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Predictive Factors of *De Novo* Overactive Bladder After Radical Prostatectomy in Patients With Clinically Localized Prostate Cancer: A Prospective Observational Study

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Purpose: To evaluate the incidence of *de novo* overactive bladder (OAB) and the factors related to its occurrence following radical prostatectomy (RP) in patients with clinically localized prostate cancer (PCa).

Materials and Methods: We prospectively examined 50 patients without OAB who underwent RP for clinically localized PCa in our institution from August 2019 to February 2020. We performed assessments using the International Prostate Symptom Score (IPSS), the Overactive Bladder Symptom Score (OABSS), and uroflowmetry before surgery and 3 months after RP. OAB was defined as a score of 1 or more on the urgency components of the OABSS. Three months after RP, the patients were divided into 2 groups based on the presence of *de novo* OAB symptoms. We evaluated the patients' demographics and outcomes after RP according to their *de novo* OAB grouping. The predictive factors of *de novo* OAB after RP were analyzed using a multivariate logistic regression model.

Results: Of the 50 patients, 22 (44%) had *de novo* OAB 3 months after RP. The patients in the *de novo* OAB group were older, had higher preoperative IPSS storage subscores, and had larger volumes of postvoid residual urine on preoperative uroflowmetry than those in the non-*de novo* OAB group. Multivariate analysis showed that age and preoperative IPSS storage subscores were predictive factors of *de novo* OAB after RP.

Conclusions: *De novo* OAB was observed in 44% of the patients 3 months after RP. Age and preoperative IPSS storage subscores were predictive factors of *de novo* OAB following RP.

Key Words: Prostate cancer, Prostatectomy, Overactive urinary bladder

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INTRODUCTION

Prostate cancer (PCa) is a common cancer in men, and its incidence is rapidly increasing.[1] Although radical prostatectomy (RP) is considered the definitive standard treatment for clinically localized PCa,[2] it can cause surgical complications, including urinary incontinence and erectile dysfunction, adversely affecting the patients' quality of life (QoL).[3] Postprostatectomy incontinence is an especially well-recognized complication with a negative impact on the QoL.[4]

Urinary incontinence is classified into stress urinary incontinence (SUI) and urge urinary incontinence (UUI); however, most studies on postprostatectomy incontinence have focused on SUI. Although several studies on SUI after RP were conducted,[5-7] patients can present with various

lower urinary tract symptoms (LUTS) following a radical surgery.[8] Although the deterioration of urinary storage symptoms such as *de novo* overactive bladder (OAB) is expected after RP, the prevalence of and predisposing factors of the development of urinary storage symptoms after RP are not well known. Recently, studies have shown the prevalence of *de novo* OAB and its negative impact on the QoL in men following treatment for localized PCa.[9-13] In this study, we investigated the incidence of *de novo* OAB and the predisposing factors related to its occurrence after RP in patients with clinically localized PCa.

MATERIALS AND METHODS

1. Study Participants

This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Chilgok Hospital (IRB NO. KNUCH 2019-06-007). Between August 2019 and February 2020, 113 patients underwent robot-assisted RP (RARP) and 32 patients underwent open RP (ORP) for PCa at our institution. Of them, we prospectively enrolled 50 patients without preoperative OAB. We included patients with clinically localized PCa (clinical stage ≤ T2cN0M0) and urgency subscore (Q3)/UUI subscore (Q4)=0/0 on the preoperative Overactive Bladder Symptom Score (OABSS) questionnaire. We excluded patients who had a history of receiving hormonal therapy or radiotherapy before RP; medical or surgical treatment for OAB; neurological disorders such as stroke, Parkinson disease, and multiple sclerosis; spinal cord injuries (neurogenic bladder dysfunction); bladder calculi; active urinary tract infections; severe cardiac diseases; renal dysfunctions; and hepatic dysfunctions. In addition, we excluded those without a follow-up period of >3 months from the study. During the study period, we did not prescribe OAB medications including muscarinic antagonists and β3 agonists to the patients included in the study during the 3-month period after RP.

2. Surgical Procedures

A single surgeon performed all operations. The RARP and ORP procedures were conducted via a transperitoneal approach using the da Vinci Xi or Si system and a retropubic approach, respectively. Previously, we reported a modified technique for RARP and ORP at our institution.[14] Briefly, the bladder neck was dissected first. After the dissection of the vas deferens and seminal vesicle, the prostate was dissected in an antegrade fashion from the bladder neck with nerve sparing depending on the patient's cancer status. Finally, the urethra was cut at the prostate apex. After a Rocco suture[15] was applied, urethrovesical anastomosis was performed using continuous sutures. The urethral catheter was removed on postoperative day 6.

