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Influence of multinerve-sparing, robot-assisted radical prostatectomy on the recovery of erection in Japanese patients

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Abstract

Purpose: To evaluate in Japanese patients their sexual function after robot-assisted radical prostatectomy (RARP) and to investigate the influence of the multinerve-sparing (NS) grade on their sexual function.

Methods: In total, 225 patients were reviewed with localized prostate cancer who underwent RARP at the authors' institution. They underwent RARP >3 months ago, without pre- and posthormone therapy and salvage radiation. Self-administered International Index of Erectile Function (IIEF) questionnaires were used for assessment preoperatively and 1–48 months postoperatively. In all, 129 patients were evaluated with the preoperative IIEF-Question 1 and who achieved a score of ≥2 by being divided into five NS groups. The recovery rates of erection (postoperative IIEF-Question 1 score of ≥2) were calculated by using the Kaplan–Meier analysis.

Results: Seventy-four percent of all the patients had not attempted sexual intercourse, but 60% had felt sexual desire at 24 months postoperatively. In those patients with a preoperative erection, the recovery rate of erection was 58% at 24 months after the RARP. Across the five NS groups, as the procedure was more nerve-sparing, the recovery rate of erection became significantly higher. The postoperative effects on erection in the bilateral and unilateral NS groups were significantly superior to those in the other NS groups.

Conclusion: In Japanese patients, erection after a RARP is improved with multiNS grade procedures.

KEYWORDS

erection, nerve-sparing, prostate cancer, radical prostatectomy, robotic surgery

1 | INTRODUCTION

Prostate cancer (PCa) is the most common cancer in men and a radical prostatectomy (RP) remains the gold-standard surgical treatment for patients with clinically localized disease and a life expectancy of >10 years. Following the first report of robotic prostatectomy in 2000,[1] robot-assisted RP (RARP) rapidly has become widely used in the USA, Europe, and Asia.

In Japan, the RARP was introduced in 2006 and, in April 2012, the National Health Insurance Program, administered by the Japanese Ministry of Health, Labor and Welfare, began to cover the cost of RARPs, resulting in the nationwide proliferation of this

procedure. The RARP is the most commonly performed robotic surgery in the world and is a standard option for the treatment of localized PCa.

The RP is associated with a variable loss of erectile function (EF) due to injury to the autonomic cavernous nerve and negatively affects the postoperative quality of life of patients.[2] However, a study reported that the incidence of erectile dysfunction could be reduced by the preservation of the neurovascular bundle.[3] Subsequently, the approach of RP changed from open surgery to laparoscopic and robotic surgery. In the RARP, surgeons are able to perform precise and accurate movements in order to preserve the pelvic neurovascular bundle. In fact, several studies have shown the RARP to be superior to other approaches regarding its functional outcome.[4–6] Globally, many reports have evaluated the effects of various nerve-sparing (NS) procedures on erection,[7–11] but the influence of the NS grade on the sexual function of Japanese patients who have undergone a RARP seldom has been reported.

The International Index of Erectile Function (IIEF) questionnaire is a multidimensional, validated questionnaire with 15 questions in the five domains of sexual function (erectile and orgasmic functions, sexual desire, satisfaction with intercourse, and overall sexual satisfaction) and is approved by the National Institutes of Health. Thus, several reports have evaluated the postoperative EF using this measure.[7,12,13] However, the level of sexual activity of Japanese patients was lower than that of Western men.[14] Therefore, sexual function after a RARP should not be assessed by using the IIEF-EF, based on sexual intercourse, for Japanese patients. Therefore, erection was evaluated by using IIEF-Question (Q)1.

In this study, the level of erection recovery of Japanese patients who underwent a RARP was evaluated by using IIEF-Q1 and the influence of the NS grade on the sexual function of Japanese patients was investigated.

2 | MATERIALS AND METHODS

2.1 | Patients

Ethical approval for the collection and analysis of the data was obtained from the Ethics Committee of Tottori University Faculty of Medicine, Yonago, Japan. Written consent was obtained from all the patients. At the authors' institution, the RARP had been performed on patients with localized PCa and no metastasis. The patients who were operated on from October, 2010 to July, 2016 were included in this analysis. A retrospective analysis was performed of the prospectively collected data on 305 patients who underwent a RARP. The inclusion criterion was patients who had completed the IIEF questionnaire at 3 months' follow-up. The exclusion criteria were patients who had undergone a RARP <3 months ago, those who had not completed the IIEF questionnaire preoperatively, and those who had undergone pre- or postoperative hormone therapy and salvage radiation. In total, 225 patients remained for analysis. The preoperative and intraoperative variables were prospectively collected and were followed up at the authors' institution.

