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Risk Factors of Salvage Procedure for Refractory Morcellation During Holmium Laser Enucleation of the Prostate

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Purpose: We aimed to identify the risk factors for salvage procedure (SP) required for refractory adenomatous tissue resistant to morcellation during holmium laser enucleation of the prostate (HoLEP).
Methods: Patients who underwent HoLEP between January 2010 and April 2020 at Seoul National University Hospital were analyzed. SPs were defined as cases of conversion to resection of the prostatic tissue using an electrosurgical loop after morcellation or secondary morcellation a few days after surgery or conversion to open cystotomy.
Results: Among a total of 2,427 patients, 260 were identified as having SP (SP group) (transurethral resection-nodule [n=250, 96.1%], secondary morcellation a few days after surgery [n=9, 3.5%], and conversion to open cystotomy [n=1, 0.4%]). Patients in the SP group were older and had higher 5-α reductase inhibitors use, higher prostate-specific antigen, larger total prostate volume, and larger transition zone volume (TZV) than those in the non-SP group. In the multivariable logistic regression analysis, only age and TZV were associated with SP. Compared to 40s and 50s, the odds ratios (ORs) were 3.84 in 60s (95% confidence interval [CI] 1.37–10.78, P=0.011), 4.53 in 70s (95% CI, 1.62–12.62, P=0.004), and 6.59 in 80s or older (95% CI, 2.23–19.46, P=0.001). The ORs of the SP were analyzed per TZV quartile. Compared to TZV ≤ 20.3 mL, the OR was 3.75 in 32.0 mL < TZV ≤ 50.4 mL (95% CI, 2.00–7.04, P<0.001) and 8.25 in 50.4 mL < TZV (95% CI, 4.06–16.77, P<0.001).
Conclusions: The risk of refractory morcellation increased in patients aged >60 years or those with TZV >32 mL. In order to more efficiently remove these resistant adenomas, it is necessary to develop more efficient morcellators in the future.

Keywords: Transurethral resection of prostate; Prostatectomy; Holmium-YAG Lasers; Morcellation

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- **Research Ethics:** This retrospective cohort study was approved by the Institutional Review Board (IRB No. H-2211-129-1380) of Seoul National University Hospital (SNUH).
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Holmium laser enucleation of the prostate (HoLEP) is widely performed as a surgical treatment for benign prostatic hyperplasia (BPH). HoLEP has been demonstrated to be safe and effective as a surgical treatment for BPH [1]. In addition, HoLEP surgery is effective in patients with large prostate, and can even replace open prostatectomy [2,3].

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HoLEP surgery is performed by enucleation of enlarged prostatic tissue, followed by morcellation to remove the enucleated prostate adenoma tissue [4]. During the morcellation process, we commonly encounter cases in which morcellation is difficult because the enucleated prostatic adenoma is very hard. This is the so-called "crazy ball effect," in which hard spherical tissue fragments escape from the blade of the morcellator [5]. In such cases, an additional procedure is required to remove the enucleated adenoma tissue from the bladder. An additional procedure, which includes the resection of the prostatic tissue floating in the bladder using an electrosurgical loop and fragmentation using grasping forceps, is usually performed. However, these procedures are difficult, time-consuming, and cause risk of damage to the bladder mucosa.

Our previous study analyzed the pathological characteristics of hard nodules that were resistant to morcellation [6]. However, to the best of our knowledge, no studies have investigated the risk factors that make morcellation difficult during HoLEP surgery. This is the first study to address this issue. We analyzed the clinical characteristics of patients who underwent HoLEP surgery to identify risk factors that make morcellation difficult.

MATERIALS AND METHODS

Study Design

We analyzed the clinical factors of patients who underwent HoLEP surgery between January 2010 and April 2020.

In this study, patients aged >40 years who were diagnosed with BPH and underwent HoLEP surgery were enrolled. Patients with neurogenic bladder or neuropathy were excluded from the study. Transrectal ultrasound-guided prostate needle biopsy was performed to rule out prostate cancer in patients with a preoperative serum prostate-specific antigen (PSA) >3 ng/mL or with a palpable nodule on digital rectal examination. Subsequently, patients diagnosed with prostate cancer were excluded from the study. Patients diagnosed with prostate cancer from postoperative pathology were also excluded.

