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ORIGINAL RESEARCH

Long-term function and oncologic outcomes following nerve spare or wide resection during radical prostatectomy

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Cite as: Nayak AL, Pupulin S, Nagee A, et al. Long-term function and oncologic outcomes following nerve spare or wide resection during radical prostatectomy. *Can Urol Assoc J* 2026;20(8):265-71. http://dx.doi.org/10.5489/cuaj.9503

Published online March 30, 2026

Appendix available at cuaj.ca

ABSTRACT

INTRODUCTION: Nerve sparing during radical prostatectomy (RP) is associated with improved postoperative erectile function and urinary continence but may increase the risk of positive surgical margins. This study sought to compare the long-term outcomes of patients treated with nerve spare (NS) compared to wide resection (WR).

METHODS: A historical cohort of consecutive patients was reviewed. A standardized surgical approach of lobe-specific NS or WR was performed. The primary outcome was treatment failure, defined as prostate-specific antigen (PSA) recurrence (PSA ≥0.2 ng/mL) or receipt of postoperative radiation. Secondary outcomes included time to metastases, urinary continence, and erectile function.

RESULTS: Of 193 consecutive patients, 123 (63%) received bilateral NS, 36 (19%) received unilateral NS, and 34 (18%) bilateral WR. Patients undergoing any NS had lower preoperative PSA, tumor stage, and grade group compared to WR patients (all $p<0.05$). Adjusting for these variables, the risk of treatment failure (PSA ≥2 ng/mL or postoperative radiation) was increased in patients who underwent NS compared to WR (hazard ratio [HR] 2.46, 95% confidence interval [CI] 1.25-4.83). Urinary continence recovered more quickly after NS, but by 24 months post-RP, this difference was not statistically significant (bilateral NS: risk ratio [RR] 1.10, 95% CI 0.95-1.30; unilateral NS: RR 1.01, 95% CI 0.82-1.24). Postoperative erectile function was better in patients receiving unilateral or bilateral NS (unilateral: 21%, bilateral: 59%, WR: 0%).

CONCLUSIONS: NS during RP was associated with higher risk of treatment failure, but better functional outcomes compared to WR. These results indicate that NS presents a tradeoff of outcomes that must be matched to individual patient's values and preferences.

INTRODUCTION

Radical prostatectomy (RP) requires a balance between complete cancer removal and preservation of patient quality of life. While it may seem intuitive that the decision to pursue nerve sparing (NS) during RP should be based on cancer risk, baseline sexual function, and patient preference, the evidence for a direct association between periprostatic dissection technique and outcomes such as positive surgical margins is often counterintuitive.[1–7]

In multiple systematic reviews of the NS approach and positive surgical margin risk, no randomized trials of NS have been conducted.[1-3] In observational studies, NS was counterintuitively associated with decreased risk of positive surgical margins (pT2 pooled risk ratio [RR] 0.92, 95% confidence interval [CI] 0.75–1.13; pT3 pooled RR 0.83, 95% CI 0.71–0.96).[1] This surprising result may reflect a selection bias beyond pathologic stage (i.e., volume of cancer) or because non-NS surgery was not necessarily an extra-fascial wide dissection (i.e., variations of lateral/extra-fascial dissection). In fact, the risk of bias assessment for all included studies in these systematic reviews was high, where the majority of studies did not report or correct for clinical T stage, biopsy Gleason score, and initial prostate-specific antigen (PSA).[3] Furthermore, the definition of NS was heterogenous or poorly defined within studies.

