Prostate International 9 (2021) 119–124

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Research Article

Width of spared neurovascular bundle after robot-assisted laparoscopic prostatectomy in patients with prostate cancer: is it a reliable factor for predicting postoperative sexual outcome?

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ARTICLE INFO

Article history:
Received 29 January 2020
Received in revised form
22 July 2020
Accepted 26 July 2020
Available online 17 August 2020

Keywords:
Erectile dysfunction
Nerve tissue
Prostatic neoplasms
Prostatectomy

ABSTRACT

Purpose: To investigate the relationship between the width of spared neurovascular bundle (NVB) measured during robot-assisted laparoscopic prostatectomy and postoperative sexual outcomes.
Methods: Patients with localized prostate cancer with erectile hardness score ≥2 ($N = 105$) who underwent NVB-sparing robot-assisted laparoscopic prostatectomy were included. Patients were divided into three groups [first (Q1) vs. second and third (Q2-3) vs. fourth (Q4) quartile] according to width of spared NVB measured with a flexible ruler after prostate removal. Preoperative and postoperative sexual function was evaluated according to erectile hardness score and Expanded Prostate Cancer Index Composite questionnaires.
Results: The proportion of patients with postoperative erectile hardness score ≥2 at postoperative 6 months was as follows: 38.9% (Q1), 48.6% (Q2–3), and 83.3% (Q4) ($P = 0.016$). The preoperative/postoperative 6-month sexual function score was 40.7/16.9 (Q1), 48.1/19.0 (Q2–3), and 51.2/28.1 (Q4). Postoperative sexual function was significantly associated with preoperative sexual function in Q4 ($P = 0.006$) and Q2–3 ($P = 0.030$) but not in Q1. On multivariate analysis, the width of spared NVB was a significant predictor for postoperative 6-month erectile hardness score ≥2. Limitation includes selection bias and short follow-up duration.
Conclusions: Not only the performance but also the degree and quality of NVB sparing thought to be important for postoperative sexual function. Measurement of the width of NVB during surgery could be an easy intraoperative method for assessing the quality of NVB sparing.

1. Introduction

Although prostate cancer is mainly diagnosed in the elderly, its incidence has rapidly increased in younger men [1, 2]. In these young prostate cancer patients, radical prostatectomy (RP) tends to be more commonly offered because of the superior oncological outcomes [3]. However, the quality of life (QoL) could be more severely deteriorated after surgery in these young patients [4]. Among several variables consisting QoL, RP-induced erectile dysfunction (ED) thought to be one of the most serious life-long problems for these patients. RP has been reported to show worse postoperative sexual function outcomes than active surveillance or radiotherapy [5].

Currently, nerve-sparing RP is considered a safe option for preserving sexual function in patients with localized prostate cancer. Nevertheless, previous studies reported that >70% of patients developed ED after RP [6], although at least 50% of patients who underwent RP expected recovery of their sexual function to the preoperative level [7]. After the introduction of robotic-assisted laparoscopic prostatectomy (RALP), sexual function outcomes were reported to improve compared with the outcomes of open surgery [6]. However, ED was reported to develop postoperatively in a considerable number of patients despite RALP [8], and in other words, not only the surgical methods (open RP vs. RALP) but also the degree of nerve sparing could be crucial for postoperative sexual function outcomes.

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https://doi.org/10.1016/j.prnil.2020.07.005

Accordingly, the quality of nerve sparing during RP has been a topic of investigations, and several methods for evaluating the quality of nerve-sparing surgery have been proposed [9-11]; however, these techniques were not easily applicable because of their subjectivity and technical difficulties. Evaluating the quality of nerve-sparing surgery during surgery could be helpful for predicting postoperative sexual function if the technique is objective and easy to use. Moreover, it may be helpful for clinicians to perform nerve-sparing surgery more carefully. Owing to technical improvements, the spared neurovascular bundle (NVB) could be precisely visualized and measured during RALP. Therefore, we hypothesized that postoperative sexual function might be influenced by the width of spared NVB (wNVB). In this regard, we evaluated the effects of wNVB on postoperative sexual function, as measured using patient-reported questionnaires.