2.2 | Surgical technique

The operations were performed by five different surgeons. The standard placement of a six-trocar system has been adopted at the authors' institution. The patients were placed in the Trendelenburg position, with their feet higher than their head by 25–30°. The trocar to guide the surgical scope was placed 16 cm above the superior border of the pubic symphysis. As a rule, the trocars were placed at least 8 cm apart and adjusted according to the patient's body type. In all cases, antegrade surgery was performed via the transperitoneal approach.

A multistage NS grade method, described in the previous study, was used for all the patients with the goals of function preservation and tumor control by using four approaches properly for the nerve-preservation method.[15,16] The NS procedures were performed on the basis of the National Comprehensive Cancer Network criteria, as follows: (1) Grade I, intrafascial dissection for very low-risk cases; (2) Grade II, interfascial dissection for low-risk cases; (3) Grade IV, wide dissection for high-risk cases; and (4) Grade III, extrafascial dissection (partial nerve-sparing, PNS) for all the other cases. The NS methods were defined as "NS" (intra- and interfascial dissection), "PNS" (extrafascial dissection), or "non-NS" (wide dissection). There was no difference in the NS technique distribution by the surgeons. The NS grades were evaluated by the intraoperative findings of the surgeons and assistants.

The self-administered IIEF questionnaire was used for assessment preoperatively and at 1, 3, 6, 9, 12, 18, 24, 36, and 48 months postoperatively. The attempts at sexual intercourse were evaluated by using IIEF-Q6. The frequency of sexual desire was evaluated by using IIEF-Q11. The postoperative recovery of erection was defined as an IIEF-Q1 score of ≥2 in the patients with a preoperative IIEF-Q1 score of ≥2.

The included patients were divided into five NS groups, as follows: (1) bilateral (bil) NS group (patients who underwent bil-NS); (2) unilateral (uni) NS group (patients who underwent NS–non-NS and NS–PNS); (3) bil-PNS group (patients who underwent bil-PNS); (4) uni-PNS group (patients who underwent uni-PNS); and (5) bil non-NS group (patients who underwent bil non-NS).

All the statistical analyses were performed by using IBM SPSS Statistics for Windows (v. 21.0; IBM Corporation, Armonk, NY, USA). Differences in the IIEF-Q1 were compared among groups by using the *t* test, Wilcoxon's Signed Rank test, and Holm–Bonferroni method. A *P*-value of <.05 was considered to be statistically significant.

3 | RESULTS

Detailed patient characteristics are listed in Table 1. In all the patients, the RARP could be completed without open conversion. The count rates of the questionnaires were 100% preoperatively and 89%, 97%, 95%, 95%, 92%, 90%, 87%, 80%, and 76% at 1, 3, 6, 9, 12, 18, 24, 36, and 48 months, respectively, after the RARP. The results of all the patients are shown in Figure 1. At baseline, the mean IIEF-EF domain score of the 225 patients was 11.37. In this study, time-dependent