Similar shortcomings may have also skewed patient-impactful outcomes, such as treatment failure (cancer recurrence, metastases, or

KEY MESSAGES

- Oncologic and functional long-term outcomes of a consecutive cohort of patients undergoing radical prostatectomy by a single surgeon were assessed in this study.
- Patients treated with nerve-sparing prostatectomy experienced more treatment failures compared to wide-resection prostatectomy.
- Patients treated with nerve-sparing prostatectomy experienced better postoperative sexual function and earlier recovery of continence, although the rate of continence is not statistically different than patients treated with wide-resection prostatectomy in long-term followup.
- These data can allow better counseling of patients preoperatively to incorporate patient values and preferences into treatment decisions.

need for salvage treatment). Based on published literature, NS prostatectomy is associated with similar rates of biochemical recurrence (BCR) as non-NS surgery, and even reduced risk of metastatic disease and decreased need for additional treatments;[1,3-5] however, patients undergoing non-NS surgery had more aggressive disease in these cohorts[4,5] and these conclusions have been based on unadjusted analyses and are prone to confounding by indication.[3]

It is also possible that wide dissection during RP does not achieve the desired oncologic outcomes theorized. To address this issue, we previously performed a consecutive patient cohort study of patients with preplanned surgical dissection. In that study, adjusting for grade, stage, and PSA, wide resection was associated with a reduction in lobe-specific positive surgical margins (adjusted RR 0.43, 95% CI 0.26–0.71, p=0.001).[8] The purpose of this study was to assess long-term patient-important functional and oncologic outcomes.

METHODS

This historical cohort study reviewed consecutive patients by a single surgeon (RHB) between August 2010 and November 2014 at one tertiary care centre (The Ottawa Hospital, Ottawa, ON, Canada). The surgical margin outcomes of these data were published in the *Canadian Urological Association Journal* in 2015, with the promise to update long-term, patient-important outcomes when followup was mature. Baseline patient factors and disease characteristics were collected from clinical notes, radiology reports, and pathology reports in the electronic medical record using standardized abstraction. All patients completed baseline functional assessment using the expanded prostate cancer index (EPIC, EPIC 24, or EPIC-CP). Institutional ethics review board approval was obtained.

Surgical technique

The study included consecutive patients with prostate cancer treated with bilateral NS, unilateral NS, or wide resection (WR) during RP. The surgical techniques for NS and WR have been previously described.[8] Wide resection involved resection posterior to Denonvillier's fascia and incision on the perirectal fat lateral to the neurovascular bundles. Indication for dissection technique was determined based on preoperative cancer risk, erectile function, and patient values/preferences.

Followup

Patients were assessed three, six, 12, and 24 months, then annually postoperatively until discharged from followup (usually between five and 10 years if disease-free and functionally well).

Outcomes

The primary outcome of this study was treatment failure, which was a composite outcome of PSA recurrence or receipt of postoperative radiation therapy. PSA recurrence was defined as at least one PSA concentration ≥0.2 ng/mL. Postoperative radiation could be either adjuvant (PSA <0.02 ng/mL at the time of radiation) or salvage (PSA ≥0.02 ng/mL at the time of radiation).

PSA recurrence and postoperative radiation were also examined individually as secondary outcomes. Secondary outcomes also included occurrence of distant metastases, which was determined by review of radiographic imaging and verified by clinical progress and response to systemic treatment to confirm accurate designation of metastatic prostate cancer. Radiographic imaging was only performed in the presence of PSA recurrence. Continence was defined as no pad usage over 24 hours (0 on the EPIC urinary continence domain). Erectile function was defined as erections sufficient for penetration (3 on the EPIC erectile function domain), with or without the use of phosphodiesterase type 5 (PDE-5) inhibitors.

Table 1. Patient demographics and baseline disease characteristics stratified by nerve-spare status