2. Materials and Methods

2.1. Study Population

This study was approved by our institutional review board. Consecutive patients with biopsy-confirmed prostate cancer who underwent RALP by a single surgeon (C-S Kim) at our institute from July 2014 to December 2015 were primarily eligible for this study. Before the study period, this single surgeon performed over 300 cases of nerve-sparing RALP. Among 234 patients, those who underwent neoadjuvant hormone therapy, with preoperative prostate-specific antigen level $\geq$20 ng/mL, with locally advanced disease on preoperative magnetic resonance imaging (MRI), with suspicious lymph node and/or distant metastasis, with biopsy Gleason score $\geq$8, who did not underwent bilateral nerve-sparing surgery, and with erectile hardness score (EHS) < 2 were excluded. Finally, 105 patients with prostate cancer with preoperative EHS $\geq$2 were included in the analysis.

2.2. Evaluation and management

In addition to tumor visibility on preoperative MRI, prostate size and the area of NVB were also measured with preoperative MRI. The NVB area on MRI was measured at 5 and 7 o'clock positions of the prostate and summated. We defined NVB area on MRI as the area surrounded by NVB components on MRI [12] on both sides of prostate in the imaging with the largest prostate. During RALP, both endopelvic fasciae were incised to measure spared NVB, and the dorsal vascular complex was ligated at the beginning of the procedure. Prostatectomy was performed via an antegrade approach [13], and NVB sparing was generally performed via interfascial technique. Electrocauterization was not used during NVB sparing, and bleeding control was performed with 4-0 chromic and metal clips. After prostate removal, wNVB was measured at the distal, mid, and proximal NVB using a flexible ruler (Supplementary figure 1). wNVB was defined as the summated value (wNVB = 38.0 ± 6.3 mm) of the following widths at several points. Mean width of NVB at several points were as follows: right distal, 4.4 ± 1.1 mm; left distal, 5.1 ± 1.2 mm; right middle, 5.3 ± 1.5 mm; left middle, 6.1 ± 1.6 mm; right proximal, 8.4 ± 2.2 mm; and left proximal, 8.6 ± 2.0 mm. In general, routine usage of daily postoperative phosphodiesterase-5 inhibitor (PDE5i) was recommended for sexually active patients although postoperative PDE5i was prescribed after sufficient consultation. Median duration of postoperative PDE5i usage was 6.1 months (interquartile range: 2.8–6.9 months).

2.3. Outcomes

Sexual function was evaluated preoperatively and at 3, 6, and 12 months postoperatively using the EHS, which was reported as a simple, reliable, and valid scoring system for assessing the rigidity of the penis in clinical practice and clinical trials [14], and Expanded Prostate Cancer Index Composite (EPIC) questionnaires. Moreover, the proportion of patients taking phosphodiesterase type 5 (PDE-5) inhibitors was also evaluated. Preoperatively and at 3, 6, and 12 months postoperatively, the response rate of the EHS questionnaire was 100% (105 of 105), 92.4% (97 of 105), 67.6% (71 of 105), and 31.4% (33 of 105), respectively, whereas that of the EPIC questionnaire was 99.0% (104 of 105), 76.2% (80 of 105), 72.3% (76 of 105), and 32.4% (34 of 105), respectively. Although potency was generally defined as EHS $\geq$3 (the ability to have an erection sufficient for intercourse), EHS $\geq$2 was also considered to indicate the presence of erectile function. The primary outcome of this study was the recovery of EHS $\geq$2 after surgery and the secondary outcome was changes in sexual function and bother score. Because of the low response rate of questionnaire at 12 months after surgery, we determined to evaluate the postoperative EHS at postoperative 6 months. The mean and each score of the EPIC questionnaire were converted to a 100-point scale and compared. Overall sexual function score was defined as the mean score of nine sexual function–related questions [15]. Overall sexual bother score was defined as the mean score of four sexual bother–related questions. Changes in overall sexual function and bother score was calculated and compared according to the wNVB.