Patients were divided into 2 groups; one group included those who underwent salvage procedures (SPs) after morcellation (SP group) and another group included those who did not (non-SP group). The clinical characteristics of the 2 groups were compared. SP is an additional procedure performed when the enucleated adenoma tissue is very hard and resistant to morcellation for approximately 10 minutes. SP includes excision of adenoma floating in the bladder using an electrosurgical loop (transurethral resection-nodule), another morcellation a few days after surgery with enucleated prostate tissue left in the bladder (secondary morcellation procedure), and conversion to open surgery, in which adenoma tissue is removed through direct bladder incision (conversion to open cystotomy).

We compared various parameters of the 2 groups before, during, and after surgery. The preoperative parameters included age, body mass index, medication history, underlying disease, International Prostate Symptom Score (IPSS), quality of life (QoL) scores, PSA, maximum flow rate (Qmax), postvoid residual (PVR), sonographic total prostate volume (TPV), and transition zone volume (TZV). Intraoperative parameters included operative time, enucleation time, morcellation time, enucleation weight, and intraoperative complications (prostate capsular perforation). The postoperative parameters were IPSS, QoL score, Qmax, and PVR volume at 2 weeks, 3 months, and 6 months after surgery.

Surgical Procedures

All HoLEP surgeries were performed using the 3-lobe technique [4,7]. A 26F resectoscope (Karl Storz, Tuttlingen, Germany) with a 550-μm end-firing laser fiber (SlimLine, Lumenis Ltd., Yokneam, Israel) and an 80-W Ho: YAG laser machine (VersaPulse Power-Suite, Lumenis Ltd.) were used for the enucleation process. Energy power was usually set at 2.0 J and 40 Hz in this process. After enucleation, meticulous hemostasis was performed. During this process, the energy power was set to 0.5 J and 40 Hz. A VersaCut electric morcellator (Lumenis Ltd.) with a 0° rectangular nephroscope (Karl Storz, Tuttlingen, Germany) was used for the morcellation process. SPs were performed using either an electric bipolar working element (27040EB, Karl Storz) or an electric monopolar working element (27050E, Karl Storz) if the prostatic tissue was difficult to remove even after 10 minutes of morcellation. The type of SP was immediately recorded in the electronic medical records. After complete morcellation, a 22F 3-way urethral catheter was inserted for continuous bladder irrigation with normal saline.

Statistical Analysis

The means and proportions of various parameters before, during, and after surgery between the SP and non-SP groups were compared using an independent Student t-test and chi-square test. The risk factors for SP were analyzed using univariable and multivariable logistic regression analyses. Among the statistically significant variables in the univariable logistic regression

analysis, those considered to be related to SP were included in the multivariable logistic regression analysis. The dependent variable was whether SP was implemented. Statistical significance was set at $P<0.05$. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Among the 2,427 patients, 260 (10.7%) were in the SP group and 2,167 (89.3%) were in the non-SP group. In the SP group, 250 patients (96.1%) underwent TUR-nodule, 9 patients (3.5%) underwent a secondary morcellation procedure, and 1 patient (0.4%) underwent conversion to open cystotomy.

Regarding patient demographics, the SP group was older (71.8±6.9 years vs. 69.5±7.1 years, $P<0.001$) and had higher 5-α reductase inhibitors (5-ARIs) use (38.8% vs. 30.0%, $P=0.004$) than the non-SP group (Table 1). In the comparison of the preoperative parameters, the SP group had higher QoL score (4.3±1.1 vs. 4.1±1.2, $P=0.045$), higher PSA (5.6±5.3 ng/mL vs. 3.9±4.5 ng/mL, $P<0.001$), larger TPV (89.6±40.3 mL vs. 65.0±32.4 mL, $P<0.001$), and larger TZV (58.4±31.3 mL vs. 36.6±24.5

Table 1. Patient's demographics

Variable	SP (n=260)	Non-SP (n=2,167)	P-value
Baseline characteristics			
Age (yr)	71.8±6.9	69.5±7.1	<0.001
BMI (kg/m^2)	24.3±2.8	24.2±2.9	0.614
Duration of LUTS (mo)	57.9±51.1	59.1±58.1	0.782
Previous TURP	14 (5.4)	91 (4.2)	0.375
Comorbidities			
Hypertension	135 (51.9)	1,057 (48.8)	0.338
Diabetes mellitus	56 (21.5)	479 (22.1)	0.835
Medical treatments			
Anticoagulants	88 (33.8)	732 (33.8)	0.983
α-Blocker	212 (81.5)	1,711 (79.0)	0.332
5-ARIs	101 (38.8)	651 (30.0)	0.004
Anticholinergics	50 (19.2)	487 (22.5)	0.234
Desmopressin	16 (6.2)	177 (8.2)	0.257

Values are presented as mean±standard deviation or number of patients (%).
SP, salvage procedure; BMI, body mass index; LUTS, lower urinary tract symptoms; TURP, transurethral resection of the prostate; 5-ARIs, 5-alpha reductase inhibitors.

