



Changes in Nocturia and Lower Urinary Tract Symptoms after Radical Prostatectomy

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Purpose: The goal of this study was to evaluate changes in nocturia and other lower urinary tract symptoms (LUTS) after laparoscopic radical prostatectomy (LRP) and robot-assisted laparoscopic radical prostatectomy (RALP).

Materials and Methods: We reviewed the medical records of 96 patients who underwent LRP or RALP for clinically localized prostate cancer and completed the International Prostate Symptom Score (IPSS) questionnaire, which provided a basis for assessing their symptoms. We also evaluated maximal flow rate and post-void residual urine volume over a follow-up period of at least 24 months. We divided the patients into three groups according to postoperative changes in the frequency of nocturia.

Results: Voiding symptoms significantly improved over the course of 24 months in patients who underwent LRP or RALP. However, most patients showed persistent or increased nocturia after LRP or RALP. Moreover, more than one third of the patients (33/96) presented with exacerbated nocturia (1.0 ± 0.9 episodes of preoperative nocturia vs. 3.0 ± 1.3 episodes of postoperative nocturia). Multiple regression analysis showed that preoperative IPSS storage sub-score had negative association with the nocturia after radical prostatectomy ($p = 0.005$). However, patients' age, body mass index, preoperative prostate specific antigen, Gleason score, T-stage, and prostate volume had no association.

Conclusions: The present study showed that nocturia was influenced by a range of factors, including other storage LUTS and the relief of bladder outlet obstruction after radical prostatectomy. Moreover, the preoperative storage symptoms are regarded as an important factor which influences the changes of nocturia after radical prostatectomy.

Key Words: Laparoscopy; Lower urinary tract symptoms; Nocturia; Robotic surgical procedures

INTRODUCTION

Since many more cases of localized prostate cancer are

now being detected than in the past, the number of patients who undergo radical prostatectomy is also increasing. In addition to the oncologic outcome after radical prostatec-

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tomy, functional outcomes, such as urinary incontinence or erectile dysfunction, are important. Most patients who undergo radical prostatectomy have a long life expectancy, and quality of life is also an important issue for these patients [1,2]. Moreover, most patients diagnosed with prostate cancer complain of lower urinary tract symptoms (LUTS) with or without benign prostatic hyperplasia (BPH). Therefore, it is necessary to evaluate changes in LUTS after radical prostatectomy [3,4]. Previous investigators have reported improvements in LUTS after open retropubic prostatectomy, especially in patients with severe preoperative LUTS [5-7]. They proposed that the relief of bladder outlet obstruction (BOO) caused the LUTS to improve after radical prostatectomy [8].

Nocturia is one of the most bothersome LUTS in men. The etiologies of nocturia include overactive bladder, BPH, fluid imbalances, endocrine problems such as changes in anti-diuretic hormone levels, and sleep disturbances [9]. Generally, nocturia has a multifactorial etiology, in which factors such as aging, bladder function, and endocrine factors play a role in addition to BOO [10,11]. Therefore, nocturia may show a different clinical course than other LUTS after radical prostatectomy, because BOO is not the only cause of nocturia in elderly prostate cancer patients. According to a study that analyzed changes in LUTS after radical perineal prostatectomy, postoperative nocturia was exacerbated in patients with mild preoperative nocturia, although other LUTS had improved by 12 months after surgery [12]. Moreover, another study presented similar results regarding the adverse effect of radical prostatectomy on nocturia, finding that the severity of nocturia never returned to the baseline level within two years after surgery [13].

In comparison with urinary incontinence and other LUTS, fewer studies have been conducted regarding changes in nocturia after radical prostatectomy, although nocturia is the one of the most problematic LUTS in elderly patients [14]. Therefore, we analyzed changes in nocturia and other LUTS after radical prostatectomy in prostate cancer patients treated with laparoscopic radical prostatectomy (LRP) or robot-assisted laparoscopic radical prostatectomy (RALP).

MATERIALS AND METHODS

We performed a retrospective review of the medical records of 96 patients who underwent LRP or RALP for clinically localized prostate cancer (TxN0M0) at Department of Urology, Seoul St. Mary's Hospital who did not show biochemical indicators of recurrence during 24 months of follow-up. All patients included in this study completed the International Prostate Symptom Score (IPSS) questionnaire, which provided a basis for assessing their symptoms, and were evaluated for maximal flow rate (Qmax) and post-void residual urine volume (PVR). LRP and RALP were performed by three surgeons using the same surgical technique. Patients were categorized according to validated scores as follows: 0~7, no/mild symptoms; 8~19, moderate symptoms; ≥ 20 , severe symptoms. We divided the patients into three groups according to postoperative changes in the frequency of nocturia, based on question #7 of the IPSS, which deals with nocturia.

