

# Does nerve-sparing radical prostatectomy increase the risk of positive surgical margins and biochemical progression?

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## Abstract

**Background:** Since the introduction of nerve-sparing radical prostatectomy (NSRP), there have been concerns about the increased risks of positive surgical margins (PSM) and biochemical progression (BP). We examined the relationship of NSRP with PSM and BP using a large, mature dataset.

**Materials and Methods:** Patients who underwent RP for clinically localized prostate cancer at our center between 1997 and 2008 were identified. Patients who received neoadjuvant therapy were excluded. We examined the relation of NSRP to the rate of PSM and BP in univariate and multivariate analyses adjusting for clinical and pathological variables including age, pretreatment prostate-specific antigen (PSA) levels and doubling time, and pathological stage and grade.

**Results:** In total, 856 patients were included, 70.9% underwent NSRP and 29.1% had non-NSRP. PSM rates were 13.5% in the NSRP group compared to 17.7% in non-NSRP ( $P=0.11$ ). In a multivariate analysis, non-NSRP was performed in patients with a higher pathological stage (HR 1.95, 95% CI 1.25–3.04,  $P=0.003$ ) and a higher baseline PSA level (HR 1.04, 95% CI 1.01–1.08,  $P=0.005$ ). With a median follow-up of 41 months, BP-free survival was 88% for non-NSRP compared to 92% for the NSRP group (log rank  $P=0.018$ ); this difference was not significant in a multivariate Cox regression analysis (HR 0.54, 95% CI 0.28–1.06,  $P=0.09$ ).

**Conclusion:** When used in properly selected patients, NSRP does not seem to increase the risk of PSM and disease progression. The most effective way of resolving this issue is through a randomized clinical trial; however, such a trial is not feasible.

**Key Words:** Radical prostatectomy, nerve-sparing, positive surgical margins, biochemical progression

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## INTRODUCTION

Radical prostatectomy is the one of the main treatment options for clinically localized prostate cancer.<sup>[1]</sup> Nerve-sparing radical prostatectomy (NSRP) was introduced to help preserve potency postoperatively.<sup>[2]</sup> Since its introduction, there have been concerns with regards to the increased risk of having higher rates of positive surgical margins (PSM) when cutting through the capsule in order to preserve the neurovascular bundle. This concern is more evident in clinical stage T2 disease because these patients are the ones in whom NSRP is performed

more frequently and they are the ones in whom surgery alone is usually curative. Therefore, the consequence of PSM in this group of patients is more evident in terms of increasing their risk of biochemical progression.

Reports from different centers with different experiences have looked into the relation between NSRP and the risk of PSM as well as biochemical progression-free survival (BDFS). Most groups did not find that NSRP increased the risk of PSM and biochemical progression.<sup>[3-7]</sup> Given some inconsistencies in these findings, we sought to clarify this issue using a large

dataset with a long follow-up of patients treated for localized prostate cancer in our institution.

## MATERIALS AND METHODS

### Patients and follow-up

A retrospective, longitudinal cohort study was performed using our prospectively collected prostate cancer database. We identified all patients who underwent RP (either open or laparoscopic) by multiple surgeons at our institution for clinically localized prostate cancer (cT1/cT2) between the years 1997 and 2008. We excluded patients who received any form of neoadjuvant therapy and those whose surgical records did not detail which type of surgery was performed, i.e., NSRP versus non-NSRP. Patients who received adjuvant therapy were excluded from the analysis of the relation of PSM to BPFS as well.

We assessed various clinical variables including: age, preoperative PSA levels and PSA doubling time (<3 months versus  $\geq 3$  months) as well as the type of nerve-sparing surgery performed (NSRP versus non-NSRP). Pathological variables included pathological T-stage and Gleason total score as well as surgical margin status.