	Wide resection	Unilateral NS	Bilateral NS	p
Total, n (%)	34 (17.6)	36 (18.7)	123 (63.7)	
Age, mean ± SD (yrs)	66.8±5.1	62.5±5.2	60.6±6.5	<0.0001
Preoperative PSA (µg/L)	11.5±10.8	10.2±8.6	7.7±5.1	0.01
Preoperative erectile function, n (%)				<0.0001
EPIC = 0/1 (None at all)	12 (35.2)	1 (2.8)	5 (4.1)	
EPIC = 2 (Firm enough for masturbation only)	11 (32.4)	7 (19.4)	11 (8.9)	
EPIC = 3 (Firm enough for intercourse)	11 (32.4)	28 (77.8)	107 (87.0)	
Biopsy grade group, n (%)				<0.0001
1	2 (5.9)	2 (5.6)	41 (33.3)	
2	13 (38.2)	11 (30.6)	59 (48.0)	
3	5 (14.7)	11 (30.6)	15 (12.2)	
4	6 (17.7)	7 (19.4)	6 (4.9)	
5	8 (23.5)	5 (13.8)	2 (1.6)	
Clinical T-stage, n (%)				<0.0001
T1c	10 (29.4)	6 (16.7)	58 (47.2)	
T2	16 (47.1)	16 (44.4)	63 (51.2)	
T3	8 (23.5)	14 (38.9)	2 (1.6)	
Pathologic T-stage, n (%)				0.002
pT2	12 (35.3)	13 (36.1)	78 (63.4)	
pT3a	17 (50.0)	17 (47.2)	39 (31.7)	
pT3b	5 (14.7)	6 (16.7)	6 (4.9)	
Pathologic N-stage, n (%)	5 (14.7)	2 (5.6)	2 (1.6)	0.04
RP grade group, n (%)				<0.0001
1	1 (2.9)	0 (0)	12 (9.8)	
2	17 (50.0)	9 (25.0)	78 (63.4)	
3	6 (17.7)	22 (61.1)	28 (22.8)	
4	1 (2.9)	1 (2.8)	2 (1.6)	
5	9 (26.5)	4 (11.1)	3 (2.4)	
Cancer volume, mean ± SD (cc)	8.2 ± 9.8	7.1 ± 5.8	4.7 ± 4.8	0.006
Prostate volume, mean ± SD (cc)	50.0±21.6	42.6 ±20.9	38.3±21.9	0.02
Surgical margin, n (%)				0.04
Negative	29 (85.3)	30 (83.3)	83 (67.5)	
Positive	5 (14.7)	6 (16.7)	40 (32.5)	
RP modality, n (%)				0.03
Open	11 (32.4)	10 (27.8)	18 (14.6)	
Robotic	23 (67.6)	26 (72.2)	105 (85.4)	

EPIC: Expanded Prostate Cancer Index Composite; NS: nerve spare; PSA: prostate-specific antigen; RP: radical prostatectomy; SD: standard deviation.

Statistical analyses

Descriptive analyses were used to compare baseline patient and disease characteristics. Student's t-tests were used for comparison of continuous values, and Chi-squared was used for categorical variables. For all time-to-event outcomes, the date of RP was considered time-zero. Kaplan-Meier curves were generated, censoring at last followup or death. Associations between nerve dissection technique (i.e., NS [either bilateral or unilateral] compared with WR) and oncologic outcomes were adjusted for preoperative PSA, grade group, and pathologic T-stage. For functional outcomes, univariable and multivariable analyses were performed using log binomial regression at each time point (three, six, 12, and 24 months). Statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, U.S.).

RESULTS

The cohort consisted of 193 patients, of which 34 (18%) underwent WR and 158 (82%) received uni-