Statistical analysis was performed using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Variables were reported as mean \pm standard deviation. The influence of variables on nocturia after radical prostatectomy was assessed using multiple regression analysis. Preoperative and postoperative metrics in the LRP and RALP groups were compared using the Wilcoxon signed-rank test. A comparative analysis between the two groups was performed using the Mann-Whitney U-test. p-values < 0.05 were considered to indicate statistical significance.

RESULTS

1. Baseline characteristics

The mean follow-up period was 38 months (range, 24~78 months). The mean age of patients was 68.0 years, and 74.0% (71/96) were over 65 years of age. The mean body mass index (BMI) was 24 kg/m² (range, 18~33 kg/m²). None of the subjects took any medications for nocturia or LUTS. The mean total IPSS score, mean IPSS voiding subscore, and mean IPSS storage subscore were 12.0 \pm 7.0, 7.0 \pm 5.0, and 5.0 \pm 3.0, respectively. The mean IPSS quality of life score was 2.0 \pm 1.6. The mean baseline International Index of Erectile Function-5 score was 11.0 \pm 8.2. The baseline Qmax and PVR values were 10.0 mL/s

(range, 2~28 mL/s) and 63.0 mL (range, 0~400 mL), respectively. The staging of the tumors was T1 in 15.6% of patients (15/96), T2 in 71.9% (69/96), and T3 in 12.5% (12/96) (Table 1).

Table 1. Baseline characteristics of the patients (total=96)

Characteristic	Value
Age at diagnosis (yr)	68±6.1
< 65	25 (26.0)
≥65	71 (74.0)
BMI	24.0±2.8 (18~33)
Total IPSS score	12.0±7.0
IPSS voiding subscore	7.0±5.0
IPSS storage subscore	5.0±3.0
IPSS QoL score	2.0±1.6
Qmax (mL/s)	10.0 (2~28)
PVR (mL)	63.0 (0~400)
Preoperative PSA levels (ng/dL)	11.0±11.9
< 4	3 (3.1)
4~10	64 (66.7)
10~20	27 (28.1)
> 20	7 (7.3)
Gleason score	
Preoperative biopsy	6.0±0.9
≤6	54 (56.3)
≥7	42 (43.8)
Postoperative pathologic score	6.9±0.7
≤6	21 (21.9)
≥7	75 (78.1)
T stage ^a	
Preoperative clinical stage	
1C	15 (15.6)
2A, 2B, 2C	69 (71.9)
3A, 3B	12 (12.5)
Postoperative pathologic stage	
2A, 2B, 2C	71 (74.0)
3A, 3B	25 (26.0)
Laparoscopic radical prostatectomy	39 (40.6)
Robot-assisted laparoscopic radical prostatectomy	57 (59.4)
Prostate volume (g)	
<20	1 (1.0)
20~30	25 (26.0)
≥30	70 (72.9)

Values are presented as mean±standard deviation only, number (%), mean±standard deviation (range), or median (range). BMI: body mass index, IPSS: International Prostate Symptom Score, Qmax: maximal flow rate, QoL: quality of life, PVR: post-void residual urine volume, PSA: prostate-specific antigen.

^aClassification according to the standard of 7th edition of the American Joint Committee on Cancer staging system.

2. Changes in lower urinary tract symptoms after laparoscopic radical prostatectomy and robot-assisted laparoscopic radical prostatectomy

Over the course of 24 months, the total IPSS scores and IPSS storage symptoms subscores remained similar to their baseline values, with no significant differences observed. The postoperative IPSS quality of life score was also similar to the preoperative score. However, the postoperative IPSS voiding subscore significantly decreased in comparison with the baseline value ($p < 0.05$) (Table 2) Overall, the mean number of nocturia episodes did not change after surgery. Qmax increased after surgery, but not to a statistically significant extent.

3. Factors influencing nocturia after radical prostatectomy

Multiple regression analysis showed that preoperative IPSS storage subscores were negatively associated with nocturia after radical prostatectomy (Table 3). Preoperative and postoperative voiding symptoms showed no such associations. Moreover, preoperative nocturia status was not associated with postoperative nocturia. Age, BMI, preoperative prostate-specific antigen levels, Gleason score, T stage, and prostate volume likewise had no associations with postoperative nocturia.