3. Symptom Scoring

In this study, the International Prostate Symptom Score (IPSS), the OABSS, and uroflowmetry were assessed before surgery (within 1 month preoperatively) and 3 months after surgery. In addition, the total scores and the voiding, and storage symptom subscores of the IPSS were evaluated. A postvoid residual volume (PVR) greater than 50 mL was considered significant as a categorized variable. *De novo* OAB was defined as a score of one or more on the urgency components of the OABSS 3 months after surgery. Additionally, the absence of stress incontinence (involuntary leakage of urine with exertion) was defined as the use of zero pads per day. We evaluated the incidence of *de novo* OAB after dividing the patients into 2 groups (the *de novo* OAB and non-*de novo* OAB groups)

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based on the presence of *de novo* OAB symptoms 3 months after RP. We compared the patients' demographics and outcomes after RP according to their *de novo* OAB grouping.

4. Statistical Analysis

We assessed the associations between variables in the 2 groups using Student t-test and the chi-square test. A multivariate logistic regression analysis was conducted to identify the predictive factors of *de novo* OAB in patients who underwent RP. The statistical analyses were performed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA), and p-values of <0.05 were used to denote statistical significance.

RESULTS

Fifty patients without preoperative OAB who underwent RP were included in this study. *De novo* OAB was observed in 22 patients (44.0%) 3 months after RP, while 28 patients (56.0%) did not have any *de novo* OAB symptoms after RP. Preoperative patient demographics between the 2 groups are presented in Table 1. The mean age of the patients was 64.9 years. The patients in the *de novo* OAB group were significantly older than those in the non-*de novo* OAB group (67.4±5.5 years vs. 63.1±6.7 years, respectively, p=0.018). Although stress-type urinary incontinence was observed in 16% (8 of 50) of the patients 3 months after RP, there was no significant difference between the groups. The prostate size, preoperative prostate-specific

Table 1. Comparison of the clinical and pathological characteristics according to *de novo* overactive bladder after radical prostatectomy

Characteristic	Total patients (n=50)	*De novo* OAB (n=22)	Non-*de novo* OAB (n=28)	p-value
Age (yr)	64.9±6.5	67.4±5.5	63.1±6.7	0.018
Prostate size (mL)	30.1±9.9	31.7±12.8	28.8±7.0	0.353
BMI (kg/m^2)	23.7±3.0	23.9±2.2	23.5±3.6	0.646
PSA (ng/mL)	8.7±8.2	7.7±4.3	9.6±10.3	0.425
IIEF-5	11.4±6.7	10.2±6.8	12.4±6.5	0.240
Drinking, -/+	39/11	17/5	22/6	0.912
Smoking, -/+	34/16	18/4	16/12	0.063
HTN, -/+	31/19	13/9	18/10	0.707
DM, -/+	34/16	15/7	19/9	0.981
Biopsy GS, 6/7/8/9	21/21/6/2	9/7/4/2	12/14/2/0	0.190
Total positive core number	2.8±1.5	2.7±1.9	2.9±1.4	0.615
Positive core number, <3/≥3	26/24	10/12	16/12	0.412
Clinical T stage, T1c/T2	22/28	9/13	13/15	0.696
D'Amico group				0.172
Low	17	7	10	
Intermediate	25	9	16	
High	8	6	2	
Operative methods, robot/open	42/8	20/2	22/6	0.439
Nerve sparing, uni-/bilateral	13/37	6/16	7/21	0.856
Operative time (min)	131.7±35.0	135.9±24.6	128.4±40.8	0.426
Pathologic T stage, T2/T3	31/19	13/9	18/10	0.707
Pathologic GS, 6/7/8/9	18/19/11/2	8/7/5/2	10/12/6/0	0.478
Positive surgical margin, -/+	38/12	17/5	21/7	0.852
Stress incontinence, -/+	42/8	16/6	26/2	0.116

Values are presented as mean±standard deviation or number.
OAB: overactive bladder, BMI: body mass index, PSA: prostate-specific antigen, IIEF: International Index of Erectile Function, HTN: hypertension, DM: diabetes mellitus, GS: Gleason score.

antigen, D'amico risk classification, operative methods (robot vs. open), degree of nerve sparing, operative time, pathological T stage, pathological grade, and margin status were not significantly different between the 2 groups.