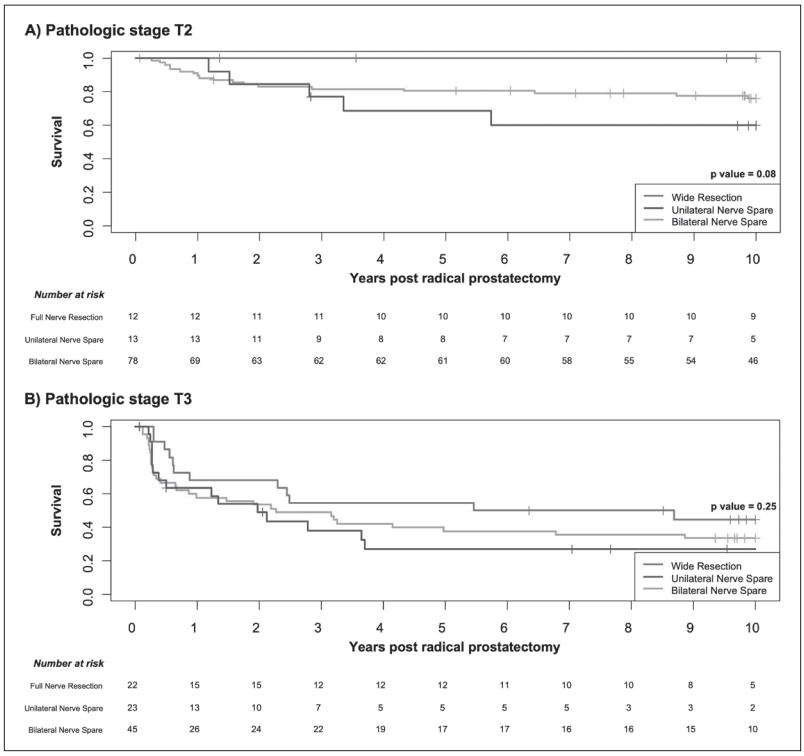

Figure 1. Treatment failure-free survival (prostate-specific antigen and radiation-free) after radical prostatectomy, stratified by pathologic T-stage: A) pathologic stage T2; B) pathologic stage T3.

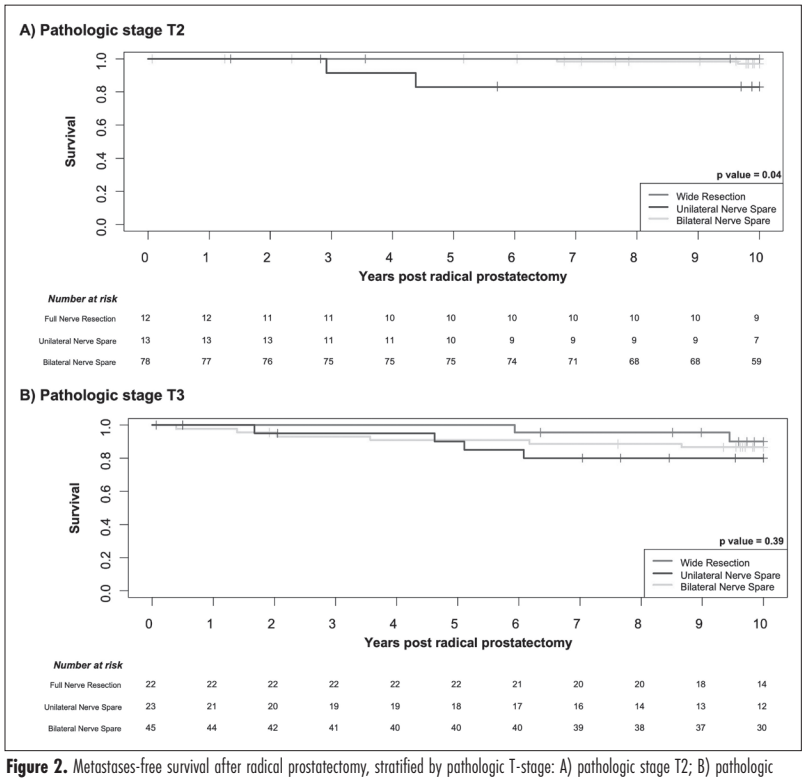

Figure 2. Metastases-free survival after radical prostatectomy, stratified by pathologic T-stage: A) pathologic stage T2; B) pathologic stage T3.

lateral (36; 19%) or bilateral (121; 63%) NS. Patient and disease characteristics are summarized in Table 1 and Supplementary Table 1 (available at *cuaj.ca*). Patients who received WR had a higher risk disease compared with those who underwent NS surgery, with higher preoperative PSA, pathologic tumor stage, grade group, cancer volume, and lymph node metastases (all $p<0.05$).

Median followup was 10.6 years (interquartile range 9.7–11.6). No patients were lost to followup during the study period but some patients were censored if discharged to a primary care physician without BCR. Figures 1 and 2 demonstrate unadjusted Kaplan-Meier survival curves for treatment failure and metastases, stratified by pathologic T stage. Time to PSA recurrence and radiation are presented in Supplementary Figures 1 and 2 (available at *cuaj.ca*). In general, without adjusting for prognostic factors, patients undergoing NS procedures had worse BCR-free survival, radiation-free survival, and metastases-free survival; however, not all the associations were statistically significant.