Table 2. Comparison of the baseline and postoperative IPSS scores, Qmax, and PVR

Variable	Baseline	Postoperative (≥24 months of follow-up)
Total IPSS score	12.0±7.0	11.0±6.9
IPSS voiding subscore	7.0±5.0	5.0±4.5 ^a
IPSS storage subscore	5.0±3.0	5.0±3.2
No. of nocturia episodes	2±1.1	2±1.2
QoL score	2.0±1.6	3.0±1.7
Qmax (mL/s)	10.0±5.2	15.0±8.1
PVR (mL)	68.0±103.9	28.0±37.4

Values are presented as mean±standard deviation.

IPSS: International Prostate Symptom Score, Qmax: maximal flow rate, PVR: post-void residual urine volume, QoL: quality of life.

^a $p < 0.05$ compared to the baseline value.

Table 3. Multiple regression analysis of factors influencing nocturia after radical prostatectomy

Variable	Standard β	t	p-value
Age (yr)	0.011	0.046	0.965
BMI (kg/m ²)	-0.0136	-0.612	0.567
Preoperative PSA (ng/dL)	-0.025	-0.110	0.917
Gleason score	-0.029	-0.128	0.903
T stage ^a	-0.239	-1.113	0.316
Prostate volume (g)	-0.344	-1.991	0.103
Preoperative IPSS score			
Total IPSS score	-0.356	-1.241	0.269
IPSS voiding subscore	-0.241	-1.241	0.269
IPSS storage subscore	0.873	4.389	0.005*
Preoperative number of nocturia episodes	0.363	0.968	0.378
Postoperative IPSS score			
Total IPSS score	-0.171	-0.835	0.442
IPSS voiding subscore	-0.241	-1.227	0.274
IPSS storage subscore	0.248	1.196	0.285

BMI: body mass index, PSA: prostate-specific antigen, IPSS: International Prostate Symptom Score.

*p<0.05. ^aClassification according to the standard of 7th edition of the American Joint Committee on Cancer staging system.

