J Chin Med Assoc

ORIGINAL ARTICLE

Effects of nerve-sparing procedures on surgical margins after robot-assisted radical prostatectomy

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Abstract

Background: Nerve-sparing (NS) techniques could potentially increase positive surgical margins after robot-assisted radical prostatectomy (RARP). Nevertheless, the available studies have revealed ambiguous results among distinct groups. This study purposed to clarify the details of NS techniques to accurately estimate their influence on margin status.

Methods: We studied RARPs performed by one surgeon from 2010 to 2018. Surgical margins were evaluated by the laterality and levels of NS techniques in site-specific prostate lobes. The multivariable analysis evaluated the effects of nerve-sparing procedures, combined with other covariate factors, on margin status.

Results: Overall, 419 RARPs involving 838 prostate lobes were analyzed. Notably, 181 patients (43.4%) had pT2-stage, and 236 (56.6%) had pT3-stage cancer. The PSM rates for patients who underwent unilateral, bilateral, and non NS procedures were 30.3%, 28.8%, and 50%, respectively ($p = 0.233$) or in stratification by pT2 ($p = 0.584$) and pT3 ($p = 0.116$) stage. The posterolateral PSM rates among site-specific prostate lobes were 10.9%, 22.4%, and 18.9% for complete, partial, and non NS techniques, respectively ($p = 0.001$). The partial NS group revealed a significant increase in PSM rate compared with the complete NS (OR 2.187, 95% CI: 1.19–4.03) and non NS (OR 2.237, 95% CI: 1.01–4.93) groups in site-specific prostate lobes.

Conclusion: Partial NS procedures have a potential risk of increasing the positive surgical margins rate than complete and non NS procedures do. Therefore, correct case selection is required before performing partial NS techniques.

Keywords: Margins of excision; Prostatic neoplasms; Prostatectomy; Robotic surgical procedures

1. INTRODUCTION

In 1982, Dr. Patrick Walsh intraoperatively identified the neurovascular bundle (NVB) and performed the first nerve-sparing (NS) prostatectomy. Postoperatively, the patient experienced an excellent recovery of sexual function and no prostate-specific antigen (PSA) elevation for 25 years.[1] Typically, NS procedures are performed on a minimal and tight dissection plane to resect all prostatic tumors without leaving positive margins.[2] Currently, the da Vinci robotic system provides the advantage of minimal trauma with excellent operative visions.[3] The availability of various NS techniques helps surgeons identify the landmark planes and perfect the procedures.[4] However, these procedures remain the most challenging techniques for urologists because they comprise several complex anatomic components. The positive surgical margins (PSM) rate is at risk of increasing during the initial learning curve of NS techniques.[5,6]

NS techniques can be modified through unilateral, bilateral, complete, partial, or non NS approaches according to the status of prostate cancer invasion.[7,8] Walz et al[4] compared several surgical plane classifications and indicated that the higher the level of NVB preservation, the higher the risk of PSM was. Nonetheless, various study designs regarding this aspect have yielded ambiguous results. Some studies have revealed a positive relationship between NS procedures and PSM rate, whereas others have reported contradictory results.[9–11] Therefore, the current study was conducted to ascertain the effects of NS techniques on PSM.

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Conflicts of interest: Dr. William J. Huang, an editorial board member at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 1131-1135.

Received March 28, 2022; accepted August 18, 2022.

doi: 10.1097/JCMA.0000000000000810.

2. METHODS

2.1. Data collection

We analyzed the robot-assisted radical prostatectomy (RARP) database from 2010 to 2018 at Taipei Veterans General Hospital. The institutional Review Board and Human Research Protection Center of Taipei Veterans General Hospital (No.: 2020-05-001BC) approved the protocol and agreed to waive the need for informed consent. De-identification and anonymization were properly done before analyzing the patients records. All study procedures involving data collection and management were in accordance with relevant guidelines and regulations. The indication for RARP was prostate cancer proven through prostate biopsy. Clinical data were collected for analysis, including patient characteristics, operation profiles, PSA level, and International Society of Urological Pathology (ISUP) grade for biopsy or radical prostatectomy (RP) specimens. The prostate specimens were total embedded and ink with different colors in each sites. PSMs were defined as the presence of tumor tissue on the inked surface of the specimen and were categorized into four groups based on the locations: posterolateral, bladder neck, apical and multifocal regions. Minimal two qualified pathologists interpreted final pathological reports. NS procedures were classified as unilateral, bilateral, and non NS techniques according to the general status of the margins in model 1, which included 419 patients. Each patient was recorded as having two specific prostate lobes with two margin statuses (marked only for posterolateral PSM) in model 2, which included 838 prostate lobes, wherein the influence of complete, partial, and non NS techniques on the PSM rate was analyzed. PSA recurrence is defined as PSA level ≥ 0.2 ng/mL in two separate measurements within 5 years after RP.

