Usefulness of a novel classification based on perioperative changes of membranous urethral length using hierarchical cluster analysis of urinary incontinence and overactive bladder symptoms after robot-assisted radical prostatectomy: A prospective observational study

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ABSTRACT

Aims: The aim of the present study was to construct a novel classification based on perioperative changes of membranous urethral length (MUL) using hierarchical cluster analysis to predict urinary incontinence (UI) and overactive bladder (OAB) symptoms after robot-assisted radical prostatectomy (RARP).

Methods: A total of 299 patients who underwent RARP with complete pre- and postoperative MUL data were included in the present study. Hierarchical cluster analysis was performed to identify the groups with similar perioperative MUL and prostate size. UI and OAB symptoms after RARP were evaluated in each cluster for 12 months after RARP.

Results: Four groups were identified by the cluster analysis of these factors: preservation of MUL type (cluster 1, n=92); standard type (cluster 2, n=137); large prostate type (cluster 3, n=23) and loss of MUL type (cluster 4, n=47). Although there was significantly more UI in clusters 3 and 4 than in clusters 1 and 2 up to 3 months after RARP, UI improvement was the most delayed in cluster 3. Improvement of OAB symptoms was also most delayed in cluster 3. Urinary QOL was significantly worse in cluster 4 than in clusters 1 and 2.

Conclusions: Cluster analysis successfully classified patients after RARP into 4 characteristic groups based on perioperative MUL. Recovery from UI and OAB symptoms and urinary QOL after RARP were significantly different among these groups. This classification based on cluster analysis might be useful to predict recovery from UI and OAB symptoms when following QOL after RARP.

Keywords: membranous urethral length, robot-assisted radical prostatectomy, cluster analysis, urinary incontinence, overactive bladder.

INTRODUCTION

Even in the era of robotic surgery, there is still a constant percentage of patients with urinary incontinence (UI) and overactive bladder (OAB) symptoms after radical prostatectomy (RP).[1-4] Several studies investigated the associations between UI or OAB symptoms after RP and preoperative or postoperative membranous urethral length (MUL).[5-10] These previous studies independently investigated only the associations between UI or OAB symptoms and preoperative or postoperative MUL. [7,9,10] However, some patients with longer preoperative MUL lose part of their MUL due to operative procedures, and the postoperative MUL is severely shortened after RP. On the other hand, other patients with shorter preoperative MUL maintain their MUL postoperatively because of meticulous maneuvers during surgery. In these patients, postoperative MUL is relatively longer. In addition, prostate size affects the change of MUL after RP.[11] As just described, several characteristics of MUL and prostate size can be seen in patients during the perioperative period. Therefore, multiple factors, rather than a single factor, related to perioperative MUL should be considered when discussing the association between MUL and postoperative UI and OAB.

Cluster analysis is a useful method to classify subjects into groups with similar characteristics and is now often used in the medical field.[12-16] Thus, we presumed that post-RP patients could be divided into groups by cluster analysis using multiple factors related to MUL, and each cluster might have characteristic symptoms. To evaluate the usefulness of cluster analysis using multiple factors related to MUL as a predictior of UI and/or OAB symptoms after robot-assisted radical prostatectomy (RARP), the present study investigated whether post-RARP patients could be classified into characteristic groups and examined the associations between each group and postoperative UI and OAB symptoms.

MATERIALS AND METHODS

Patients

This prospective cohort study involved 359 consecutive patients who underwent RARP at our institution between February 2012 and December 2017. All cases underwent RARP using the 4-arm Da Vinci Si surgical system (Intuitive Surgical, Sunnyvale, CA, USA) with combined posterior and anterior intraperitoneal approaches and early exposure of the seminal vesicles and vasa deferentia.[17] The Rocco stitch was performed for posterior reconstruction of Denonvilliers' fascia.[18] Magnetic resonance imaging (MRI) was performed before and 9 months after RARP to evaluate pre- and postoperative MUL. Lower urinary tract symptoms (LUTS) and lower urinary tract function were evaluated before and, 1, 3, 6, 9, and 12 months after RARP.