TABLE 1 Patients' characteristics

Variable	All patients	IIEF-Q1 score (≥2)	IIEF-Q1 score (0 or 1)	*P*-value
N	225	129	96	–
Age (years, range)	65.10 (48.00–76.00)	63.30 (48.00–75.00)	67.60 (54.00–76.00)	.001
Body Mass Index (kg/m^2, range)	23.70 (18.00–30.60)	23.50 (18.00–29.50)	24.00 (18.10–30.60)	.146
Prostate volume (mL, range)	32.70 (10.00–109.00)	32.50 (10.00–109.20)	33.10 (11.70–98.00)	.745
Preoperative PSA (ng/mL, range)	9.37 (1.17–39.20)	9.19 (2.67–39.20)	9.61 (1.17–34.60)	.570
Preoperative IIEF-EF domain	11.37 (0.00–30.00)	18.10 (4.00–30.00)	2.40 (0.00–9.00)	.001
Gleason score (N, %)				.723
6	45 (20.0)	28 (21.7)	17 (17.7)	
7	105 (46.6)	58 (45.0)	37 (38.5)	
≥8	75 (33.4)	43 (33.3)	42 (43.8)	
Clinical stage (N, %)				.697
T1c	47 (20.9)	25 (19.4)	22 (22.9)	
T2	158 (70.2)	93 (72.1)	65 (67.7)	
T3	20 (8.9)	11 (8.5)	9 (9.4)	
NCCN criteria (N, %)				.816
Low	27 (12.0)	17 (13.2)	10 (10.4)	
Intermediate	109 (48.4)	62 (48.1)	47 (49.0)	
High	89 (39.6)	50 (38.8)	39 (40.6)	
Surgical data				
Total operation time (minimum, range)	324 (148.00-575.00)	325 (195.00-514.00)	324 (148.00-575.00)	.926
Estimated blood loss (mL, range)	200 (0.00-1300.00)	209 (0.00-1100.00)	188 (0.00-1300.00)	.427
Positive surgical margin (N, %)	33 (14.7)	17 (13.2)	17 (13.2)	.699
Nerve-sparing (N, %)				.193
Bilateral	17 (7.6)	13 (10.0)	4 (4.2)	
Unilateral	92 (40.9)	54 (41.9)	38 (39.6)	
Bilateral PNS	35 (15.6)	21 (16.3)	14 (14.6)	
Unilateral PNS	55 (24.4)	25 (19.4)	30 (31.3)	
Non-nerve-sparing (N, %)	26 (11.6)	16 (12.4)	10 (10.4)	

IIEF-EF, International Index of Erectile Function-erectile function; NCCN, National Comprehensive Cancer Network; PNS, partial nerve-sparing; PSA, prostate specific antigen.

improvement was noted in the postoperative IIEF-EF, with scores of 1.96, 3.36, 3.63, 3.43, 4.01, 4.72, 5.76, 5.38, and 6.60 at 1, 3, 6, 9, 12, 18, 24, 36, and 48 months, respectively, after the RARP. According to IIEF-Q6, 57% of all the patients did not attempt sexual intercourse preoperatively and 81%, 74%, 72%, and 70% at 12, 24, 36, and 48 months postoperatively, respectively, did not attempt sexual intercourse. According to IIEF-Q11, 76% of all the patients felt sexual desire more than a few times preoperatively and 59%, 60%, 60%, and 62% felt sexual desire more than a few times at 12, 24, 36, and 48 months postoperatively, respectively. Therefore, the recovery of