2.2. NS procedures

All RARPs were performed by one surgeon with more than 15 years of laparoscopic experience. For the cases with obvious extraprostatic extension (EPE) by magnetic resonance imaging (MRI), non NS procedures (extrafascial, following the dissection plane outside the levator ani fascia and posterior to the periprostatic fascia and Denonvilliers fascia) were performed. For the cases without EPE, complete NS procedures (intrafascial, following the plane along pseudocapsule and internal to periprostatic fascia) were done. In cases of suspicious EPE, partial (interfascial, following the plane of periprostatic fascia with incremental nerve preservation) were attempted based on PSA level and digital-rectal finding.[4] The procedure involved lifting the vas deferens gently to disclose the fascial planes near Denonvilliers' fascia. The posterior plane of dissection was developed following the planned NS strategy with the antegrade approach. The plane between the NVB and the ventral prostate was meticulously dissected anteriorly and laterally until the prostate was utterly exposed. The apex was dissected from the anteromedial components of the levator ani laterally, ensuring maximum preservation of the urethral stump.

2.3. Statistical analysis

IBM SPSS version 20 was used for statistical analysis. Pearson's chi-square and student's *t* test were used to assess categorical and continuous data, respectively. The predictive factors of the PSM rate were compared using multivariable logistic regression analysis with models 1 and 2.

3. RESULTS

3.1. Baseline characteristics

Overall, 419 robot-assisted radical prostatectomy (RARP) involving 838 prostatic lobes were analyzed. Baseline characteristics by study cohort were shown in Table 1. The overall PSM rate was 30.1% (126 of 419), stratified as 22% in pT2 (23 of 103) and 44% in pT3 (102 of 236). The specific PSM rate for the posterolateral region was 22.1%, and that of the multifocal regions was 7%. Ninety-five percent of patients received at least one type of NS procedure in RARP. The 3-year biochemical recurrence rate was higher in positive than negative SM groups (38.9 % vs 18.1%, $p < 0.001$).

3.2. Effects of NS procedures on margin status

Model 1 estimated the impact of NS laterality on PSM in RARP patients (Table 2). The PSM rates were 30.3%, 28.8%, and 50% for unilateral, bilateral, and non NS methods, respectively ($p = 0.233$). However, when the patients undergoing unilateral and bilateral NS were grouped, the PSM rate in this NS group was significantly lower than that of the non NS group (29.1% vs 50%; $p = 0.047$). Furthermore, the selection of unilateral, bilateral, and non NS procedures was not significantly different from the PSM rates based on stratification by pT2 or pT3 stage.

Model 2 evaluated the influence of NS levels on PSM in site-specific prostatic lobes (Table 2). The estimated average PSM rate in the posterolateral region was 13.7%, and those for complete, partial, and non NS approaches were 10.9%, 22.4%, and 18.9%, respectively, indicating significant differences ($p < 0.001$). Nevertheless, when the patients receiving partial and complete NS were combined into one group, no significant difference in PSM rate was observed between the NS and non NS groups (12.8% vs 18.8%, $p = 0.073$). Regarding laterality, both right-sided and left-sided NS procedures yielded a similar PSM rate (13.4% vs 14.1%, $p = 0.763$). For stage-pT2 tumors, the site-specific PSM rate was significantly different for complete, partial, and non NS techniques ($p = 0.011$). However, the PSM rates were similar when different levels of NS techniques were used for stage-pT3 cancer ($p = 0.336$).

3.3. Multivariable analysis for PSM

In multivariate analysis (Table 3), pT stage, PSA, and estimated blood loss were all significant predictors of the PSM rates in models 1 and 2. Notably, a higher cT stage was significantly associated with a lower PSM rate ($p = 0.026$; odds ratio [OR], 0.538), which was opposite of the effect of pT stage ($p < 0.001$; OR, 7.923) on the margin status in model 2. The unilateral and bilateral NS methods exhibited no significant differences in PSM rate compared with non NS methods in model 1. However, partial NS procedures had significantly increased the PSM rate compared with the non NS procedures ($p = 0.046$; OR, 2.237) and complete NS procedures ($p = 0.012$; OR, 2.187) in model 2.