Table 2. Comparison of pre- and intraoperative parameters

Variable	SP (n=260)	Non-SP (n=2,167)	P-value
Preoperative parameters			
Total IPSS	19.3±8.0	19.2±7.6	0.810
QoL score	4.3±1.1	4.1±1.2	0.045
Qmax (mL/sec)	8.9±4.4	9.3±4.7	0.184
PVR (mL)	67.1±87.4	67.9±91.0	0.933
PSA (ng/mL)	5.6±5.3	3.9±4.5	<0.001
Total prostate volume (mL)	89.6±40.3	65.0±32.4	<0.001
Transition zone volume (mL)	58.4±31.3	36.6±24.5	<0.001
Intraoperative parameters			
Operation time (min)	86.4±38.7	58.8±31.2	<0.001
Enucleation time (min)	48.2±18.5	39.0±19.1	<0.001
Morcellation time (min)	16.5±12.2	9.1±7.6	<0.001
Enucleation weight (g)	38.9±45.8	22.6±20.7	<0.001
Intraoperative capsular perforation	7 (2.7)	54 (2.5)	0.845

Values are presented as mean±standard deviation or number of patients (%).
SP, salvage procedure; IPSS, International Prostate Symptom Score; QoL, quality of life; Qmax, maximum flow rate; PVR, postvoid residual; PSA, prostate-specific antigen.

Table 3. Comparison of postoperative outcomes

Variable	SP (n=260)	Non-SP (n=2,167)	P-value
Postoperative parameters at 2 weeks after surgery			
Total IPSS	12.3±7.3	11.6±7.1	0.262
QoL score	2.7±1.7	2.6±1.6	0.452
Qmax (mL/sec)	19.4 ±9.4	19.9±9.8	0.470
PVR (mL)	24.6±32.1	21.0±37.3	0.316
Postoperative parameters at 3 months after surgery			
Total IPSS	7.5±6.2	8.1±6.0	0.176
QoL score	1.7±1.4	1.8±1.5	0.200
Qmax (mL/sec)	22.4±11.2	21.5±10.9	0.320
PVR (mL)	15.4±26.5	15.8±33.7	0.920
Postoperative parameters at 6 months after surgery			
Total IPSS	6.4±6.2	6.6±5.8	0.616
QoL score	1.3±1.4	1.4±1.4	0.167
Qmax (mL/sec)	22.2±11.1	21.6±11.6	0.569
PVR (mL)	10.8±27.8	13.7±34.7	0.385

Values are presented as mean±standard deviation.
SP, salvage procedure; IPSS, International Prostate Symptom Score; QoL, quality of life; Qmax, maximum flow rate; PVR, postvoid residual.

mL, P < 0.001) than the non-SP group. All intraoperative parameters, including operation time, enucleation time, morcellation time, and enucleation weight, except intraoperative capsular perforation, were significantly greater in the SP group than in the non-SP group (P < 0.001) (Table 2).

The postoperative outcomes are shown in Table 3. All factors, including total IPSS, QoL score, and Qmax at 2 weeks, 3 months, and 6 months after surgery, were not significantly different between the 2 groups (P > 0.05).

Table 4 shows the univariable and multivariable logistic regression analyses of the risk factors for SP for refractory morcellation. In the univariable logistic regression analysis, age, 5-ARIs use, preoperative QoL score, PSA, TPV, and TZV correlated with SP. In the multivariable logistic regression analysis, only age and TZV were associated with SP. Compared to those in their 40s and 50s, the odds ratios (ORs) were 3.84 for those in their 60s (95% confidence interval [CI], 1.37–10.78, P = 0.011), 4.53 for those in their 70s (95% CI, 1.62–12.62, P = 0.004), and

Table 4. Univariable and multivariable logistic regression analysis for salvage procedure for refractory morcellation