Patients were followed up postoperatively every 3 months for the first year, every 6 months for the second year, and annually thereafter. The follow-up consisted of clinic visits that included history and physical examination, IPSS and IIEF questionnaires at least once a year, and PSA testing. A median follow-up was defined as the last available follow-up of individual patients from the time of surgery until the last recorded visit and biochemical progression was defined as a postprostatectomy serum PSA level of 0.4 ng/ml or higher.<sup>[8]</sup>

### Surgical technique and pathology review

The surgery was performed either open or laparoscopically by multiple surgeons at our institution. The decision to preserve the neurovascular bundle was the individual responsibility of the operating surgeon. The preoperative potency, pathological features of the disease as well as intra-operative features were the key determinants of decision making. Nerve-sparing surgery was performed using standard techniques and frozen sections were not usually obtained. The pathological evaluation of the surgical specimens was done by dedicated urological pathologists using standard techniques and reporting.

### Statistical analysis

Patients were divided into two groups, NSRP and non-NSRP. The clinical and pathological features of each group were compared using chi-square tests for categorical variables and analysis of variance (ANOVA) for continuous variables.

Kaplan–Meier survival curves were used to calculate the BPFS for each of the two groups and the log rank test was used to compare differences in survival.

A logistic regression analysis was used to identify the independent predictors of having PSM and a multivariate Cox proportional hazards model was developed to compare the two groups as well as to identify which clinical and pathological features were significant predictors of BPFS. The proportional hazards assumption was tested using Schoenfeld residuals.

Statistical analyses were performed using SPSS software (version 16), and a *P* value of 0.05 was considered statistically significant.

## RESULTS

### Patient characteristics

A total of 991 patients were identified. Out of them 47 patients were excluded because they received neoadjuvant therapy and 88 patients were excluded because their operative records did not indicate which type of surgery they had (i.e., NSRP versus non-NSRP). A total of 856 patients were analyzed for the relation of PSM to NSRP. A further 79 patients were excluded because they received adjuvant therapy, leaving 777 patients for analysis of the relation of BPFS to NSRP. Mean age at surgery was 61.2 years (median 61, range 40-77 years). Out of the 856 patients, 618 patients (79.4%) had pT2 disease and 176 patients (20.6%) were pT3. Nerve-sparing surgery was performed in 607 patients (70.9%) while the remaining 249 patients (29.1%) underwent non-nerve-sparing surgery. The median follow-up was 41 months (mean 48.6, range 3–178 months).

In a univariate analysis [Table I], patients in the NSRP group compared to non-NSRP group were significantly younger (mean age 60.2 versus 63.4 years, respectively,  $P < 0.001$ ), had a significantly lower mean pretreatment PSA level (6.4 versus 8.6 ng/ml, respectively,  $P < 0.001$ ), had a significantly lower pathological T-stage ( $P = 0.02$ ), and lower grade disease ( $P < 0.001$ ). The pretreatment PSA-doubling time was not different between the two groups ( $P = 0.33$ ).

### Nerve sparing and surgical margins

As shown in Table I, the overall rates of PSM were 13.5% for the NSRP group compared to 17.7% for the non-NSRP group; this difference was not statistically significant in a univariate analysis ( $P = 0.11$ ). PSM rates for pT2 disease were 10.4% for the NSRP group compared to 15.7% for the non-NSRP ( $P = 0.07$ ), while PSM rates in pT3 disease were 26.3% and 24.1%, respectively ( $P = 0.76$ ). In a multivariate logistic regression analysis, independent predictors of having PSM were

pretreatment PSA (HR 1.04, 95% CI 1.01–1.08,  $P=0.005$ ), and pathological T-stage (HR 1.95, 95% CI 1.25–3.04,  $P=0.003$ ), while age, pretreatment PSA-doubling time, and the type of nerve-sparing surgery performed remained statistically nonsignificant in predicting the surgical margin status [Table 2].

**Nerve sparing and biochemical progression**

Kaplan–Meier analysis [Figure 1] showed a statistically significant difference in BPFS between NSRP (96.4%) and non-NSRP (87%) groups in a univariate analysis (log rank  $P=0.018$ ).