No patients had baseline lower urinary tract abnormalities, such as neurogenic bladder, or a past history of transurethral resection of the prostate. Patients who underwent preoperative and postoperative MRI and whose LUTS and lower urinary tract function were evaluated for 12 months after RARP, fit the inclusion criteria. Thus, 299 patients were finally assessed in the present study (Figure 1).

Evaluations of MUL

Measurements of MUL were performed using a 1.5-T, whole-body, magnetic resonance scanner (Signa, GE Medical Systems, Milwaukee, WI) before and after RARP. MRI was reviewed by one reviewer (Y.K with seven years of experience in pelvic imaging) to assess the MUL. This observer was blinded to the patients' characteristics. Preoperative MUL was defined as the distance from the apex of the prostate to the urethra at the level of the penile bulb (Figure 2A).[7] Postoperative MUL was defined as the distance from the bladder neck to the urethra at the level of the penile bulb (Figure 2B).[7] Both measurements were done in the sagittal plane on T2-weighted images (Figures 2A and 2B). The percent change of MUL was calculated by dividing the difference between preoperative and postoperative MULs by the preoperative MUL.[7]

Evaluation of UI, OAB symptoms, and lower urinary tract function

UI was evaluated by the 1-h pad test.[19] LUTS was evaluated by the Overactive Bladder Symptom Score (OABSS), International Prostate Symptom Score (IPSS), and quality of life (QOL) index. The maximum flow rate (MFR) was evaluated by uroflowmetry, and post-void residual urine volume

(PVR) was evaluated by ultrasonography.

Parameter selection in hierarchical cluster analysis

Pre- and postoperative MUL, percent change of MUL between pre- and postoperative MUL, and prostate size were used in this cluster analysis. Because large prostate size is related to the reduction of MUL after RP,[11] prostate size was included in this analysis. The weight of the prostate removed by RARP was used as the prostate size. After clustering, LUTS and lower urinary tract function were compared among the clusters.

This study was performed with the approval of the Ethics Committee at our institution (clinical trial registration No. 2334). The purpose and methods of this study were explained to the patients, and informed consent was obtained from all patients before the study. UI was evaluated as a primary endpoint, and other factors including LUTS and lower urinary tract function were evaluated as secondary endpoints among the clusters.

Statistical analysis

Continuous variables are presented as means ± standard deviation, and categorical variables are shown as percentages. Hierarchical clustering analysis of the factors related to UI after RARP was performed based on Ward's method of assessing the Euclidean distance between objects. The appropriate number of clusters was estimated based on the cubic clustering criterion.[13] The distribution of background factors and urinary function were compared among the clusters using analysis of variance (ANOVA) and/or the Tukey-Kramer honestly significant difference (HSD) test for continuous variables and the chi-squared test for categorical variables. In all analyses, $p<0.05$ was considered significant. The results were analyzed using the JMP 14.0 software packages (SAS Institute Japan, Tokyo Japan).

RESULTS

Patients' characteristics and cluster analysis

The baseline characteristics of the 299 patients are summarized in Table 1A. When the patients were clustered by 4 factors the cubic clustering criterion indicated that 4 clusters may be the appropriate number. These 4 clusters also resulted in the clinically optimal classification on ANOVA and Turkey-Kramer HSD testing (Tables 1B and 1C). The characteristics of each cluster are shown as radar charts in Figure 3.

Cluster 1 was the second largest group, accounting for 30.8% (92/299) of the present cohort (Table 1B). In this cluster, MUL was almost the same before and after RARP, with a shorter preoperative MUL than the average value. This cluster was called the "preservation of MUL" type. Cluster 2 was the largest group, accounting for 45.8% (137/299) of the present cohort (Table 1B). Pre- and postoperative MUL, percent change of MUL, and prostate size in this cluster were almost the average values in this study. Thus, this cluster was called "standard" type. Cluster 3 accounted for

7.7% (23/299) of the present cohort (Table 1B). The patients in this cluster had the largest prostate size and longer preoperative MUL than all clusters, but more MUL was lost after RARP than the average value. In this cluster, although preoperative MUL was the longest of all clusters, postoperative MUL was the second shortest of all clusters. This cluster was called “large prostate” type. Cluster 4 accounted for 15.7% (47/299) of the present cohort (Table 1B). The patients in this cluster also lost more MUL after RARP, with shorter preoperative MUL than the average value. In this cluster, postoperative MUL was the shortest of all clusters. This cluster was called “loss of MUL” type.