When adjusted for pathologic T-stage, grade group, and preoperative PSA, bilateral and unilateral NS surgeries were associated with increased risk of treatment failure vs. WR (RR 2.56, 95% CI 1.26–5.20; RR 2.32, 95% CI 1.10–4.93, respectively) (Table 2). These associations were also seen when assessing PSA recurrence and receipt of radiation independently.

Nerve-sparing procedures were associated with increased risk of BCR compared with WR (bilateral NS RR 2.67, 95% CI 1.23–5.28; unilateral NS RR 1.57, 95% CI 1.13–5.84) (Table 2). Patients were more likely to receive adjuvant or salvage radiation therapy after bilateral and unilateral NS compared to WR (RR 3.42, 95% CI 1.44–8.13; RR 3.23, 95% CI 1.38–7.54, respectively) (Table 2). Eighteen patients developed metastases during the study period (95.7%, 95% CI 91.6–97.8) free from recurrence at five years; 91.1% (95% CI 85.9–94.4) free from recurrence at 10 years). Nerve-spare patients had a higher incidence of metastases compared to WR, but this was not statistically significant (RR 1.61, 95% CI 0.34–7.63; RR 3.83, 95% CI 0.79–18.5, respectively) (Table 2).

Patients who underwent NS surgery, particularly bilateral NS surgery, were more likely to be continent after surgery (Figure 3). This difference was more apparent closer to the time of surgery; by 24 months postoperatively, NS patients had similar continence to those with WR. On multivariable analysis, no statistically significant differences in postoperative continence were observed between groups at 24 months post-

operatively (bilateral NS: RR 1.10, 95% CI 0.95–1.30; unilateral NS: RR 1.01, 95% CI 0.82–1.24) (Figure 3).

At 12 months and 24 months post-RP, NS procedures were associated with improved erectile function vs. WR (associations not estimable; Figure 4). Patients who underwent bilateral NS surgery had better erectile function postoperatively compared to unilateral NS, with some improvement over time.

DISCUSSION

Radical prostatectomy can be performed using a WR or NS approach. Contrary to several previous publications, this study found that patients treated with WR were associated with fewer treatment failures, fewer BCR, decreased need for adjuvant/salvage radiation, and lower risk of metastases compared to NS approaches. Similar to previous publications, patients treated with WR experienced substantially worse postoperative sexual function and slightly worse urinary continence. Thus, these data highlight the careful considerations required when discussing and planning RP with patients.

Oncologic outcomes

Previous studies have reported NS during RP did not increase the risk of positive surgical margins or BCR compared with non-NS RP;[1,3] however, important prognostic factors (e.g., biopsy grade group, clinical stage, and preoperative PSA) were lower in the NS compared to non-NS groups.[2] In a large cohort of patients undergoing open RP, WR has been associated with a higher risk of positive surgical margins and worse survival; however, with adjustment for clinical and pathologic variables, these differences are not statistically significant.[9] Contemporary cohorts of high-risk patients undergoing robotic prostatectomy also do not show an increased risk of BCR; however, no adjusted analyses were performed.[5,10,11] This suggests that unadjusted confounding may partly explain the lack of association with outcomes reported in the literature.