In a multivariate Cox proportional hazards regression analysis, independent predictors of BPFS were pretreatment PSA-

doubling time (HR 1.24, 95% CI 0.11–1.96,  $P=0.04$ ), pathological T-stage (HR 3.1, 95% CI 1.61–5.98,  $P=0.001$ ), and pathological Gleason score (HR 5.38, 95% CI 1.26–6.29,  $P=0.02$  for Gleason 7 and HR 10.5, 95% CI 2.10–15.25,  $P=0.004$  for Gleason 8 or higher), while the type of nerve-sparing surgery performed was not statistically significant (HR 0.54, 95% CI 0.28–1.06,  $P=0.09$ ) [Table 3].

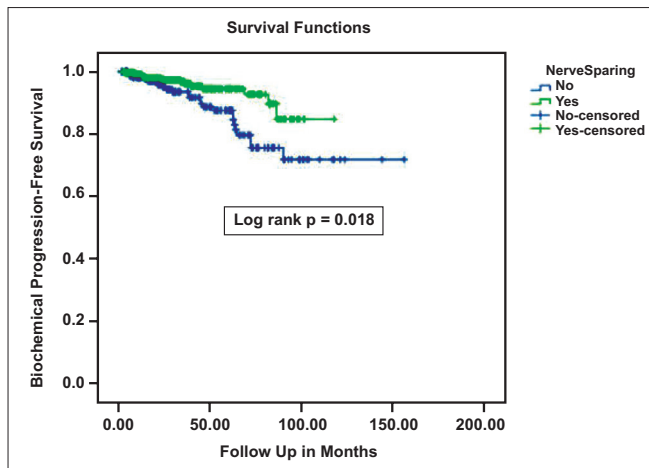
**DISCUSSION**

We examined the rate of PSM and BPFS in patients with clinical T1/T2 disease stratified by the type of nerve-sparing RP approach. Among 856 patients, the overall PSM rate for the NSRP group was 13.5% (10.4% for pT2 and 26.3% for pT3 disease) compared to 17.7% (15.7% for pT2 and

**Table 1: Differences in clinical and pathological features and rates of PSM between NSRP and non-NSRP patients**

	Type of surgery		P value
	NSRP	non-NSRP	
Number of cases (%)	607 (70.9)	249 (29.1)	
Age, mean (years)	60.2	63.4	< 0.001
Preoperative PSA, Mean (ng/ml)	6.4	8.6	< 0.001
< 3 months	73 (12.0)	37 (14.9)	0.33
> 3 months	135 (22.2)	61 (24.5)	
Unknown	399 (65.7)	151 (60.6)	
Pathological T-stage			
pT2	489 (80.6)	191 (76.7)	0.02
pT3	118 (19.4)	58 (23.3)	
Pathological Gleason score			
6 or less	226 (37.2)	43 (17.3)	<0.001
7	365 (60.1)	180 (72.3)	
8 or more	16 (2.6)	26 (10.4)	
PSM rates (%)			
Overall	(13.5)	(17.7)	0.11
pT2	(10.4)	(15.7)	0.07
pT3	(26.3)	(24.1)	0.76

NSRP - Nerve sparing radical prostatectomy; PSM - Positive surgical margin,  $P$ -value is based on univariate analysis, Figures in parentheses are in percentage



**Figure 1:** Kaplan–Meier survival curves showing the difference in biochemical progression survival between the nerve sparing and non-nerve-sparing groups

**Table 2: Clinical and pathological predictors of PSM by multivariate logistic regression analysis**

	HR	95% CI	P value
Age at surgery	0.99	0.96–1.02	0.79
Preoperative PSA	1.04	1.01–1.08	0.005
PSA doubling time			
> 3 months	Ref.		
< 3 months	0.94	0.50–1.74	0.84
Pathological T-stage			
pT2	Ref.		
pT3	1.95	1.25 – 3.04	0.003
Pathological Gleason score			
6 or less	Ref.		
7	1.65	1.00 – 2.71	0.08
8 or more	1.50	0.59 – 3.81	0.39
Type of surgery			
Non-NSRP	Ref.		
NSRP	0.88	0.57 – 1.36	0.57

PSM - Positive surgical margin; NSRP - Nerve sparing radical prostatectomy; Ref. - Referent

**Table 3: Clinical and pathological predictors of biochemical progression-free survival in the multivariate Cox proportional hazards model**