Table 2 shows the IPSS, OABSS, and uroflowmetry variables before surgery and 3 months after surgery. The preoperative IPSS storage symptom score was significantly higher in the *de novo* OAB group than that in the non-*de novo* OAB group (5.3±2.9 and 2.9±1.7, respectively, p=0.002). Although the total IPSS score was also higher in the *de novo* OAB group than that in the non-*de novo* OAB group, this difference was not statistically significant (10.6±8.8 and 6.9±5.8, respectively, p=0.074). Preoperatively, the patients in the *de novo* OAB group demonstrated a higher prevalence of PVR of >50 mL than those in the non-*de novo* OAB group (36.4% and 7.1%, respectively, p=0.014). The preoperative IPSS voiding symptom score, OABSS, maximal flow rate, and voided volume did not show any significant differences between the groups.

Multivariate analysis showed that age and preoperative IPSS storage symptom score were significant factors related to the development of *de novo* OAB after RP (odds ratio [OR], 1.169; 95% confidence interval [CI], 1.020–1.339; p=0.025 and OR, 1.690; 95% CI, 1.180–2.422; p=0.004, respectively) (Table 3). Receiver operating curve analysis determined that the optimal cutoff value for age was 64.5 years old (sensitivity, 72.7%; specificity, 57.1%) and that for the preoperative IPSS storage symptom score was 3.5 (sensitivity, 72.7%; specificity, 64.3%).

DISCUSSION

Although various LUTSs may occur after RP,[8] many studies have only focused on stress-type urinary incontinence.[5-7] Therefore, we assessed the incidence of *de novo* OAB and the significant factors related to its occurrence after RP in patients with clinically localized PCa. In this study,

Table 3. Multivariable logistic regression analyses of the predictive factors associated with *de novo* overactive bladder after radical prostatectomy

Variable	OR (95% CI)	p-value
Age (yr)	1.169 (1.020–1.339)	0.025
IPSS storage symptom score	1.690 (1.180–2.422)	0.004
PVR (mL)	1.011 (1.003–1.020)	0.445

OR: odds ratio, CI: confidence interval, IPSS: International Prostate Symptom Score, PVR: postvoid residual volume.

Table 2. Comparison of the preoperative questionnaire and uroflowmetry according to *de novo* overactive bladder after radical prostatectomy

Variable	Total patients (n=50)	*De novo* OAB (n=22)	Non-*de novo* OAB (n=28)	p-value
IPSS total score	8.5±7.4	10.6±8.8	6.9±5.8	0.074
IPSS voiding symptom score	4.6±5.8	5.4±6.8	4.0±4.9	0.415
IPSS storage symptom score	3.9±2.6	5.3±2.9	2.9±1.7	0.002
OABSS	1.9±0.8	1.8±0.8	1.9±0.9	0.662
UFM				
Maximal flow rate (mL/sec)	12.7±5.3	13.1±6.2	12.4±4.6	0.633
VV (mL)	224.1±110.4	245.5±130.6	207.3±90.4	0.228
PVR (mL)				0.014
≤50	40	14	26	
>50	10	8	2	

OAB: overactive bladder, IPSS: International Prostate Symptom Score, OABSS: overactive bladder symptom score, UFM: uroflowmetry, VV: voided volume, PVR: postvoid residual volume.

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we observed a high prevalence (44.0%) of *de novo* OAB 3 months after RP. In addition, multivariate logistic regression analysis showed that both age and preoperative IPSS storage symptom scores were significant factors related to the development of *de novo* OAB following RP.

Even though studies, including the ProtecT trial, revealed that men with PCa have similar LUTS to control patients at baseline,[16] following PCa therapy, they can present with various LUTS.[8] In addition, RP is associated with the considerable deterioration of LUTSs compared to other treatment strategies such as active surveillance, radiotherapy, and hormone therapy, despite the high survival rate after RP.[17,18] Therefore, in addition to the eradication of PCa itself, it is also important to recognize and control the nuisance and discomfort of postoperative LUTSs in patients. The epidemiology, pathophysiology, and treatment of SUI after RP have been investigated in detail, and the main etiological factor of SUI is the dysfunction of the urethral sphincter.[5-7] Although urinary storage symptoms are reported to be more bothersome and more likely to reduce the QoL than voiding and postmicturition symptoms,[19,20] few studies have described and clarified the causes of urinary storage dysfunctions such as UUI and *de novo* OAB after RP. Because many patients undergo RP for clinically localized PCa globally, it is meaningful to investigate the prevalence and related factors of *de novo* OAB after RP.