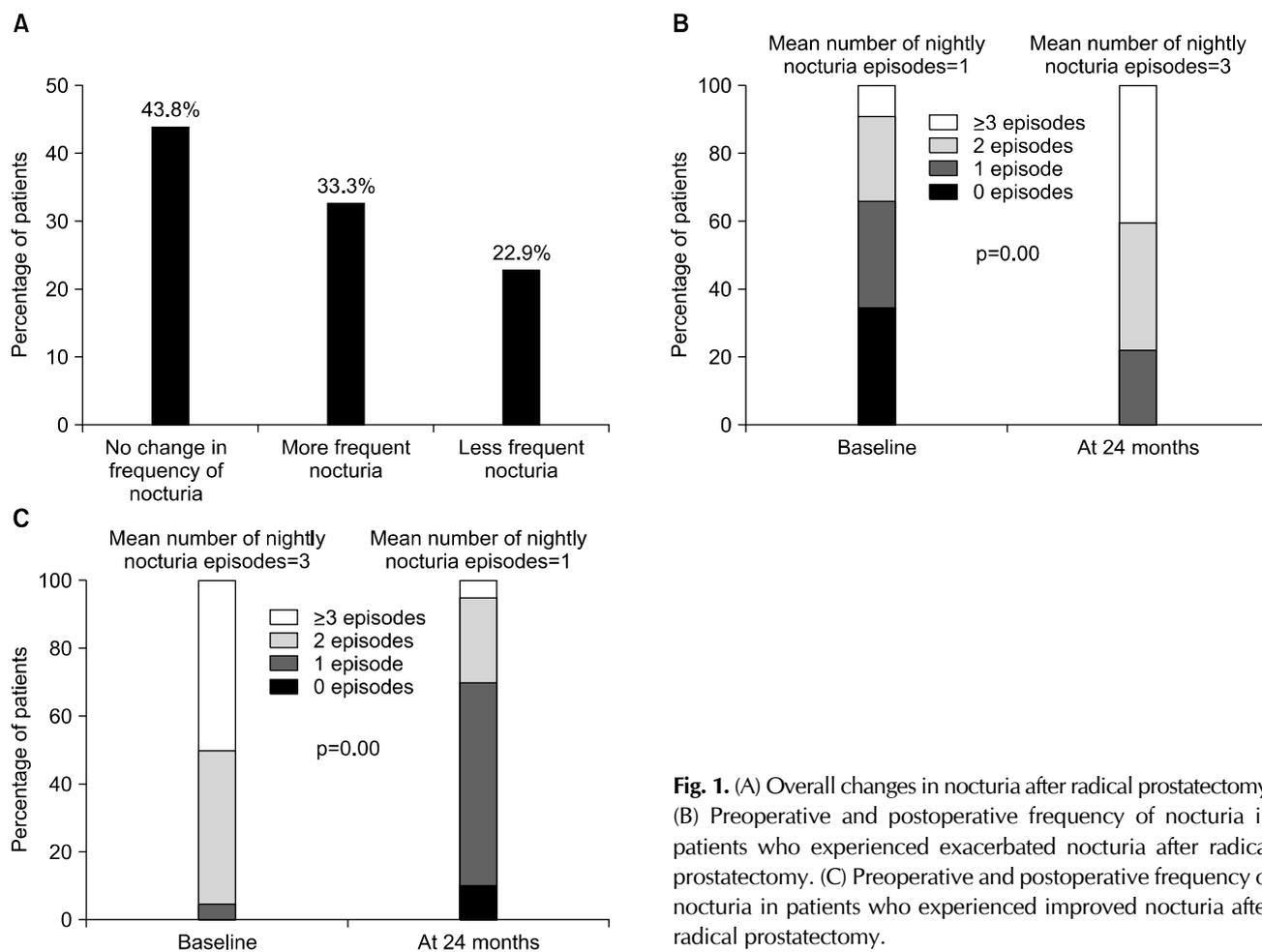


Fig. 1. (A) Overall changes in nocturia after radical prostatectomy. (B) Preoperative and postoperative frequency of nocturia in patients who experienced exacerbated nocturia after radical prostatectomy. (C) Preoperative and postoperative frequency of nocturia in patients who experienced improved nocturia after radical prostatectomy.

4. Changes in nocturia after laparoscopic radical prostatectomy and robot-assisted laparoscopic radical prostatectomy

No postoperative changes in the frequency of nocturia were reported by 43.8% of the patients (42/96) (2.0 ± 1.1 preoperatively vs. 2.0 ± 1.1 postoperatively; Fig. 1A). In 33.3% of the patients (32/96), postoperative nocturia was more frequent than preoperative nocturia (3.0 ± 1.3 episodes vs. 1.0 ± 0.9 episodes, respectively). Improvements were reported by 22.9% of patients (22/96), in whom the number of episodes of nocturia decreased from 3.0 ± 0.7 to 1.0 ± 0.7 .

One episode of nocturia was reported by 35.7% of the patients (15/42) who exhibited the same number of nocturia episodes after radical prostatectomy. Two and three episodes of nocturia were reported by 35.7% (15/42) and 23.8% (10/42) of such patients, while 4% reported no episodes of nocturia either preoperatively or postoperatively.

Of the 32 patients who experienced an increase in the frequency of nocturia postoperatively, 34.4% (11/32) reported no symptoms of nocturia preoperatively. Within the subset of patients in whom nocturia was exacerbated postoperatively, 31.3% (10/32), 25.0% (8/32), and 9.4% (3/32) complained of one, two, and three episodes of nocturia before radical prostatectomy, respectively (Fig. 1B). However, after radical prostatectomy, 40.6% of these patients (13/32) complained of more than three episodes of nocturia, and the number of patients with more than three nightly episodes of nocturia significantly increased after radical prostatectomy (9.4%; $p=0.00$, Fig. 1B). One and two episodes of nocturia were observed postoperatively in 21.9% (7/32) and 37.5% (12/32) of these patients, respectively.

Of the patients who exhibited a postoperative decrease in the frequency of nocturia, 45.5% (10/22) initially complained more than three episodes of nocturia. However, within this group, only 4.5% of patients (1/22) complained of more than three episodes of nocturia after radical prostatectomy ($p=0.00$, Fig. 1C). Among the subjects who experienced postoperative improvements in nocturia, 4.5% (1/22) and 40.9% (9/22) experienced one and two episodes of nocturia preoperatively, respectively. After radical prostatectomy, 54.5% (12/22) and 22.7% (5/22) of

these patients reported one and two episodes of nocturia, respectively. Two patients reported a complete resolution of nocturia symptoms after radical prostatectomy.