Comparisons of UI, OAB symptoms, and lower urinary tract function

UI was significantly more severe in cluster 3 than in cluster 2 at 3, 6, and 9 months after RARP ($p=0.0135$, $p=0.0002$, and $p=0.0395$, respectively) and in cluster 1 at 6 months after RARP ($p=0.0132$) (Figure 4A). It was significantly more severe in cluster 4 than in clusters 1 and 2 at 1 month after RARP ($p=0.0206$, $p=0.0016$, respectively) and at 3 months after RARP ($p=0.0016$, $p<0.0001$, respectively) (Figure 4A). Thus, improvement of UI was delayed most in cluster 3.

LUTS evaluated by OABSS, IPSS, and the QOL index worsened transiently at 1 month after RARP in all clusters, but it then gradually improved with time (Figures 4B,4C and 4D). The OABSS total score was significantly higher in cluster 3 than in clusters 1 and 2 at 6 months after RARP ($p=0.0161$, $p=0.0061$, respectively) (Figure 4B). However, the IPSS total score was not significantly different among the clusters during the observational period (Figure 4C). The QOL index was significantly higher in cluster 4 than in cluster 1 at 3 and 6 months after RARP (p=0.0327, p=0.0245, respectively), and it was significantly higher in cluster 4 than in cluster 2 at 6 months after RARP (p=0.0127) (Figure 4D).

MFR after RARP was not significantly different among the clusters (Figure 4E). In addition, a significant difference in PVR was observed only between clusters 1 and 2 at 1 month after RARP (p=0.0276) (Figure 4F).

DISCUSSION

On cluster analysis with multiple factors, patients are separated into groups with similar characteristics without an a priori hypothesis.[13] Until now, cluster analysis was used in the field of oncology to identify groups of patients with similar symptoms or genetic profiles.[14,15] In addition, patients who underwent orthotopic neobladder reconstruction for bladder cancer were successfully categorized into several groups by cluster analysis using their voiding patterns.[16] Further, our group has previously reported that men with LUTS were classified into several groups by cluster analysis using the IPSS, and we demonstrated the efficacy of tamsulosin in each symptom groups.[12,13] In this way, cluster analysis was useful to identify discriminative patterns in subjects with many factors.

In the present study, based on the factors related to perioperative MUL, post-RARP patients were successfully divided into 4 clusters: preservation of MUL type (cluster 1); standard type (cluster 2);

large prostate type (cluster 3); and loss of MUL type (cluster 4). Improvement of UI was most delayed in the large prostate type (cluster 3). Regarding patients' reported outcomes evaluated by OABSS and the QOL index, improvement of OAB symptoms was also the most delayed in the large prostate type (cluster 3). QOL was significantly worse in the loss of MUL type (cluster 4) than in the preservation of MUL type (cluster 1) and the standard type (cluster 2).

Several studies demonstrated that preoperative MUL was an important factor associated with early resolution of UI after RP.[20,21] However, in this study, although preoperative MUL was longest in the large prostate type (cluster 3), UI was most prolonged in this type among these 4 clusters. On the other hand, although preoperative MUL was shortest in the preservation of MUL type (cluster 1), postoperative UI was less in this cluster than in the large prostate type (cluster 3) and the loss of MUL type (cluster 4). As well as preoperative MUL, several studies demonstrated that postoperative MUL was an important factor involved in the early resolution of UI after RP.[9,10] Although postoperative MUL was significantly shorter in the loss of MUL type (cluster 4) than in the large prostate type (cluster 3), UI was more prolonged in the large prostate type (cluster 3) than in the loss of MUL type (cluster 4). These data imply that only one preoperative parameter, i.e., preoperative MUL or postoperative MUL, could not predict postoperative UI. Because UI after RP would be influenced by multiple parameters consisting of patients' and perioperative factors, cluster analysis that could comprehensively evaluate the multiple parameters at one time is an ideal tool for evaluating UI after RP.