2.4. Statistical analysis

Patients were divided into three groups according to wNVB [first (Q1) vs. second and third (Q2–3) vs. fourth (Q4) quartile]. The wNVB was 21–34 mm in Q1, 35–41 mm in Q2-3, and 42–59 mm in Q4. The patient and tumor characteristics were compared using Pearson's Chi-squared test and Student's t test. The proportion of patients with EHS $\geq$ 2, sexual intercourse, and use of a PDE-5 inhibitor preoperatively and at 3, 6, and 12 months postoperatively were interpreted and compared. Changes in overall sexual function and bother scores at all time points were also compared among groups. Moreover, the relationship of preoperative overall sexual function/bother score and its components with the postoperative score was presented with the correlation coefficient (r). The relationship between clinical characteristics and wNVB was also analyzed. Univariate and multivariate analyses were performed to assess the impact of wNVB on sexual function at 6 months after surgery. Sexual function at postoperative 6 months was selected for the final outcomes based on the response rate. All statistical analyses were performed with IBM SPSS Statistics version 21 (IBM Corporation, Armonk, NY, USA). A P value < 0.05 was considered indicative of a statistically significant between-group difference.

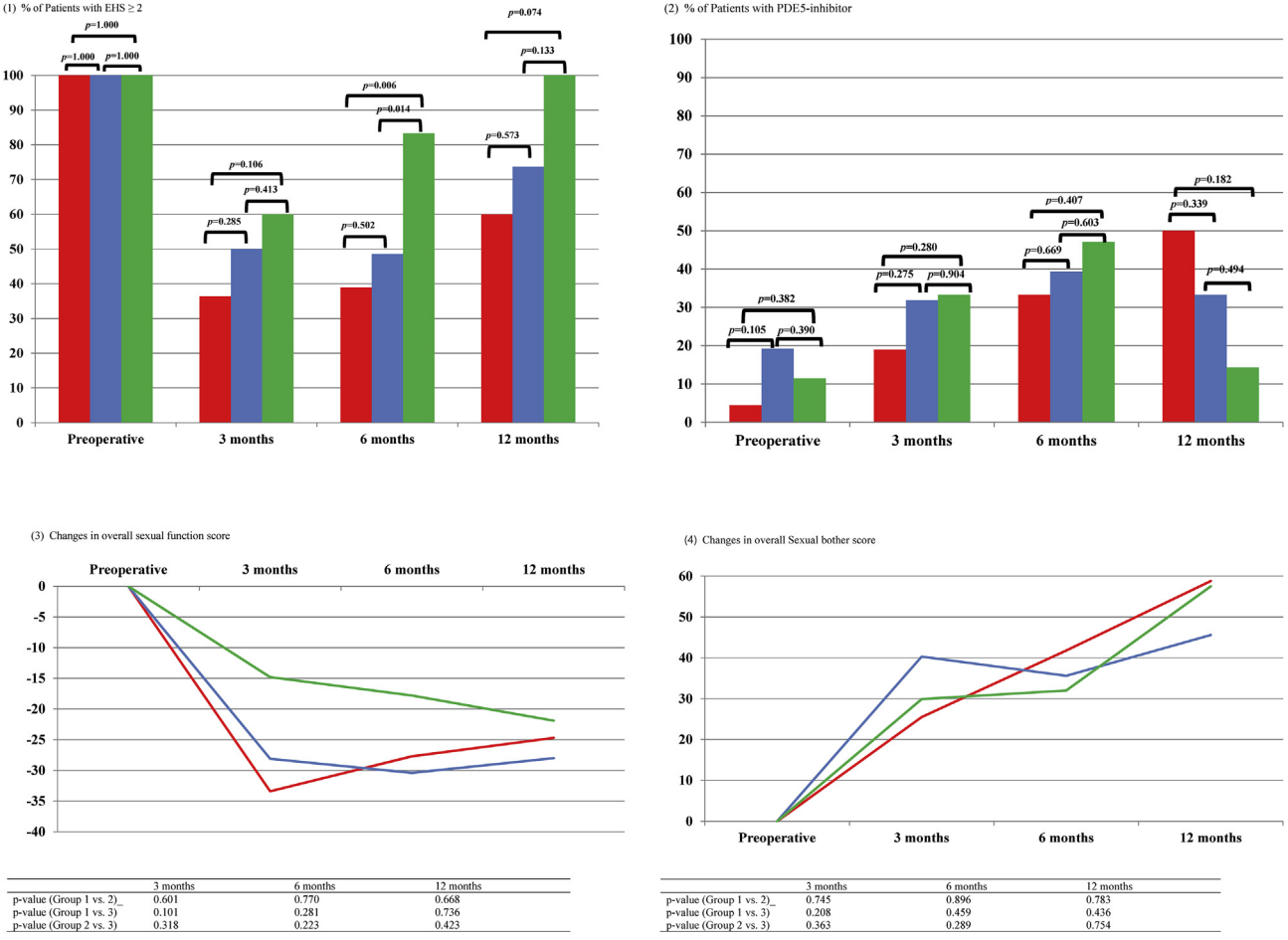
3. Results

There was no difference in patient characteristics, including mean age at surgery (64.0 vs. 64.1 vs. 62.2 years, $P = 0.422$), mean preoperative testosterone level (4.8 vs. 4.4 vs. 5.1 ng/mL, $P = 0.142$), and mean prostate size (36.9 vs. 34.8 vs. 34.5 cm^3, $P = 0.776$) (Table 1). The mean preoperative prostate-specific antigen level was also similar (6.2 vs. 5.7 vs. 5.4 ng/mL, $P = 0.584$). Moreover, there was no difference in pathologic characteristics, including pathologic tumor stage ($P = 0.497$), Gleason score ($P = 0.525$), and percentage tumor volume ($P = 0.884$). Among study population, 25 patients (23.8%) had pathologically advanced disease, defined as pathologic T3a or greater, and pathologic Gleason score was 7 or