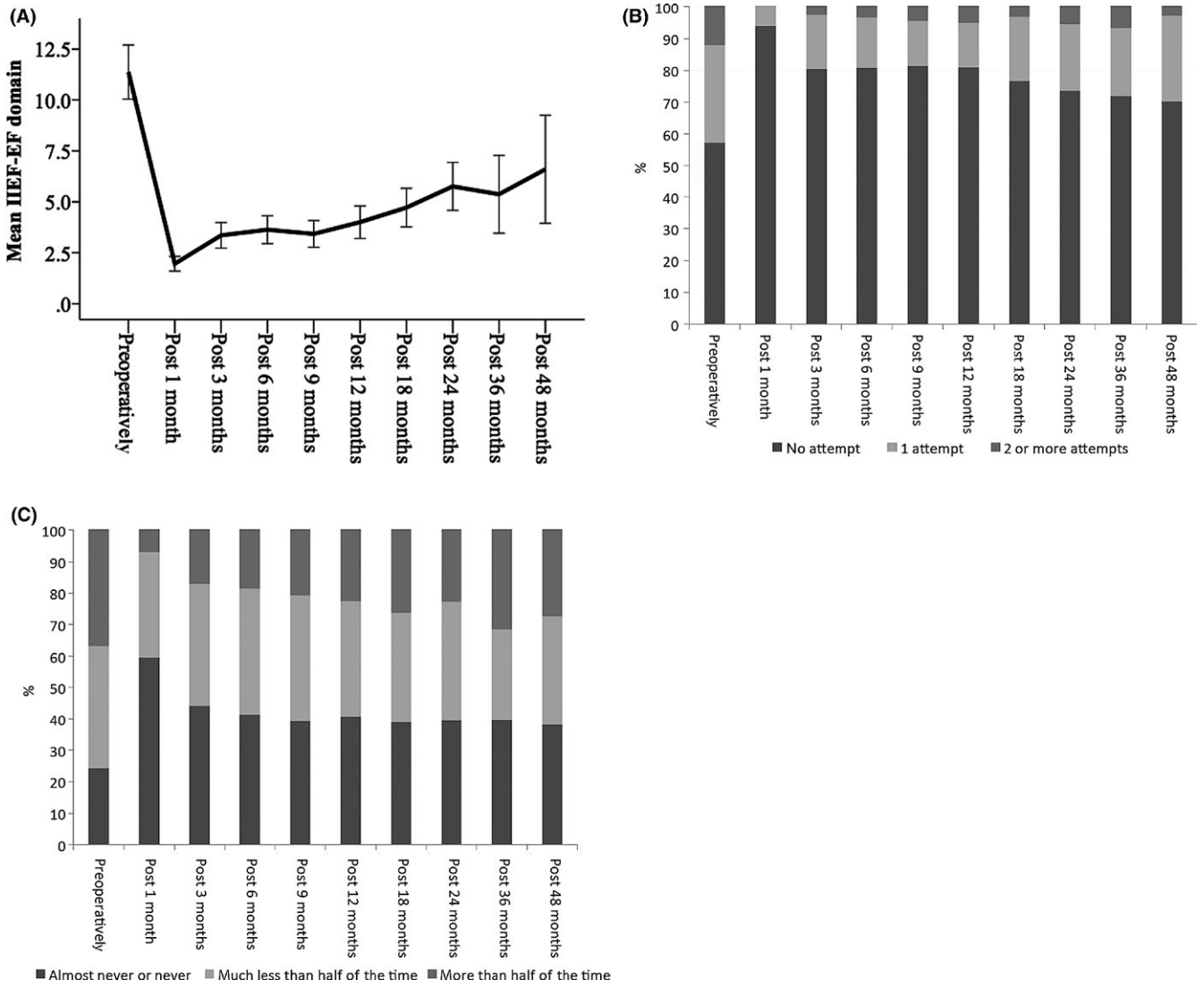


FIGURE 1 Results of all the patients (n = 225). (a) The International Index of Erectile Function (IIEF)-Erectile Function (EF) score. (b) The attempts at sexual intercourse (IIEF-Q6). (C) The frequency of sexual desire (IIEF-Q11)

erection in 129 patients with a preoperative IIEF-Q1 score of ≥2 was evaluated by using the postoperative IIEF-Q1.

The results of the patients with a preoperative IIEF-Q1 score of ≥2 are listed in Fig. 2. The results of the IIEF-EF domain (Fig. 2a), the attempts at sexual intercourse (IIEF-Q6) (Fig. 2b), and the frequency of sexual desire (IIEF-Q11) (Fig. 2c) were similar to those in all the patients. However, the recovery rates of erection were 51.7%, 58.0%, 60.4%, and 67% at 12, 24, 36, and 48 months, respectively, after the RARP (Fig. 2d). The recovery rates of erection are shown in comparison with the NS groups in Fig. 3. For the NS group, the recovery rates of erection were higher ($P < .001$, Wilcoxon's Signed Rank test) via the Kaplan–Meier analysis. Moreover, an erection did not significantly differ because the surgery was performed by different surgeons ($P = .550$, Wilcoxon's Signed Rank test).

The results of the positive surgical margin rate and the recovery rate of erection according to the NS grade are shown in Table 2. There was no significant difference in the positive surgical margin rates for any NS grade in the patients with a preoperative IIEF-Q1 score of ≥2 ($P = .792$). There was a significant difference in the recovery rate of erection at 24 months after the RARP for any NS grade ($P = .001$).

4 | DISCUSSION

The RARP has become a widely accepted surgical approach for men with clinically localized PCa. In the current study, the cancer control outcomes in relation to the RARP were similar to those of open and laparoscopic RP, whereas urinary continence and potency recovery were superior to those of open and laparoscopic RP.[8,17,18] However, one study reported racial differences in the sexuality profiles among Japanese and Westerners, with lower sexual activity in Japanese than in Western men.[14] Therefore, it remains unclear whether the postoperative findings on RARP in Japanese patients can be

compared with those in previously published studies in Western by using IIEF-Q1. The definition of the recovery of erection was an