4. DISCUSSION

Previous studies have reported an increased incidence of positive margins in posterolateral regions in patients undergoing NS procedures.[12,13] However, most studies have not analyzed the PSM rate based on prostate lobes when discussing the influence of NS procedures.[14–16] Soeterik et al evaluated 5148 prostatic lobes that underwent RARP by different surgeons and reported that NS procedure ($p = 0.005$; OR, 1.42) was an independent predictor of ipsilateral PSM.[17] Nevertheless, this study enrolled 14 surgeons from 4 hospitals whose surgical experience varied from 0 to 500 RARPs annually, and they had high variation in modified NS techniques. Moreover, the pathological reports were not limited to the posterolateral regions, and bias in correlation interpretation remained. Therefore, the strength of our study lies in its focus on the effects of NS on posterolateral PSM and stratification based on the prostate lobe involved, thereby reducing the interference of PSM locations.

Table 1

Baseline Characteristics of RARP Patients

Parameters	Mean (range)
Age, year	66 (43–85)
Body mass index, kg/m^2	25.2 (15.2–35.5)
PSA level, ng/mL	11.9 (1–89.8)
Prostate weight, g	35.8 (6–170)
PSA follow up, months	31.3 (2–60)
MRI clinical-stage, n (%)	
≤T2	299 (71.4)
>T2	120 (28.6)
ISUP grade at biopsy, n (%)	
≤3	327 (78.1)
>3	92 (21.9)
ISUP grade at RP, n (%)	
≤3	338 (80.6)
>3	81 (19.4)
Pathological T stage, n (%)	
T2	181 (43.4)
T3	236 (56.6)
Surgical margins, n (%)	
Positive, overall	126 (30.1)
Positive, posterolateral region	93 (22.1)
Positive, bladder neck region	17 (4.1)
Positive, apical region	35 (8.4)
Positive, multifocal regions	29 (7.0)
Nerve-sparing, n (%)	
Yes	399 (95.2)
No	20 (4.8)
3-year biochemical recurrence, n(%)	
Positive surgical margin	49 (38.9)
Negative surgical margin	53(18.1)
5-year biochemical recurrence, n(%)	
Positive surgical margin	73 (58.1)
Negative surgical margin	84 (28.6)

ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; RARP = robot-assisted radical prostatectomy; RP = radical prostatectomy.

Current findings reported postoperative stage-pT3 cancer ($p < 0.001$; OR, 7.923) was the most crucial parameter in predicting PSM after RARP. However, the PSM rate in the non NS group was significantly higher than in the NS group (29.1% vs 50%; $p = 0.047$) in model 1. Similarly, the PSM rate in the NS group decreased by 6% in the posterolateral region compared with the non NS group in model 2. This finding probably occurred because of the higher percentage of stage-pT3 than stage-pT2 cancer in the non NS group compared with the NS group (83% vs 17%, $p < 0.001$, model 2). This difference might have obliterated the influence of NS techniques. Notably, tumor biology, tumor stage, and intraoperative bleeding are all influential factors of PSM rates.[18] Nonetheless, high PSM rates have been reported in the posterolateral area, especially in high-risk pT3 diseases.[19,20] Eastham et al reported the presence of abundant neurovascular tissue in the posterolateral region, which might enhance the migration of tumor cells for local invasion. Furthermore, the PSA recurrence rate was higher (hazard ratio, 2.80) in cases with posterolateral positive margins than those with negative margins.[21]

Walz et al described modified NS surgical techniques that were performed using the complete, partial, and non NS by the different prostatic fascial planes.[4] The complete NS procedure was observed to offer total NVB preservation, whereas the non NS method enabled maximal excision of prostate tumors. It is reasonable to believe that the higher the preservation of NVB, the higher the risk of PSM.[4] Theoretically, complete NS techniques are feasible in pT2 (organ-confined) cancer, and a low PSM rate can be obtained by stringently selecting patients. However, if complete NS procedure is performed with a high risk of EPE, the oncological outcome might be worse.