Table 1
Patient and tumor characteristics

	Q1	Q2–3	Q4	*P*
Number of patients, *n*	24 (22.9)	55 (52.4)	26 (24.8)	
Age at surgery, y ±SD	64.0 ± 5.5	64.1 ± 6.3	62.2 ± 7.7	0.422
Body mass index, kg/m^2 ±SD	24.2 ± 2.1	24.9 ± 2.4	24.8 ± 2.9	0.444
Diabetes, *n* (%)	3 (12.5)	8 (14.5)	3 (11.5)	0.925
Hypertension, *n* (%)	9 (37.5)	17 (30.9)	3 (11.5)	0.089
PSA level, ng/mL ±SD	6.2 ± 2.6	5.7 ± 2.7	5.4 ± 2.6	0.584
Testosterone level, ng/mL ±SD	4.8 ± 1.3	4.4 ± 1.4	5.1 ± 1.8	0.142
Prostate size, cm^3 ±SD	36.9 ± 13.7	34.8 ± 13.1	34.5 ± 13.4	0.776
Biopsy Gleason score, *n* (%)				0.775
6 or less	8 (33.3)	23 (41.8)	10 (38.5)	
7	16 (66.7)	32 (58.2)	16 (61.5)	
% Tumor volume, cm^3 ±SD	9.6 ± 9.6	9.5 ± 10.3	8.3 ± 12.2	0.884
Findings on MRI, *n* (%)				0.645
Nonvisible	2 (8.3)	2 (3.6)	1 (3.8)	
Locally confined	22 (91.7)	53 (96.4)	25 (96.2)	
Pathologic stage, *n* (%)				0.497
pT2	18 (75.0)	40 (72.7)	22 (84.6)	
pT3a	5 (20.8)	13 (23.6)	2 (7.7)	
pT3b	1 (4.2)	2 (3.6)	2 (7.7)	
Pathologic Gleason score, *n* (%)				0.525
6 or less	7 (29.2)	12 (22.2)	8 (30.8)	
7	15 (62.5)	40 (74.1)	18 (69.2)	
8 or greater	2 (8.3)	2 (3.7)	0 (0.0)	
Postoperative PDE5i, *n* (%)	17 (70.8)	42 (79.2)	22 (84.6)	0.488

MRI, magnetic resonance imaging; PDE5i, phosphodiesterase-5 inhibitor; PSA, prostate-specific antigen; SD, standard deviation.



	3 months	6 months	12 months
p-value (Group 1 vs. 2)	0.601	0.770	0.668
p-value (Group 1 vs. 3)	0.101	0.281	0.736
p-value (Group 2 vs. 3)	0.318	0.223	0.423

	3 months	6 months	12 months
p-value (Group 1 vs. 2)	0.745	0.896	0.783
p-value (Group 1 vs. 3)	0.208	0.459	0.436
p-value (Group 2 vs. 3)	0.363	0.289	0.754

Fig. 1. Preoperative and postoperative sexual function (Red: Q1, Blue: Q2-3, Green: Q4).