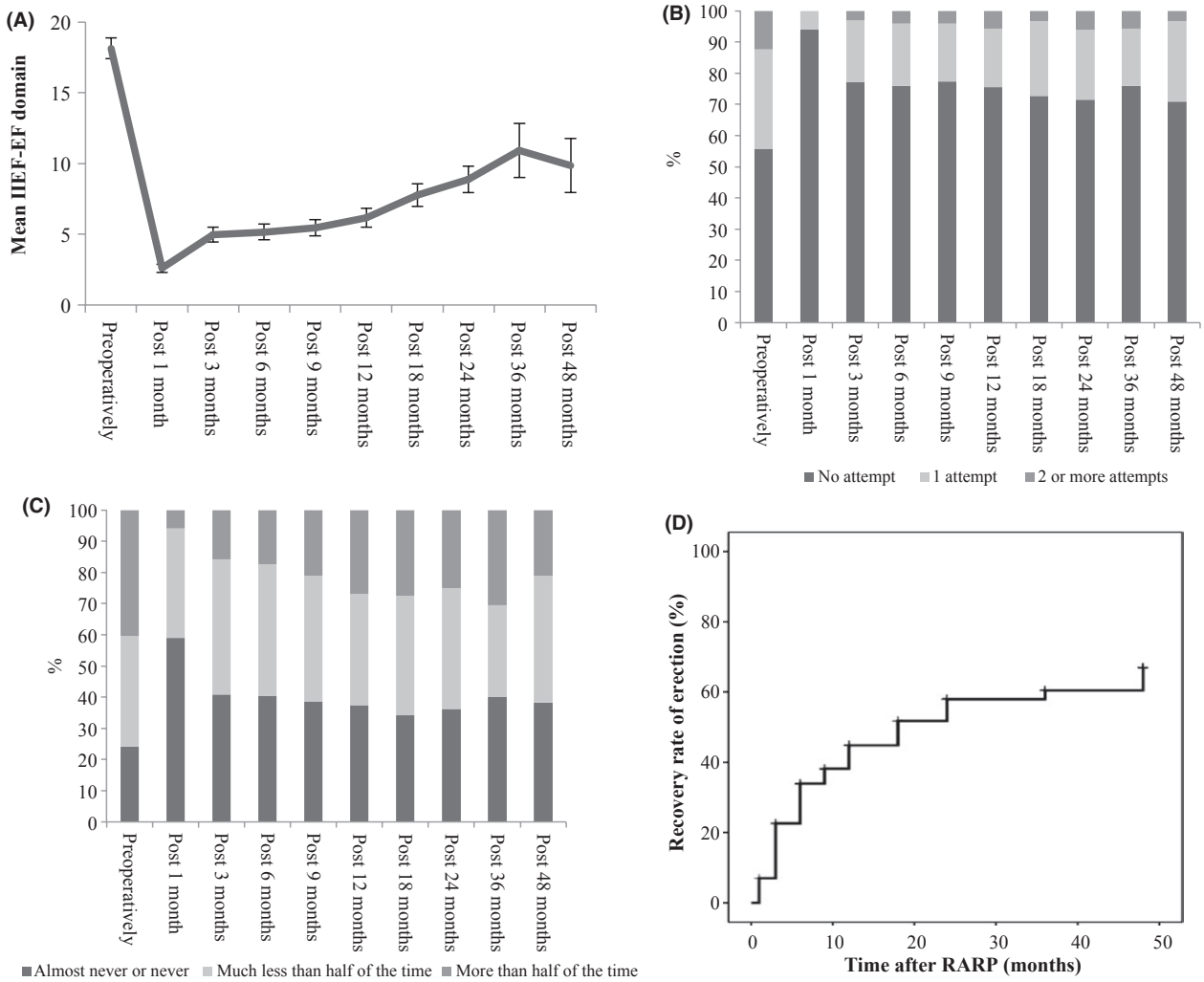
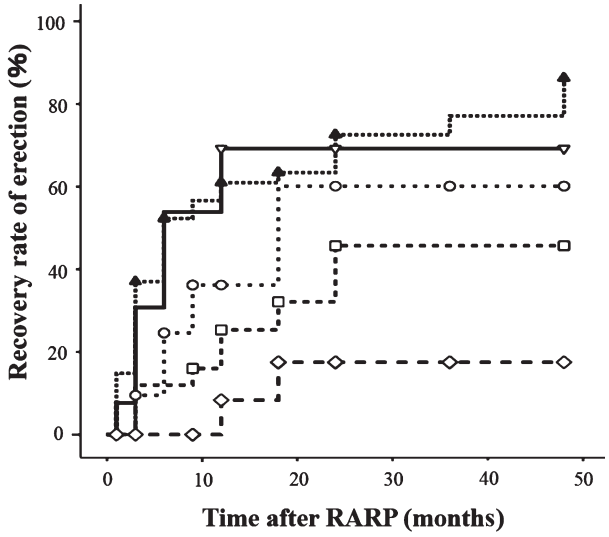