Potdevin et al reported higher PSM rates in patients with pT3 disease who underwent RARP in the complete NS cases; however, no such findings were reported regarding the T2 stage.[9] Wang et al conducted a meta-analysis that compared complete with partial NS techniques and revealed that the complete NS technique was superior to the partial NS in terms of continence and potency recovery without worsening the PSM rate.[22] Secin et al noted that partial NS procedures increased the PSM rate by 11% in pT2 and 30% in pT3 disease compared with complete NS procedures. However, no differences were noted between complete and non NS procedures.[23] This study supports our findings related to side-specific prostate lobes; we observed that the partial NS group had a higher PSM rate than the complete NS group ($p = 0.012$; OR, 2.187). Moreover, the PSM rate in partial NS groups increase by 9% in pT2 stage and 7% in the pT3 stage compared with complete NS groups. However, no such significant differences were noted between the complete NS and non NS groups ($p = 0.949$).

First, for pT3 cancer, the reasons for patients undergoing partial NS procedure have the higher positive margin rate than complete NS groups are the decision-making based on preoperative imaging information wherein the surgeon intends to preserve partial NVB in PCa patients with a suspicion of EPE. As a result, PSMs occur in partial NS groups due to incomplete resection

Table 2

Comparison of Laterality and Levels of NS Procedures in 419 Patients (Model 1) Involving 838 Prostate Lobes (Model 2)

Model 1	Negative Margins	Positive Margins	
No. of Patients = 419	**N = 293**	**N = 126**	***p*[a]**
Overall, n (%)			0.233
BNS	220 (71.2)	89 (28.8)	
UNS	63 (70)	27 (30.3)	
NNS	10 (50)	10 (50)	
pT2 stage, n (%)			0.584
BNS	141 (87)	21 (13)	
UNS	14 (93.3)	1 (6.7)	
NNS	4 (100)	0 (0)	
pT3, n (%)			0.116
BNS	79 (53.7)	68 (46.3)	
UNS	48 (64.9)	26 (35.1)	
NNS	6 (40)	9 (60)	
Model 2	**Negative margins**	**Positive margins[b]**	
No. of lobes = 838	**N = 723**	**N = 115**	***p*[a]**
Overall, n (%)			0.001
CNS	529 (89.1)	65 (10.9)	
PNS	90 (77.6)	26 (22.4)	
NNS	104 (81.2)	24 (18.9)	
pT2 stage, n (%)			0.011
CNS	298 (98)	6 (2)	
PNS	33 (89.2)	4 (10.8)	
NNS	20 (95.2)	1 (4.8)	
pT3 stage, n(%)			0.336
C	230 (79.6)	59 (20.4)	
PNS	57 (72.2)	22 (27.8)	
NNS	83 (79.8)	21 (20.2)	

BNS = bilateral nerve-sparing; CNS = complete nerve-sparing; NNS = nonnerve-sparing; PNS = partial nerve-sparing; UNS = unilateral nerve-sparing.

[a]chi-square test.

[b]Only included positive surgical margins in posterolateral region in model 2.

Table 3

Multivariate Logistic Regression Model for Predicting Positive Margins

	Model 1 (N = 419)		Model 2 (N = 838)[a]	
Parameters	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**
PSA level	0.025	1.03 (1.004–1.056)	0.005	1.024 (1.007–1.042)
Estimated blood loss	0.001	1.003 (1.002–1.006)	0.003	1.002 (1.001–1.004)
cT3 stage (cT3 vs cT2)	0.0394	0.762 (0.407–1.424)	0.026	0.538 (0.312–0.928)
pT3 stage (pT3 vs pT2)	<0.001	7.893 (4.023–15.484)	<0.001	7.923 (3.806–16.493)
ISUP at biopsy >3 (4–5 vs 1–3)	0.072	1.868 (0.947–3.687)	0.221	1.457 (0.798–2.659)
ISUP at RP >3 (4–5 vs 1–3)	0.995	1.002 (0.468–2.067)	0.539	0.819 (0.433–1.548)
NNS (Referent)	–		–	
UNS	0.450	0.614 (0.174–2.173)		
BNS	0.440	1.636 (0.468–5.717)		
NNS (Referent)	–		–	
PNS			0.046	2.237 (1.014–4.933)
CNS			0.949	1.023 (0.513–2.038)
CNS(Referent)	–		–	
PNS			0.012	2.187 (1.188–4.029)
NNS			0.949	0.978 (0.491–1.949)

BNS = bilateral nerve-sparing; CNS = complete nerve-sparing; NNS = nonnerve-sparing; PNS = partial nerve-sparing; UNS = unilateral nerve-sparing.