Table 2
Correlation between preoperative and postoperative sexual function and bother scores

	Q1		Q2–3		Q4	
	r	*P*	*r*	*P*	*r*	*P*
Sexual function subscales						
Overall	0.017	0.940	0.373	0.030	0.580	0.006
Level of sexual desire	0.414	0.062	0.200	0.258	0.325	0.163
Ability to have an erection	−0.330	0.156	0.219	0.229	0.478	0.033
Ability to reach orgasm (climax)	0.062	0.807	0.385	0.030	0.438	0.054
Usual quality of erections during the last 4 wk	0.000	1.000	0.333	0.051	0.157	0.508
Frequency of erections during the last 4 wk	0.229	0.318	0.402	0.019	0.575	0.006
Awakened in the morning/night with an erection during the last 4 wk	0.460	0.036	0.021	0.905	0.368	0.100
Sexual activity during the last 4 wk	0.043	0.853	0.079	0.652	0.342	0.129
Sexual intercourse during the last 4 wk	0.013	0.954	0.446	0.007	0.604	0.004
Overall rate of ability to function sexually during the last 4 wk	−0.344	0.127	0.386	0.022	0.446	0.043
Sexual bother subscales						
Overall	0.013	0.957	0.217	0.211	0.440	0.046
Problem in level of sexual desire	0.124	0.593	0.229	0.194	0.386	0.093
Problem in ability to have an erection	0.099	0.676	0.126	0.492	0.264	0.260
Problem in ability to reach orgasm (climax)	−0.111	0.651	0.337	0.059	0.385	0.094
Overall rate of problem in sexual function during the last 4 wk	−0.157	0.497	0.043	0.804	0.479	0.028

greater in 77 patients (73.3%). The resection margin was positive for prostate cancer in 6 patients (25.0%) in Q1, 26 (47.3%) in Q2–3, and 11 (42.3%) in Q4 ($P = 0.178$). Postoperative PDE5i was used in 78.6% of patients and there was no difference in PDE5i usage according to the groups.

The preoperative EHS was ≥2 in all patients and ≥3 in 101 patients (96.2%). After surgery, 49.5% at postoperative 3 months, 54.9% at 6 months, and 72.7% at 12 months had EHS ≥2. At postoperative 3 months, the proportion of patients with EHS ≥2 was slightly higher in Q4 compared to Q1 (36.4% vs. 60.0%, $P = 0.106$), although statistical significance was not achieved (Fig. 1). At postoperative 6 months, patients with EHS ≥2 were significantly common in Q4 compared to those with Q1 (38.9% vs. 83.3%, $P = 0.006$) and Q2–3 (48.6 vs. 83.3%, $P = 0.014$), although it was marginally significant at postoperative 12 months (60.0% vs. 100.0%, $P = 0.074$; 70.6% vs. 100.0%, $P = 0.133$). PDE-5 inhibitor usage was similar preoperatively and at 3, 6, and 12 months postoperatively, regardless of wNVB. Sexual function score was 42.2, 19.4, 20.9, and 24.6 at preoperative, postoperative 3, 6, and 12 months. Sexual bother score was 36.8, 69.9, 69.0, 79.4 atpreoperative, postoperative 3, 6, and 12 months. There were no differences in overall sexual function and bother score changes according to groups.

However, postoperative overall sexual function score in the Q4 ($r = 0.580$, $P = 0.006$) and Q2–3 ($r = 0.373$, $P = 0.030$) groups was significantly related to preoperative score, although it was not associated in the Q1 group ($r = 0.017$, $P = 0.940$) (Table 2). Moreover, postoperative overall sexual bother score in the Q4 was significantly associated with preoperative score ($r = 0.440$, $P = 0.046$).

Among patient and clinical characteristics, the NVB area measured with MRI was the only variable significantly related to wNVB ($r = 0.241$, $P = 0.013$; Table 3). Other variables were not related to wNVB. On multivariate analysis, prostate volume [hazard ratio (HR): 0.945, $P = 0.019$] and wNVB (Q1, HR: reference; Q2–3, HR: 1.392, $P = 0.599$; Q4, HR: 7.168, $P = 0.019$) were significant predictors for EHS ≥2 at postoperative 6 months after RALP (Table 4). Although statistical significance was not achieved, wNVB was the only variable, which was marginally associated with EHS ≥2 at postoperative 3 months (Supplementary table 1).