FIGURE 2 Results of the patients with an International Index of Erectile Function (IIEF)-Q1 score of ≥2. (n = 129). (a) The IIEF-Erectile Function (EF) score. (b) The attempts at sexual intercourse (IIEF-Q6). (c) The frequency of sexual desire (IIEF-Q11). (d) The recovery rate of erection. The recovery rate was 51.7%, 58.0%, 60.4%, and 67% at 12, 24, 36, and 48 months after a robot-assisted radical prostatectomy (RARP)

countries. In this study, ~60% of the patients who underwent the RARP had not attempted sexual intercourse preoperatively and 80% of those also had not attempted it at 12 months after the RARP; in both cases, the IIEF-EF scores were very low. The IIEF-EF is a mark on the basis of the sexual intercourse. Therefore, at baseline, the mean IIEF-EF score in the 225 patients was 11.37 preoperatively and a slight time-dependent improvement was noted in the postoperative IIEF-EF score. However, 76% of all the patients had felt sexual desire more than a few times preoperatively and 59% of those experienced it at 12 months postoperatively. Therefore, the authors believe that it is very difficult for Japanese patients to evaluate EF by using the IIEF-EF. Similarly, another study concluded that the IIEF–5 might not be suitable for use in Japanese men and it might be preferable for this cohort to use the erection hardness score as an alternative to the IIEF–5 for the precise assessment of postoperative changes in EF.[9] Therefore, erection was evaluated IIEF-Q1 score of ≥2 for those patients with a preoperative IIEF-Q1 score of ≥2. The recovery rate of erection was 51.7%, 58.0%, 60.4%, and 67% in the patients with a preoperative IIEF-Q1 score of ≥2 and 60.5% at 12, 24, 36, and 48 months, respectively, after the RARP. Several reports of potency after RARPs have appeared. The potency rate at 12, 24, and 48 months after a RARP has ranged from 54% to 90%, 63% to 94%, and 60% to 100%, respectively.[5,19] In this study, the recovery rates of erection were similar to those in these studies and the evaluation of erection by using IIEF-Q1 is valid for Japanese patients.

Nerve-sparing is the important factor for EF after RP. A study concluded that NS is an independent predictor for the preservation of potency after an open RP (ORP).[20] It was reported that the potency rate of bil-NS procedures was superior to that of uni-NS procedures after an ORP. In relation to the RARP, many reports have evaluated the effects of various NS procedures on EF, in particular,



Procedure			*P* – value*	Adjusted *P* – value **
bil-NS	*vs*	uni-NS	.8009	.8009
bil-NS	*vs*	bil-PNS	.0907	.3629
bil-NS	*vs*	uni-PNS	.0093	.0654
bil-NS	*vs*	non-NS	.0005	.0046
uni-NS	*vs*	bil-PNS	.0283	.1413
uni-NS	*vs*	uni-PNS	.0017	.0139
uni-NS	*vs*	non-NS	.0005	.0046
bil-PNS	*vs*	uni-PNS	.2219	.4437
bil-PNS	*vs*	non-NS	.0124	.0742
uni-PNS	*vs*	non-NS	.1372	.4115

FIGURE 3 Recovery rate of erection, according to the nerve-sparing grade. *The *P*-values were based on Wilcoxon's Signed Rank test; **the adjusted *P*-values were based on the Holm–Bonferroni method. (◊) bil non-NS, bilateral non-nerve-sparing; (▽) bil-NS, bilateral nerve-sparing; (○) bil-PNS, bilateral partial nerve-sparing; (▲) uni-NS, unilateral nerve-sparing; (□) uni-PNS, unilateral partial nerve-sparing. Non-NS, non-nerve-sparing; RARP, robot-assisted radical prostatectomy