[a]Only including posterolateral positive surgical margins in model 2.

of extraprostatic tumors. Second, for pT2 cancer, the mechanism of PSM is occasionally attributed to the incidental capsular incision during prostatic fascia plane dissection of NS which mainly occurs when large-volume tumors are localized near the capsule.[24] The adhesive periprostatic tissue induced by prostate biopsy causes "excessive peeling" of the prostate fascia, leading to capsule tearing and positive margins.[23] Thirdly, abundant vascular structures close to posterolateral region of the prostate easily cause hemorrhage during planes dissection. Intraoperative bleeding might mask visualization to clarify prostate margins and be also considered as an intraoperative predictor of PSM (p = 0.026, OR, 1.002). Lastly, it would be a high challenge for interfascial dissection during partial NS techniques, especially in unclear surgical field of view which potentially increase the chance of positive margins. Therefore, both preoperative image-based staging and surgical experiences are crucial in partial NS procedures.

Several studies have reported that a lower PSM rate is associated with an increase in surgical experience.[25,26] An extensive experience with open radical prostatectomy facilitated the avoidance of positive margins at the start of the RARP learning curve.[27] Similiarly, our surgeon had numerous surgical experience in laparoscopic urological surgeries over the past 15 years. Our study reported the PSM rate was constant at approximately 30% per 100 cases between 1 to 100 cases, 101 to 200 cases, 201 to 300 and 301 to 420 case series (p = 0.881) from the initial learning curve to the end of case collection. The data from a single experienced surgeon decreased the disparity in individualized surgical techniques and precisely estimated the effects of NS techniques on PSM.

Jeon et al reported a high PSM rate in posterior regions of the prostate for previous biopsy cases having positive cores in basal area.[28] The result gives us additional information to be more cautious in posterior fascia dissection during NS procedure. In clinical practice, nomograms can be used to predict the possibility of EPE and determine the extent of tumor resection.[29] Besides, a high-quality interpretation of MRI is useful in determining tumor locations inside the prostate, enabling surgeons to select the most suitable NS approach.[30] Moreover, our study noted intraoperative bleeding to be a risk factor of PSM. Therefore, the surgeon should prudently control bleeding intraoperatively to avoid visibility interference. NeuroSAFE, which is a newly developed technique to evaluate the intraoperative margin status through frozen pathology, has successfully increased the NS rate and reduced the PSM rate in RARP.[31] Nevertheless, the partial NS procedure is a highly skill-dependent technique that potentially increases the PSM rate. This unique technique is cautiously recommended, especially in cases of suspicion of T3 disease.

Biochemical recurrence is a key factor influenzing the long-term oncological outcumes.[32] Previous data shows the different correlations between PSM and BCR.[33,34] Our current data reveals a significant change in the PSM rate when choosing different levels of NS. Recently, Komori et al pointed out positive surgical margin in NS side, but not in non NS side was correlated with a rising risk of BCR during unilateral NS procedures.[35] According to the previous data reported in scientific reports, we further discover positive margins in posterolateral regions significantly increased 5-year BCR rate (p = 0.023). However, we find there was no significant difference in 5-year bichemcial recurrence rate between the NS and non NS groups (p = 0.094) in combination analysis with other covariate factors.[36] It is still the undetermined relationship between NS procedures and biochemical recurrence in the long-term consideration.

The limitations of our study include the relatively small sample size for retrospective analysis, especially for the cases without undergoing NS, which may induce a statistical bias. Moreover, the decision to proceed with different levels of NS procedures relies on the preoperative MRI interpretation and digital-rectal finding, which may result in subjective bias. Furthermore, tumor volume of RP specimens is not analyzed, which may be also associated with a high risk of PSM. Additionally, the extension of PSM and ISUP grade on the PSM are absent in current data, which may indicate a prognostic value in survival. Finally, the preoperative evaluation lacks of erectile function status, which is acknowledged to relate to postoperative outcomes and NS decision making. A future prospective multi-institution study can further investigate and confirm the effects of NS procedures on surgical margins.

ACKNOWLEDGMENTS

This work was supported by Dr. Hsiao-Jen Chung who provided the robotic surgical database from Taipei Veterans General

Hospital. We would like to convey huge thanks to the statistical support by Tao-Hsin Tung, working at the department of medical research and education in Cheng-Hsin General Hospital. This manuscript was edited by Wallace Academic Editing. The project was granted by the Taipei Veterans General Hospital (V111C-228).

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