OAB negatively impacts the QoL and often requires medications with troublesome side effects.[21] A recent survey study found that 11% and 30% of the patients treated with RP and radiotherapy, respectively, had OAB 36 months after therapy.[9] The rates of *de novo* urodynamic detrusor overactivity following RP historically were approximately 2%–77% and tended to persist in most patients (83%).[22] A contemporary literature review reported similar findings, with 2%–63% of the patients studied developing urodynamic detrusor overactivity following RP.[18] A recent large cohort retrospective study involving 875 men who underwent ORP has reported that the incidence of *de novo* OAB was 19%, with 29% of the patients developing one or more urinary storage symptoms and 6% reporting UUI at a median follow-up of 2.7 years after RP.[11] The authors suggested that adjuvant or salvage radiotherapy was associated with a significant increase in the risk of developing OAB. Furthermore, OAB symptoms progressively developed during their retrospective study, and less than half of patients received OAB treatment.[11] In the present prospective study, *de novo* OAB was observed in 44% of the patients without preoperative OAB 3 months after RP. Although this prospective study showed a higher prevalence of *de novo* OAB than other studies possibly due to its patient inclusion criteria and strict assessment method and timing, our results provided evidence that OAB and storage LUTSs are common after RP.

Several studies have shown that recovery from urinary continence after RP is related to several patient- or surgery-related factors including age,[21,23,24] body mass index,[25] prostate volume,[24,25] preoperative IPSS score,[23] the length of the membranous urethra,[26] and nerve preservation.[27] However, the predisposing factors of the development of urinary storage symptoms after RP remain relatively unknown. Recently, Matsukawa et al.[12] have reported in an RARP series a similar incidence of *de novo* OAB to the present study. They showed that preoperative IPSS–QoL scores and postoperative maximum urethral closing pressure in a urodynamic study were significant predictive factors of *de novo* OAB in a multivariable logistic analysis. In addition, Yamada et al.[13] investigated the clinical significance of preoperative urinary storage symptoms on the continence recovery 12 months

after RARP. They revealed that the presence of preoperative OAB was an independent negative predictor of continence 12 months after RARP, and both the diagnosis and severity of OAB were associated with continence recovery. Furthermore, they suggested that patients with OAB are more vulnerable to developing incontinence after RARP. Similarly, our study showed that preoperative IPSS storage symptom score was a predictor of *de novo* OAB after RP in patients without preoperative OAB. We suggest that *de novo* OAB after RP occurs postoperatively in patients with preoperative urinary storage dysfunction, even without preoperative OAB. In this study, multivariate analysis showed that age was also a predictive factor of *de novo* OAB after surgery. Studies have indicated a positive correlation between age and OAB in the general population.[28,29] Researchers assumed that age-related changes in the bladder and pelvic floor tissues including the nervous system might contribute to the high occurrence of OAB in elderly patients. Therefore, physicians should not overlook the occurrence of *de novo* OAB and its predisposing factors after surgery in patients with clinically localized PCa. Although our study did not conduct a urodynamic study, age and preoperative IPSS storage symptom score were valuable because performing an invasive study in most patients undergoing RP is difficult.

Although the mechanism of the development of *de novo* urinary storage dysfunctions after RP is still incompletely understood, we assumed that the mechanisms could be related to the neural and anatomical disruptions at the surgical site, which can lead to bladder denervation. Traction injury to the bladder during surgery may contribute to reduced bladder perfusion and later neural and detrusor dysfunction. Porena et al.[22] compared preoperative and postoperative urodynamics after surgery and found reduced compliance in 8%–39% of patients, half of whom had new symptoms commonly associated with other voiding problems (such as SUI and detrusor overactivity). This finding persisted in 28% of the patients for 3 years.[30] In addition, prolonged high intravesical pressures preoperatively may ultimately contribute to reduced bladder perfusion and later neural and detrusor dysfunction. The preoperative IPSS storage symptom score identified as a predictive factor in this study could be considered a representative feature of reduced bladder compliance.

There were several limitations to consider in this study. First, this study did not investigate the long-term outcomes of LUTSs including *de novo* OAB after RP. The high prevalence of *de novo* OAB in this study might be overestimated because the assessment timing was made at the very early period after surgery. In addition, a small number of patients were included in this prospective study because of the strict inclusion criteria. Moreover, *de novo* OAB was diagnosed using a questionnaire completed by the patients, and a urodynamic study including measurement values of the bladder and urethra were not conducted. These limitations warrant further long-term prospective studies including urodynamics with a larger number of patients to clarify the natural history and mechanism of the development of LUTSs after RP in patients with PCa.

CONCLUSIONS

In this study, we observed a considerable incidence rate (44%) of *de novo* OAB 3 months after RP in patients with clinically localized PCa. In addition, age and preoperative IPSS storage symptom scores were predictive factors of *de novo* OAB following RP. Our results suggest that physicians should consider the occurrence and predictive factors of *de novo* OAB after RP in patients with clinically localized PCa.

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CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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