4. Discussion

Nerve sparing is considered one of the most important steps for improving the postoperative QoL after RP in the view of ED. However, a considerable number of patients who underwent RP postoperatively developed ED despite nerve-sparing surgery as mentioned earlier [16, 17]. Thereby, clinicians improve their technique as much as possible to preserve NVB during surgery. In this study, we measured the wNVB after prostate removal, and evaluated the relationship between wNVB and sexual function outcomes after RALP. The results showed that not only the performance but also the degree and quality of NVB sparing were important for postoperative sexual function, which was in accordance with previous study [18]. Moreover, measuring the wNVB during RALP thought to be an easy and objective method for evaluating the quality of NVB sparing, which could also be useful for predicting postoperative sexual function outcomes. In this study, we assessed the preoperative and postoperative sexual function using EHS, which was a reliable measure for assessing erectile function recovery after RALP.[19].

In this study, wNVB was significantly associated with postoperative EHS ≥ 2. In addition, in additional analysis, wNVB was also associated with postoperative EHS ≥ 3 after adjusting other variables, although the statistical significance was not achieved (Q1: reference, Q2–3: HR:2.435, $P = 0.161$, Q4: HR: 3.855, $P = 0.052$). In other words, wNVB after surgery was thought to be significantly associated with postoperative erectile function. Although the measured tissue could contain periprostatic fat and connective tissue in addition to NVB, a recent article suggested that NVB was present along the prostatic capsule up to the 2 and 10 o'clock positions.[20] In other words, larger amount of NVB might be spared as the larger amount of tissue surrounding the prostate

Table 3
Correlation between clinical characteristics and width of spared NVB

	Width of spared NVB	
	r	*P*
Age at surgery	−0.115	0.243
Body mass index	0.001	0.995
PSA level	−0.105	0.287
Testosterone	0.103	0.296
Preoperative sexual function score	0.183	0.063
Preoperative sexual bother score	−0.155	0.117
Preoperative EHS	0.136	0.168
NVB area on MRI	0.241	0.013
Prostate size	0.011	0.910

EHS, erectile hardness score; MRI, magnetic resonance imaging; NVB, neurovascular bundle; PSA, prostate-specific antigen.

Table 4
Factors predicting postoperative EHS ≥2

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at surgery (continuous)	0.938 (0.871–1.011)	0.093		
Testosterone (continuous)	0.833 (0.609–1.141)	0.255		
Body mass index (continuous)	0.978 (0.801–1.196)	0.831		
Hypertension (yes vs. no)	1.494 (0.477–4.682)	0.491		
Diabetes (yes vs. no)	1.029 (0.252–4.203)	0.968		
PSA (continuous)	0.862 (0.707–1.050)	0.140		
Prostate size (continuous)	0.950 (0.911–0.991)	0.018	0.945 (0.902–0.991)	0.019
Biopsy Gleason score (7 vs. 6 or less)	1.244 (0.481–3.220)	0.652		
Preoperative sexual function score	1.025 (0.997–1.054)	0.085		
Preoperative sexual bother score	0.999 (0.981–1.016)	0.882		
Preoperative EHS				
2	Reference			
3	0.333 (0.033–3.418)	0.355		
4	0.667 (0.054–8.161)	0.751		
Width of spared NVB				
Q1	Reference		Reference	
Q2–3	1.484 (0.467–4.718)	0.503	1.392 (0.406–4.772)	0.599
Q4	7.857 (1.651–37.40)	0.010	7.168 (1.387–37.04)	0.019

CI, confidence interval; EHS, erectile hardness score; HR, hazard ratio; NVB, neurovascular bundle; PSA, prostate-specific antigen.

was preserved. In addition, abundant periprostatic fat and connective tissue could reduce stretching and/or crushing injury during surgery, which affects the postoperative nerve function and maximal periprostatic tissue-sparing surgery during prostatectomy could be the best way to preserve sexual function. However, because wNVB could be affected by measuring conditions, any cut-off value for evaluating the quality of NVB sparing cannot be given based on the study results. In the present study, prostate size was another significant predictor for postoperative EHS ≥2, in addition to wNVB. Prostate size might be related to the durability and vulnerability of the NVB during surgery. If the prostate size is large, the preoperative NVB might be thinner and weaker than in those with small prostate volume. Moreover, compared to smaller prostate, larger prostate need to be mobilized with stronger force to accurately visualize the surgical fields. Thereby, the NVB surrounding large prostate could be easily injured during surgery due to stretching and/or crushing that could occur during prostate manipulation. Therefore, patients with a small prostate might be more suitable for NVB-sparing surgery than patients with a large prostate; however, these results are considered only hypothesis generating and need to be verified in a future study.