In the present study, improvement of UI, OAB symptoms, and QOL had a tendency to be delayed in the large prostate type (cluster 3) and the loss of MUL type (cluster 4) compared with the other two clusters. However, the large prostate type (cluster 3) and the loss of MUL type (cluster 4) had completely different time course changes of UI and OAB symptoms. UI and OAB symptoms were significantly prolonged in the large prostate type (cluster 3), and they improved rapidly in the loss of MUL type (cluster 4) after RARP. The different time course changes of UI and OAB symptoms between the two clusters might be related to the degree of bladder neck preservation.[22] Because it is difficult to preserve the bladder neck in the large prostate,[22] less preservation of the bladder neck occurred in the large prostate type (cluster 3). Less preservation of the bladder neck could induce inflow of urine into the urethra, leading to urgency incontinence.[10] Both urgency incontinence, which was one of the OAB symptoms, and stress urinary incontinence might have occurred in the large prostate type (cluster 3), resulting in the prolonging UI and OAB symptoms after RARP. On the other hand, because the bladder neck could be preserved with a not so large prostate in the loss of MUL type (cluster 4), UI and OAB symptoms might improve rapidly 6 months after RARP.

Urinary QOL was significantly worse in the loss of MUL type (cluster 4) than in the large prostate type (cluster 3). One of the causes for this might be the preoperative LUTS and lower urinary function in the loss of MUL type (cluster 4). The preoperative OABSS total score, IPSS total score, and QOL index were identical in the loss of MUL type (cluster 4), preservation of MUL type (cluster 1) and standard type (cluster 2). Although no significant differences were observed, the large prostate type (cluster 3) had a tendency to score high on those items. Furthermore, preoperative PVR was significantly greater in the large prostate type (cluster 3) than in other clusters. Thus, preoperative LUTS, urinary QOL, and lower urinary tract function were worse in the large prostate type (cluster 3) than in the loss of MUL type (cluster 4). These preoperative differences might induce the difference in postoperative urinary QOL. That is, the patients in the loss of MUL type (cluster 4) may have worried excessively about UI and LUTS after RARP due to better lower urinary tract function before RARP, whereas the patients in the large prostate type (cluster 3) might worry little about them after RARP due to the worse preoperative LUTS and lower QOL before RARP.

Two limitations must be considered in this study. First, this study had a relatively small sample size from a single institution. However, to the best of our knowledge, the sample size of this study is the largest of the studies that evaluated UI and OAB symptoms. Second, although perioperative MUL and prostate size were considered to be among the most important factors related to UI after RP, factors other than MUL and prostate size, such as age, nerve-sparing, and so on, might be involved in the UI and LUTS after RP.[20] However, although age, pathological stage of prostate cancer, and nerve-sparing status were evaluated among each cluster, there were no significant differences in these factors among the clusters.

CONCLUSIONS

In this cluster analysis, 4 characteristic groups with different perioperative MULs and prostate sizes were identified. Recovery from UI and OAB symptoms following urinary QOL after RARP was significantly different among these clusters. Thus, cluster analysis was useful for predicting the UI and OAB symptoms after RARP, which were affected by various pre-and postoperative parameters.

Conflict of Interest

The authors declare that they have no conflict of interest.

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LEGENDS

Figure 1. Flow chart of patient selection

Figure 2. Representative magnetic resonance images of pre- and postoperative membranous urethral lengths

These figures show preoperative membranous urethral length (MUL) measured in the sagittal plane (A) and postoperative MUL measured in the sagittal plane (B). Each measurement was done on T2-weighted images. The yellow lines indicate the MUL.