5. Comparison of nocturia depending on whether nocturia remained stable, was exacerbated, or was ameliorated after laparoscopic radical prostatectomy or robot-assisted laparoscopic radical prostatectomy

Age did not have an effect on whether nocturia remained stable, was exacerbated, or was ameliorated after radical prostatectomy (Table 4). The preoperative mean prostate volume of the patients who showed the same number of nocturia episodes postoperatively was 36.0 ± 11.3 g, which was significantly lower than that of the patients in whom nocturia improved postoperatively (43.0 ± 11.9 g, $p=0.014$). However, no significant difference was observed between patients with increased (41.0 ± 17.4 g) and decreased (43.0 ± 11.9 g) frequency of nocturia postoperatively.

IPSS scores were compared among patients depending on how their nocturia symptoms changed postoperatively (Table 4). The mean postoperative total IPSS score (13 ± 7.2) of the patients who showed an increased frequency of nocturia was significantly lower than that of patients in whom nocturia improved postoperatively (8 ± 5.4 , $p=0.041$). The IPSS voiding subscores did not significantly differ depending on the postoperative course of nocturia. However, the baseline IPSS storage subscore of patients in whom nocturia improved after surgery was significantly higher than that of the patients in whom nocturia was exacerbated (6 ± 2.7 vs. 4 ± 2.4 , $p=0.003$). In contrast, the mean postoperative IPSS storage subscore of the patients in whom nocturia symptoms improved postoperatively was significantly lower than that of the patients who experienced more nocturia episodes (4 ± 2.2 vs. 7 ± 3.3 , $p=0.005$). In addition, the post-operative IPSS storage subscore (7 ± 3.3) was significantly higher than baseline (4 ± 2.4) in patients who showed an increased number of nocturia episodes after radical prostatectomy ($p=0.007$). In patients who reported more episodes of nocturia postoperatively, the postoperative IPSS storage subscore was significantly higher than baseline ($p < 0.05$), except in the nocturia domain.

Table 4. Comparison of characteristics among patients in whom the frequency of nocturia remained the same, increased, or decreased after radical prostatectomy

Variable	No change in frequency of nocturia (n=42)	Increased frequency of nocturia (n=32)	Decreased frequency of nocturia (n=22)
Preoperative age (yr)	68±6.2	68±6.7	69±4.8
Preoperative prostate volume (g)	36.0±11.3	41.0±17.4	43.0±11.9 ^a
Total IPSS score			
Baseline	13±7.5	10±6.9	13±6.0
At 24 months	11±7.1	13±7.2	8±5.4 ^b
IPSS voiding subscore			
Baseline	7±5.4	6±5.2	7±3.9
At 24 months	6±4.7	6±4.4	4±4.4
IPSS storage subscore			
Baseline	5±3.1	4±2.4	6±2.7 ^c
At 24 months	5±3.4	7±3.3	4±2.2 ^d
Sum of IPSS frequency and urgency subscores			
Baseline	3±2.5	2±1.8	3±2.3
At 24 months	3±2.9	4±2.7 ^e	3±1.8
IPSS QoL score			
Baseline	3±1.6	2±1.6	3±1.4
At 24 months	2±1.6	3±1.8	2±1.7

Values are presented as mean±standard deviation.

IPSS: International Prostate Symptom Scores, QoL: quality of life.

^ap=0.014, compared to patients with the same number of nocturia episodes after radical prostatectomy. ^bp=0.041, compared to patients with more frequent nocturia after radical prostatectomy. ^cp=0.003, compared to patients with more frequent nocturia after radical prostatectomy. ^dp=0.005, compared to patients with more frequent nocturia after radical prostatectomy. ^ep=0.007, compared to the baseline scores in patients more frequent nocturia after radical prostatectomy. ^{a~d}The Mann-Whitney U-test was used to compare the variables between two groups. ^eThe Wilcoxon signed-rank test was performed to compare the variables at baseline and at 24 months.

DISCUSSION

In this study, voiding symptoms were found to have significantly improved in patients who underwent LRP or RALP at 24 months after surgery. Overall, the post-operative frequency of nocturia was similar to the pre-operative frequency. However, a sub-analysis of post-operative changes in nocturia demonstrated that post-operative nocturia outcomes varied among the patients, with most patients showing persistent or increased nocturia after LRP or RALP. Moreover, preoperative storage symptoms showed a negative association with nocturia after radical prostatectomy.