Patient age at surgery and preoperative sexual function were not associated with postoperative sexual function outcome, in contrast to previous reports [11, 21]. This might be due to the inclusion of prostate size in the present study, which generally increases with aging. Although these results need to be confirmed, the findings of the present study are believed to be reliable because the response rate of the questionnaires was >90% at postoperative 3 months and greater than two-third at postoperative 6 months. The other strength of the present study is that we also presented the subjective sexual function and bother scores measured with the EPIC questionnaire. In this study, postoperative sexual function was more strongly associated with preoperative sexual function if NVB was sufficiently spared. In other words, preoperative sexual function, including erectile ability and erection frequency, could be recovered within 6 months in most patients if sufficient NVB tissue is spared.

However, as expected, maximal NVB sparing was related to an increased risk of surgical margin positivity. In this study, the rate of positive surgical margin was higher than in previous reports, which might come from the inclusion of patients with intermediate risk disease [22]. However, even considering this fact, the proportion of ≥pathologic T3a disease and pathologic Gleason score ≥7 thought to be high, which may be attributed to the aggressive features of prostate cancer in Asian men [23]. Nevertheless, considering the increased risk of positive surgical margin, maximal NVB sparing should be considered only in patients who desperately wanted nerve-sparing surgery after receiving sufficient explanations regarding increased risk of positive surgical margin. In other words, oncological outcomes should be considered as primary outcomes over sexual outcomes. However, because impacts of positive surgical margin on tumor recurrence is doubtable [24, 25], the results of the present study need to be carefully interpreted. In this study, the preoperative NVB area measured on preoperative MRI was associated with wNVB. In this regard, we could expect the wNVB using the NVB area measured on preoperative MRI, similar to a previous study [26]. This information could be helpful in counseling patients who want nerve preservation. In the present study, we hypothesized that the NVB area on preoperative MRI might be associated with wNVB and affect the postoperative sexual function outcomes. However, because the NVB area is not always visible on MRI, the clinical usage of MRI for these purposes should be further evaluated in the future study.

This study has several limitations. Although the patients were prospectively collected, selection bias could exist. In addition, the postoperative PDE5i usage was slightly different according to the group, although statistical significance was not achieved. Although the clinicians routinely recommend the PDE5i usage after surgery to prevent post-prostatectomy carvernosal fibrosis, some patients did not want to take PDE5i because of the several personal reasons and the results of the present study should be interpreted with cautions. The other limitation was the short follow-up duration. In a recent study, about 30–40% of patients with ED were reported to recover within postoperative 3 years. [27] However, because the erectile function outcomes at postoperative 2 years could be reliably predicted using the erectile function at 6 months, [28] the present study could be clinically useful. Furthermore, because we needed to incise the endopelvic fascia to measure the wNVB during surgery, this method cannot be used to predict postoperative sexual outcomes if incision of the endopelvic fascia is not performed. Moreover, the results of this study are only applicable if bilateral NVB-sparing surgery is performed.

According to the results of this study, not only the performance but also the degree and quality of NVB sparing thought to be

important for postoperative sexual function. Measurement of the width of NVB during surgery could be an easy intraoperative method for assessing the quality of NVB sparing. Based on the present study, the wNVB seemed to be associated with postoperative sexual function, although larger studies are need to be performed to validate the results of the present study.

Funding

This research was not supported by any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contribution

Sangjun Yoo: Data collection or management, Data analysis, Manuscript writing/editing.
Bumjin Lim: Data collection or management.
Se Young Choi: Data analysis.
Dalsan You: Critical revision.
Choung-Soo Kim: Protocol/project development.

Conflicts of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2020.07.005.

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