In the current study, the surgical approach was associated with clinically meaningful differences in BCR and adjuvant/salvage radiation. Notably, patients undergoing WR had improved oncologic outcomes, even without adjusting for substantially higher baseline risk with higher preoperative PSA, tumor stage, and tumor grade. As more patients with higher-risk disease are being offered and choosing surgical intervention, these findings support the use of WR in appropriately selected and informed patients.[12]

Table 2. Oncologic outcomes after radical prostatectomy adjusted for pathologic tumor stage, Gleason grade group, and preoperative PSA

Comparison	Adjusted HR (95% CI)			
	Treatment failure[a]	PSA recurrence[b]	Radiation[c]	Metastases
Bilateral NS vs. WR	2.56 (1.26–5.20)*	2.67 (1.23–5.82)*	3.42 (1.44–8.13)*	1.61 (0.34–7.63)
Unilateral NS vs. WR	2.32 (1.10–4.93)*	2.57 (1.13–5.84)*	3.23 (1.38–7.54)*	3.83 (0.79-18.5)
Any NS vs. WR	2.46 (1.25–4.83)*	2.63 (1.25–5.54)*	3.32 (1.49–7.38)*	2.23 (0.51–9.85)

*p<0.05. [a]Defined as biochemical recurrence or receipt of adjuvant/salvage radiation. [b]At least one PSA value ≥0.2 ng/ml after prostatectomy. [c]Receipt of adjuvant or salvage radiation after prostatectomy. CI: confidence interval; HR: hazard ratio; NS: nerve spare; PSA: prostate-specific antigen; WR: wide resection.

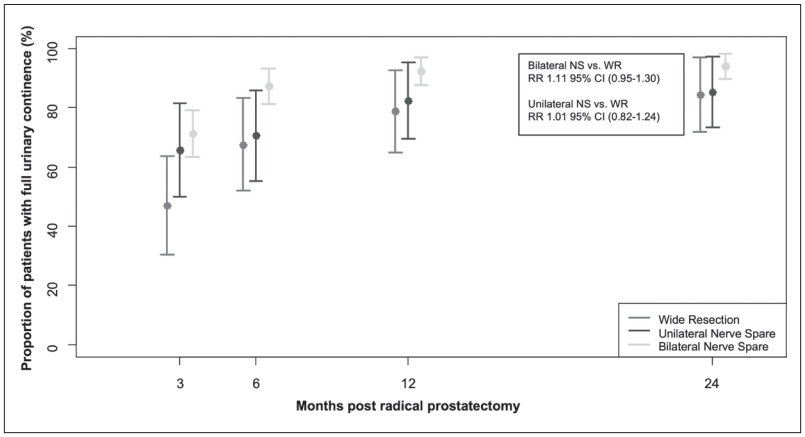

Figure 3. Recovery of urinary continence after radical prostatectomy.

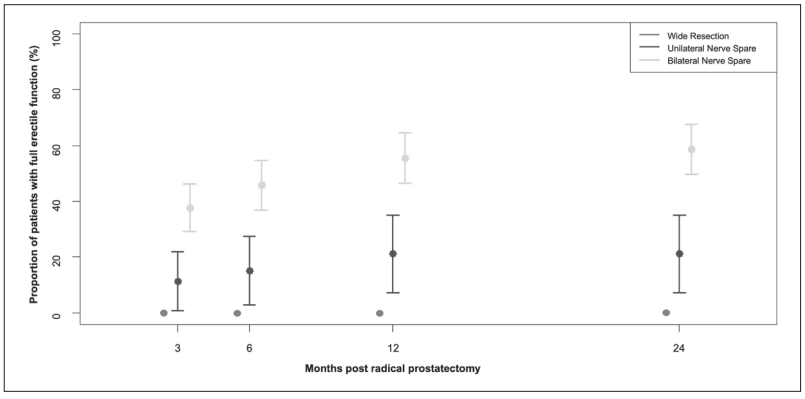

Figure 4. Recovery of erectile function after radical prostatectomy.

Crude survival curves suggested worse oncologic outcomes in the unilateral NS group in comparison to bilateral NS and WR groups, although this was not statistically significant. This finding may be due to chance or may reflect the differences in patients between groups, where those undergoing bilateral NS had more favorable pathology compared to those undergoing uni-

lateral NS and WR. Unilateral or intrafascial NS may be requested by some patients with higher-risk disease for the potential benefits of improved urinary continence and recovery of erectile function.