The improvement of voiding symptoms after radical prostatectomy and BPH surgery is associated with relief of BOO [15,16]. In a prospective cohort study of 1,788 men who underwent radical prostatectomy, Prabhu et al [15] reported that patients who exhibited clinically significant LUTS experienced immediate improvements in LUTS

symptoms after radical prostatectomy that lasted for up to 10 years, although differences were found depending on patients' national origins and preoperative metrics. Choi et al [16] reported that nocturia improved after holmium laser enucleation of the prostate, beginning three months after surgery, in a total of 472 patients. A recent long-term follow-up study investigating changes in LUTS in patients who underwent radical prostatectomy showed that clinically significant LUTS decreased over the course of 10 years after surgery [17]. The investigators compared changes in American Urological Association symptom scores (AUASS) between patients with clinically insignificant (AUASS ≤7) and clinically significant (AUASS >7) LUTS preoperatively. Immediate improvement of LUTS was noted in the patients with baseline clinically significant LUTS. In contrast, an immediate increase of AUASS scores was observed in the patients with baseline clinically insignificant LUTS. In these patients, the AUASS increased from 3.09 to 4.94, which the authors charac-

terized as a statistically significant but clinically inconsequential change. However, over 10 years of follow-up, LUTS improved regardless of the severity of baseline LUTS, with greater improvements observed among patients with baseline clinically significant LUTS. These findings indicate that the prostate is the primary contributor to the development of LUTS in men, because relief of BOO via radical prostatectomy induced the improvement of LUTS. The present study similarly found significant improvements in IPSS voiding symptom subscores after LRP and RALP. Qmax also increased from 10.0 ± 5.2 mL/s to 15.0 ± 8.1 mL/s after surgery, although this difference was not statistically significant. The previous long-term longitudinal study seems to demonstrate the importance of prostate-associated BOO. However, the investigators did not observe changes in voiding and storage symptoms in each group. Although storage symptoms could be induced by BOO, several other factors are associated with frequency, urgency, and nocturia. Therefore, it is necessary to compare changes in both voiding and storage symptoms after radical prostatectomy.

Gordon et al [17] evaluated changes in LUTS after RALP over the course of four years of follow-up by comparing preoperative and postoperative voiding and storage symptoms using AUASS. Similarly to the previous study they observed more significant improvements in LUTS in patients with baseline severe LUTS. Moreover, the sub-analysis of individual AUASS subscores showed significant improvements in weak stream, intermittency, residual urine sensation, straining while voiding, frequency, urgency, and nocturia. However, the statistical significance of the improvement in nocturia ($p < 0.05$) was lower than that found for other individual LUTS ($p < 0.0001$). This discrepancy may have occurred because the improvement of nocturia is potentially less influenced by the relief of BOO after radical prostatectomy. According to an epidemiologic study, over 70% of men with prostate cancer reported at least two episodes of nocturia, which is a finding similar to those of the present study [18]. Our results demonstrated that clinically significant nocturia is common in prostate cancer patients, although we obtained no information regarding the association of prostate cancer and nocturia. The high prevalence of nocturia in prostate cancer patients seems to be related to BOO caused by prostate

cancer. Both nocturia and prostate cancer are increasingly prevalent in the elderly population [19,20]. It is therefore necessary to investigate changes in nocturia symptoms after radical prostatectomy.

Several studies have reported that patients with mild preoperative nocturia showed increased postoperative nocturia after radical prostatectomy, independently of whether the surgical procedure was open, laparoscopic, or robotic-assisted [21]. We observed similar changes in nocturia in the present study. In particular, the present study showed that the IPSS storage subscore had a negative association with nocturia after radical prostatectomy. Moreover, the IPSS storage subscore, with the exception of nocturia, significantly increased in patients with more nocturia episodes after radical prostatectomy. Based on these findings, we propose that postoperative *de novo* frequency or urgency could be associated with increasingly severe nocturia in patients who had mild preoperative nocturia. Therefore, postoperative *de novo* overactive bladder may be a factor that aggravates nocturia in these patients, despite the fact that BOO was relieved via radical prostatectomy.

In this study, we described postoperative changes in nocturia in patients who underwent LRP or RALP.

However, the present study had some limitations. First, we analyzed a small number of patients. Moreover, we did not use a voiding diary to evaluate nocturia. Analyzing nocturia using a voiding diary could help to understand postoperative changes in nocturia in greater detail.

CONCLUSIONS

The present study showed that nocturia after radical prostatectomy was influenced by preoperative storage LUTS. The preoperative storage symptoms are regarded as an important factor which influences the changes of nocturia after radical prostatectomy. It is necessary to devote more attention to the preoperative storage symptoms associated with postoperative nocturia in order to improve quality of life in elderly patients.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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