non-NS, uni-NS, or bil-NS procedures.[5,7–11] However, there are limited reports on PNS procedures. A study reported that the level of sexual function in bil interfascial NS procedures at 6 and 12 months after a RARP was better and that the positive surgical margin rate at the mid- and posterolateral location was higher than that in PNS. It was concluded that the PNS technique reduced the positive surgical margin rate and preserved potency in high-risk PCa.[21] Another study reported that, among the patients with some degree of neurovascular bundle preservation for high-risk PCa, the recovery rate of EF was 47% at 24 months after a RARP.[22] In the current study, there was no significant difference in the positive surgical margin rates for any NS grade. The effects on erection in the bil- and uni-NS procedures postoperatively were similar to previous reports that bil- and uni-NS procedures are superior to other NS procedures regarding erection after surgery, but the authors recognized that the recovery rate of erection from the bil-PNS procedure tended to be better than that from the non-NS procedure and the meaning of bil-PNS was elucidated. Therefore, the RARP with any nerve preserved as well as possible should be the procedure of choice when considering the malignancy of cancer, progression, and hope of the patients.

In this study, the number of patients who underwent a RARP with bil intrafascial or interfascial dissection was small. One of the reasons was that cancer control comes first in Japanese patients and, at the authors' institution, cancer control is first considered as the treatment policy. In this study, the mean age at surgery was higher than in other reports. Therefore, the number of patients who underwent bil-NS surgery was small. However, some useful conclusions from these data can be drawn regarding Japanese patients. Time-dependent improvement was noted. Furthermore, it is clear that it is better for the recovery of erection to preserve the nerves as well as possible.

For penile rehabilitation, there are some reports that support phosphodiesterase type 5 inhibitors. Recently, the results from a randomized controlled trial for tadalafil treatment were published. The study concluded that 5 mg of tadalafil once daily was most effective for drug-assisted EF in men with erectile dysfunction following NS RP.[23] Another study suggested that the use of tadalafil once daily could significantly shorten the time to EF recovery postNS RP, compared with a placebo.[24] Yet another report suggested that the early initiation of 5 mg of tadalafil once daily prevented penile length loss and contributed to protection from structural cavernosal changes after NS RARP.[25] Furthermore, one study reported that chronic dosing with tadalafil improves men's quality of life and that an improvement in urinary incontinence in elderly patients also could contribute to this effect.[26] However, at the authors' institution, penile rehabilitation was attempted by using a method unlike the above; that is, 20 mg of tadalafil twice per week. As this study was intended as comprehensive, penile rehabilitation was not considered.

TABLE 2 Positive surgical margin (PSM) rate and recovery rate of erection, according to the nerve-sparing grade

Variable	Bil-NS	Uni-NS	Bil-PNS	Uni-PNS	Non-NS	*P*-value
IIEF-Question 1 2 scores (n = 129)	13.0	54.0	21.0	25.0	16.0	–
PSM (N, %)	1 (8.3)	8 (14.8)	4 (19.0)	2 (8.7)	2 (12.5)	.792
Erection at 24 months (%)	69.2	72.6	60.0	45.7	17.5	.001

bil-NS, bilateral nerve-sparing; bil-PNS, bilateral partial nerve-sparing; IIEF, International Index of Erectile Function; non-NS, non-nerve-sparing; uni-NS, unilateral nerve-sparing; uni-PNS, unilateral partial nerve-sparing.

Some limitations of this study are acknowledged. First, the number of patients included in the current study was small. In particular, the number of patients who underwent a RARP with intrafascial and interfascial dissection was small. Future studies with larger cohorts are warranted. Second, recovery was defined as an IIEF-Q1 score of ≥2. Generally, the recovery of erection is defined as an IIEF-Q1 score of ≥3. However, Japanese patients have low sexual profiles. In addition, the mean preoperative IIEF-Q1 score for all the patients who underwent a RARP in the authors' institution was two. Therefore, the recovery of erection was defined as an IIEF-Q1 score of ≥2. Third, penile rehabilitation was not considered. Future studies that consider the influence of penile rehabilitation need to be conducted.

In conclusion, time-dependent improvement of EF was noted in the Japanese patients. The IIEF-EF might not be suitable for the evaluation of EF for Japanese patients and it might be preferable to use IIEF-Q1 for the precise assessment of postoperative changes. The recovery of erection was recognized to be statistically different for every NS grade. In particular, the meaning of bil-PNS was uncovered. The more the nerve is preserved, the better is the recovery rate of erection.

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human and Animal Rights*: The protocol for the research was approved by Tottori University Faculty of Medicine, Yonago, Japan. All the procedures were followed in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all the patients to be included in the study. This article does not contain any study with animal participants that has been performed by any of the authors.

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