	HR	95% CI	P value
Age at surgery	0.97	0.93–1.02	0.28
Preoperative PSA	1.02	0.99–1.06	0.09
PSA doubling time			
> 3 months	Ref.		
< 3 months	1.24	0.11–1.96	0.04
Pathological T-stage			
pT2	Ref.		
pT3	3.1	1.61–5.98	0.001
Pathological Gleason score			
6 or less	Ref.		
7	5.38	1.26–6.29	0.02
8 or more	10.5	2.10–15.25	0.004
Type of surgery			
Non-NSRP	Ref.		
NSRP	0.54	0.28–1.06	0.09

PSM - Positive surgical margin; NSRP -Nerve sparing radical prostatectomy; Ref. - Referent

24.1% for pT3) in the non-NSRP group, with no statistically significant difference in univariate analysis. These rates are in keeping with published data by other groups with a PSM rate that ranges from 7% to 46%.<sup>[3-7]</sup>

With a median follow-up of 41 months, BDFS for the NSRP group was 96.4% compared to 87% for the non-NSRP group. This somewhat surprising finding may reflect better tumor characteristics of patients undergoing NSRP, as evidenced by this difference disappearing in a multivariate analysis adjusting for these characteristics. Importantly, however, BDFS was not worse in the NSRP group in multivariate analysis, with a 95% confidence interval effectively excluding an important excess risk. And in terms of follow-up, we believe that a median of 41 months is sufficient for biochemical progression, which usually develops during the first 2 years after surgery in the majority of cases.<sup>[9]</sup>

In a multivariate analysis, we found that neither the PSM rates nor the incidence of biochemical progression increased with performing NSRP compared to non-NSRP. Other groups reached similar conclusions.<sup>[3-7]</sup> And these findings suggest that when used in properly selected patients, NSRP does not seem to increase the risk of PSM and disease progression, whereas it is associated with important benefits in terms of potency preservation<sup>[2]</sup> and possibly urinary continence.<sup>[10]</sup>

Two important issues need to be highlighted when interpreting our results. First, patients who underwent NSRP had favorable clinical and pathological features compared to those who underwent non-NSRP. They were relatively younger, had lower pretreatment PSA levels, had lower pathological T-stage, and had lower Gleason sum scores. This represents a clear selection bias in favor of the NSRP group which is evident in all previous reports.<sup>[3-7]</sup> Second, our results represent data from a referral center with certain referral patterns and relatively low PSM rates that may not be generalizable to community-based settings. These issues could only be resolved through performing a multi-institutional randomized controlled trial, which we believe is not feasible due to clinical and ethical constraints. Therefore, a practical way of addressing this is through large, high-quality population-based studies including various types of patients, surgeons, and referral patterns.

On the other hand, the favorable clinical features of the NSRP group, along with intra-operative findings, are the tools used by most surgeons to help in the decision whether to perform nerve sparing or not. The fact that the outcomes of PSM and BDFS were not different between the NSRP and non-NSRP groups could be viewed from a different angle which indicates that these clinical features are adequate tools in selecting patients for nerve sparing.

Others have reported that individual surgeon experience and surgical volume may be an independent risk factor for PSM,<sup>[11]</sup> but our results may indirectly suggest otherwise. While our data included results from multiple surgeons with different levels of experience and through different stages of the learning curve, our PSM rates with or without NSRP remained relatively low and comparable to the published rates.<sup>[3-7]</sup>

Limitations of our study include the retrospective analysis with the inherited limitation of retrospective studies. However, our database is maintained and data are collected prospectively for patients with significant quality control measures.<sup>[12]</sup> We also did not have information regarding the location of PSM; however, the impact of the location of PSM on the outcome is controversial and it has been shown that it has no relation to the outcome (i.e., BDFS).<sup>[13,14]</sup>

## CONCLUSION

When used in properly selected patients, NSRP does not seem to increase the risk of PSM and disease progression, whereas it is associated with important benefits in terms of potency preservation and possibly urinary continence. Our findings are consistent with other clinical series that have examined this issue.

The most effective way of resolving this issue is through a randomized clinical trial; however, such a trial is not feasible and larger population-based studies are warranted.

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