Variable	Salvage procedure			
	Univariable analysis		Multivariable analysis	
	Unadjusted OR (95% Cl)	P-value	Adjusted OR (95% Cl)	P-value
Age (yr)				
40–59	Reference		Reference	
60–69	2.61 (1.19–5.73)	0.017	3.84 (1.37–10.78)	0.011
70–79	3.28 (1.51–7.15)	0.003	4.53 (1.62–12.62)	0.004
≥80	6.20 (2.70–14.23)	< 0.001	6.59 (2.23–19.46)	0.001
BMI (kg/m^2)	1.01 (0.97–1.06)	0.614	-	
Duration of LUTS	1.00 (1.00–1.00)	0.782	-	
Previous TURP	1.30 (0.73–2.31)	0.376	-	
Hypertension	1.13 (0.88–1.47)	0.338	-	
Diabetes mellitus	0.97 (0.71–1.32)	0.967	-	
Anticoagulants	1.00 (0.76–1.32)	0.983	-	
α-Blocker	1.18 (0.85–1.64)	0.333	-	
5-ARIs	1.48 (1.13–1.93)	0.004	1.07 (0.78–1.46)	0.680
Anticholinergics	0.82 (0.59–1.14)	0.235	-	
Desmopressin	0.74 (0.44–1.25)	0.258	-	
Total IPSS	1.00 (0.98–1.02)	0.809	-	
QoL score	1.14 (1.00–1.30)	0.046	-	
Qmax	0.98 (0.95–1.01)	0.978	-	
PVR	1.00 (1.00–1.00)	0.933	-	
PSA	1.06 (1.04–1.09)	< 0.001	1.01 (0.98–1.04)	0.409
TPV	1.02 (1.01–1.02)	< 0.001	1.00 (1.00–1.01)	0.456
TZV				
Q1 (0–20.3)	Reference		Reference	
Q2 (20.4–32.0)	2.15 (1.12–4.11)	0.021	1.90 (0.98–3.68)	0.056
Q3 (32.1–50.4)	4.36 (2.39–7.94)	< 0.001	3.75 (2.00–7.04)	< 0.001
Q4 (> 50.4)	11.49 (6.52–20.26)	< 0.001	8.25 (4.06–16.77)	< 0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; LUTS, lower urinary tract symptoms; TURP, transurethral resection of the prostate; 5-ARIs, 5-alpha reductase inhibitors; IPSS, International Prostate Symptom Score; QoL, quality of life; Qmax, maximum flow rate; PVR, postvoid residual; PSA, prostate-specific antigen; TPV, total prostate volume; TZV, transition zone volume; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

6.59 in those in their 80s or older (95% CI, 2.23–19.46, P=0.001). The ORs of the SP were analyzed per TZV quartile (first quartile: 0 to 20.3 mL, second quartile: 20.4 to 32.0 mL, third quartile: 32.1 to 50.4 mL, fourth quartile: >50.4 mL). Compared to the TZV ≤20.3 mL, the OR was 3.75 in 32.0 mL <TZV ≤50.4 mL (95% CI, 2.00–7.04, P<0.001) and 8.25 in 50.4 mL <TZV (95% CI, 4.06–16.77, P<0.001).

DISCUSSION

Since HoLEP surgery was initiated, efficient retrieval of enucleated prostatic adenoma tissue from the bladder has remained an important issue [8]. The transurethral prostate morcellator device (PMD) has been widely used for the retrieval of enucleated prostatic tissue in HoLEP surgery since its introduction in 1998 [9,10]. Currently, 2 PMDs are widely used for the morcellation of enucleated prostatic tissue: the Piranha (Richard Wolf Inc., Knittlingen, Germany) and VersaCut (Lumenis Inc., Santa Clara, CA, USA). The Richard Wolf Piranha operates with a rotary serrated blade mechanism, which moves prostatic tissue from side to side. In contrast, the Lumenis VersaCut operates with a reciprocating blade mechanism that moves the prostatic tissue forward and backward [11].

In most HoLEP surgeries, morcellation is performed without difficulty. However, in some cases, we experience refractory morcellation as the hard spherical prostatic tissue repeatedly escapes from the blade of the morcellator. In a previous study, this phenomenon was referred to as the "crazy ball effects" of the tissue spheres against the morcellator [5]. In another study, spherical prostatic tissue that resisted morcellation was referred to as "beach balls" [12]. Prostatic tissue that resists morcellation exhausts surgeons. In such cases, an additional procedure is required to remove the adenoma tissue. Additional procedures, which we call SPs, are usually performed with resection of the adenoma tissue floating in the bladder using an electrosurgical loop or secondary morcellation a few days after surgery. Moreover, there was only one case of a patient with a huge prostate in which the bladder was opened and enucleated prostatic tissue was removed. These additional procedures have the disadvantage of being cumbersome and time-consuming for both patients and surgeons. Furthermore, SPs used for adenoma tissue retrieval have the potential to cause bladder injuries. Despite these inconveniences and risks, SPs are inevitably required to remove adenoma tissue in some cases. In Korea, the current national health insurance system does not cover additional costs incurred during HoLEP surgery, including the cost of disposable electrodes, electrocautery depreciation, and surgeons' effort and time. The results of this study will be used as a basis for insurance coverage for additional device costs incurred during HoLEP surgery.