A challenge when comparing studies is that the extent of resection in non-NS surgery is not commonly described.[1] A small, retrospective study detailing fascial dissection showed intra-fascial NS is associated with shorter recurrence-free survival than other variations of lateral/extra-fascial dissections in pT2 tumors.[13] Here, the results show a wide resection technique involving resection posterior to Denonvillier's fascia onto the perirectal fat lateral to the neurovascular bundles is associated with better oncologic outcomes compared with NS prostatectomy.

Urinary continence

In WR prostatectomy, urinary continence is significantly worse in the early months of recovery; however, continence improves with time. By two years following surgery, continence in WR patients approaches that of the NS patients (WR: 84%; unilateral NS: 85%; bilateral NS: 94%). A similar urinary continence recovery trend stratified by NS procedures has been demonstrated in other studies.[14] In a large cohort of men undergoing RP in a tertiary care center (38% non-NS RP), patients undergoing non-NS surgery were less likely to achieve early postoperative continence but by 17 months postoperative, 94% of the entire cohort were fully continent.[15] Even in older, longitudinal cohort studies, meta-analysis demonstrated NS RP was associated with early (<6-week postoperative) urinary continence but no differences were observed at 12 or 24 months from surgery.[16]

The mechanisms by which NS prostatectomy better preserve urinary continence are likely multifactorial. Closer dissection around the prostate likely allows for better preservation of the bladder neck and periurethral tissues. Urodynamic evaluation of patients following prostatectomy have shown better preservation of urethral closing pressures in patients who had NS surgery compared to non-NS surgery.[17]

Erectile function

The major perceived benefit of NS prostatectomy is postoperative erectile function. In this cohort, 48% of patients undergoing unilateral or bilateral NS surgery were potent following surgery, consistent with other published cohorts, where good postoperative erectile function ranges from 32–82%.[9-11,18-20] As expected, bilateral NS surgery has improved outcomes at all time points compared with unilateral NS (60% and 21% recovery of erectile function at two years, respectively).

Intraoperative electrostimulation of the posterior prostate and medial aspect of the prostate pedicles elicits similar cavernosal pressures as the typical posterolateral neurovascular bundle, demonstrating a more complex periprostatic nerve network contributes to erectile function.[21] It is possible that unilateral dissection posterior to Denonvillier's fascia results in the significant decrease in erectile function in unilateral WR patients compared to bilateral NS patients. In addition to neurovascular bundle sparing, greater preservation of posterior tissues may further improve potency outcomes in patients for whom erectile function is a priority.

Strengths and limitations

This study has several strengths. Surgeries were performed by a single surgeon, allowing for a consistent surgical approach to WR and NS. Additionally, nearly all patients in this center undergo prostate biopsy with dedicated radiologists, allowing for standardization in biopsy technique and preoperative pathology findings. The use of a consecutive cohort of patients in all prostate cancer risk categories limits the risk of selection bias. Finally, the models created in this study adjust for important patient and disease factors.

The generalizability of this study is unknown, as WR/non-NS techniques may differ between surgeons and institutions. This cohort predominantly underwent robotic prostatectomy, therefore may not be applicable to smaller-volume centers without access to robotic approaches. There were also no predetermined, defined criteria for which patients underwent NS or WR, which can introduce unknown confounders and limit reproducibility in other populations.

CONCLUSIONS

From this single-surgeon experience, NS RP is associated with increased risk of PSA recurrence and adjuvant/salvage treatment compared to patients undergoing WR RP; however, NS was also associated with earlier recovery of continence and better long-term erectile function. These results indicate that a NS technique presents a tradeoff of patient outcomes that must be matched to an individual patient's values and preferences.

COMPETING INTERESTS: Dr. Lavallée has participated in advisory boards for Abbvie, Astellas, Bayer, Ferring, Knight, Merck, and Tolmar. Dr. Morash has participated in advisory boards for Abbvie, Astellas, Johnson & Johnson, Knight, TerSera, and Tolmar. Dr. Cagiannos has participated in advisory boards for and received honoraria from Abbvie, Astellas, Knight, Janssen, TerSera, and Tolmar. The remaining authors have no relevant conflicts of interest to report.

This paper has been peer reviewed

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