palisaar *et al.* [10] did not find an increased risk of a PSM with NSS on the ipsilateral side to ECE. This suggests it is the extent of the disease rather than technique of NSS, which is important in risk of PSMs.

There are several limitations to the present study. The present study applies to NSS in the hands of an experienced surgeon and does not address variation between individual surgeons as a risk factor for PSM. However, consistent surgical technique and pathological review removes potential influence of these variables on margin outcome from the analysis. This is a retrospective study, with selection bias for the more favourable patients to undergo the NSS procedure. This was addressed by using a multivariate model adjusting for known risk factors for PSMs. We do not think that the non-whole mount technique used in pathological review was a limitation of the present study as the whole prostate was embedded and all margins evaluated in a similar fashion to whole mount technique. Biochemical relapse was not included in the results due to inadequate time of follow-up of the cohort (median 24.0 months).

In conclusion, with appropriate selection of patients, NSS does not increase the risk of OCC or ECE PSMs. Furthermore the adverse impact of NSS in the hands of an experienced surgeon is minimal and is a realistic compromise to obtain the increase in quality of life offered by the NSS procedure.

#### CONFLICT OF INTEREST

None declared.

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**Abbreviations:** PSM, positive surgical margin; RP, radical prostatectomy; OCC, organ-confined prostate cancer; ECE, extracapsular extension; (N)(U)(B)NSS, (non-) (unilateral) (bilateral) nerve-sparing surgery; LN(I), lymph node (invasion); RR, risk ratio.