In the univariable logistic analysis, age, 5-ARIs use, preoperative QoL score, PSA, TPV, and TZV were correlated with SP. However, the multivariable logistic analysis showed that only age and TZV were correlated with SP. When TZV increases, TPV also increases; therefore, TZV has a close relationship with TPV. Based on the results of this study, it is difficult to explain why TPV does not correlate with SP. Previous studies have reported an increase in prostate size with age [13,14]. In addition, serum PSA levels are correlated with prostate volume and patient age [15]. The results of this study reflect those of the previous studies. However, despite the association between age and prostate volume, the multivariable logistic analysis showed that both age and TZV were risk factors for SPs. Multicollinearity analysis using linear regression confirmed the absence of multicollinearity between age and TZV (r=0.077, P<0.001). Therefore, age and TZV were independent risk factors for SPs.

Postoperative parameters, including IPSS, QoL score, Qmax, and PVR, were not significantly different between the 2 groups. Therefore, whether SPs were performed or not did not affect the therapeutic effect of HoLEP surgery. 5-ARIs use was significantly higher in the SP group than that in the non-SP group. 5-ARI, one of the representative drug treatments for BPH, is known to be accompanied by approximately 20%–30% reduction in prostate size by inhibiting the conversion of testosterone to dihydrotestosterone in prostatic tissue [16]. When 5-ARI is administered to patients with BPH, the size of the prostate is reduced through the influence of hormones and apoptosis in the prostatic tissue [17]. The hardening of prostate tissue due to apoptosis of prostate tissue by 5-ARI administration is presumed to affect the difficulty of morcellation.

Our previous study reported that the pathological finding of a hard nodule with refractory morcellation was fibrotic tissue [6]. One study reported that chronic ischemia results in thickening and fibrosis of the prostate, which changes its mechanical properties [18]. Another study reported that prostatic tissue from ischemic animals showed increased collagen deposition [19]. Another study suggested that age-related arterial insufficiency may produce ischemia and lead to fibrosis, resulting in structural changes [20]. Based on previous studies, it seems clear that ischemia is the most important factor that makes

prostatic tissue hard. This study showed that 5-ARI was not a risk factor for SPs, whereas age was a risk factor. These findings suggest that age is a more important factor affecting fibrosis of prostatic tissue than 5-ARI.

This study has some limitations. First, it was a retrospective study. In cases such as prospective patient enrollment studies, patients who did not consent before surgery are excluded from the study data, which may lead to unwanted patient selection bias. Although this was a retrospective study, it has the advantage of minimizing the possibility of patient selection bias because all patients who received HoLEP during a specific period were included in the study. This study was conducted using prospectively collected data from actual clinical settings. Second, the criteria for performing SP were subjective. Although we set the standard for the SP when the morcellation failed even after performing morcellation for more than 10 minutes, our subjective experience was inevitably involved. However, the surgeon did not routinely perform the SP, and both the SP and non-SP groups were operated with the same criteria. Over 10 years after performing HoLEP, we have constantly recognized the problem of hard prostatic tissue, which is difficult to morcellate. The transurethral PMDs currently in use show sufficient performance, but are not yet perfect. A previous study reported that the morcellation rates of different morcellators could be increased by optimizing the oscillation speed and suction power settings [21]. However, even though we tried various changes in speed and power settings in actual clinical practice, hard prostatic tissue with refractory morcellation still existed. A previous study reported no difference in morcellation outcomes and the presence of beach balls between Piranha and VersaCut [11]. Therefore, it is considered that the problem of ineffective morcellation of hard prostatic tissue has not been completely solved. Therefore, it is necessary to develop a new PMD to solve these problems.

In conclusion, age and TZV were risk factors for SPs due to refractory morcellation during HoLEP surgery. In particular, the risk of refractory morcellation increases in patients who are over 60 years of age or have TZV > 32 mL. In order to more efficiently remove these resistant adenomas, it is necessary to develop more efficient morcellators in the future.

AUTHOR CONTRIBUTION STATEMENT

· Conceptualization: *SJO*
· Methodology: *JSP, SJO*
· Data collection: *HSY, DHC*
· Formal analysis: *HSY, SJO*
· Investigation: *HSY, SJO*
· Writing - original draft: *HSY*
· Writing - review and editing: *SYC, MCC, SJO*

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