Figure 3. Radar charts showing the characteristics of each cluster

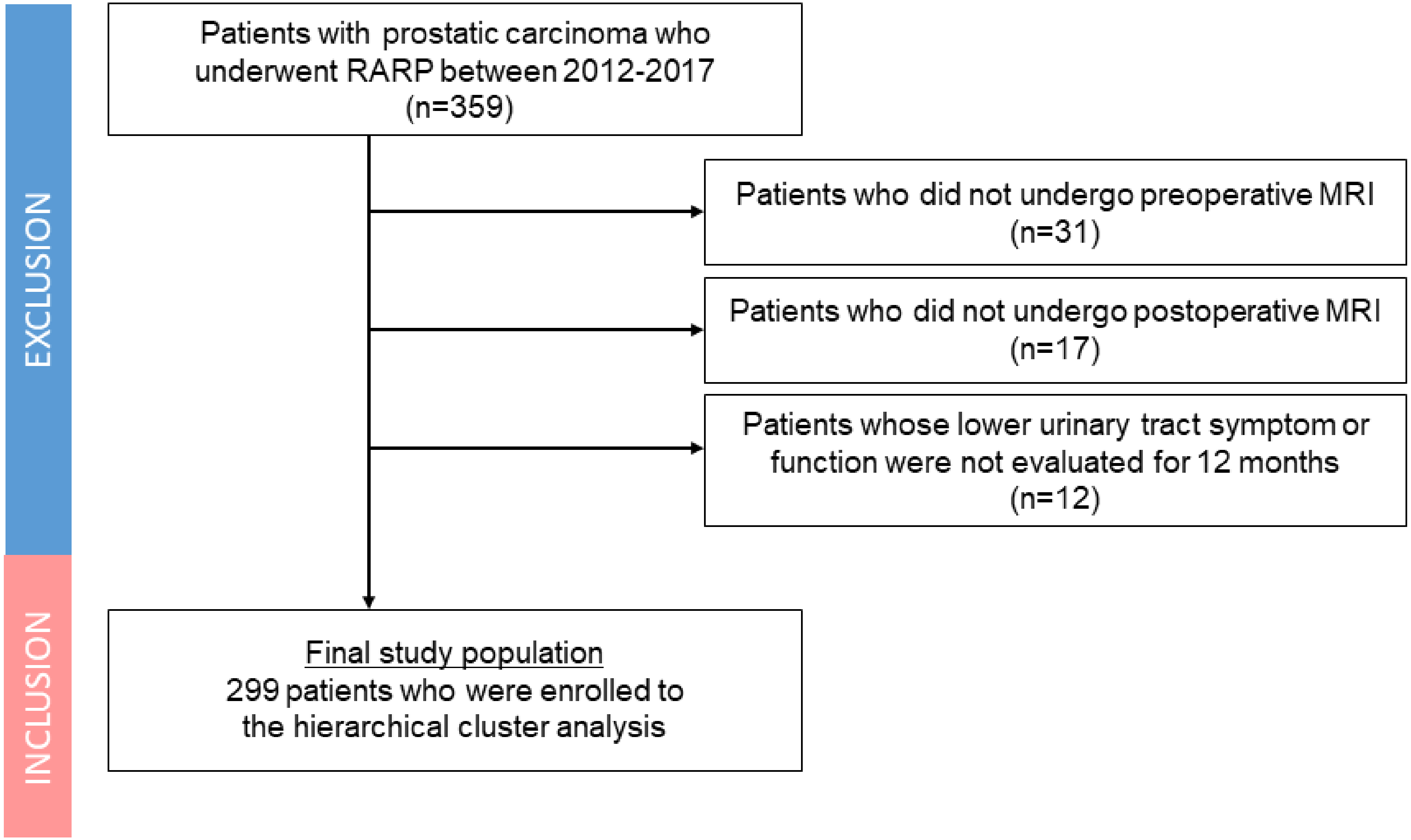
Corners represent the mean score of each factor in each cluster. The gray line shows the mean score of each factor in the present cohort.

Figure 4. Group comparison of each cluster of urinary incontinence, lower urinary tract symptoms, and lower urinary tract functions before and after RARP

OABSS, Overactive Bladder Symptom Score; IPSS, International Prostate Symptom Score; QOL, quality of life. MFR, maximum flow rate; PVR, post-voided residual urine volume. Each point represents the mean value of each cluster.

*$p<0.05$

Figure 1



EXCLUSION
INCLUSION
Patients with prostatic carcinoma who underwent RARP between 2012-2017 (n=359)
Patients who did not undergo preoperative MRI (n=31)
Patients who did not undergo postoperative MRI (n=17)
Patients whose lower urinary tract symptom or function were not evaluated for 12 months (n=12)
Final study population
299 patients who were enrolled to the hierarchical cluster analysis

Figure 2

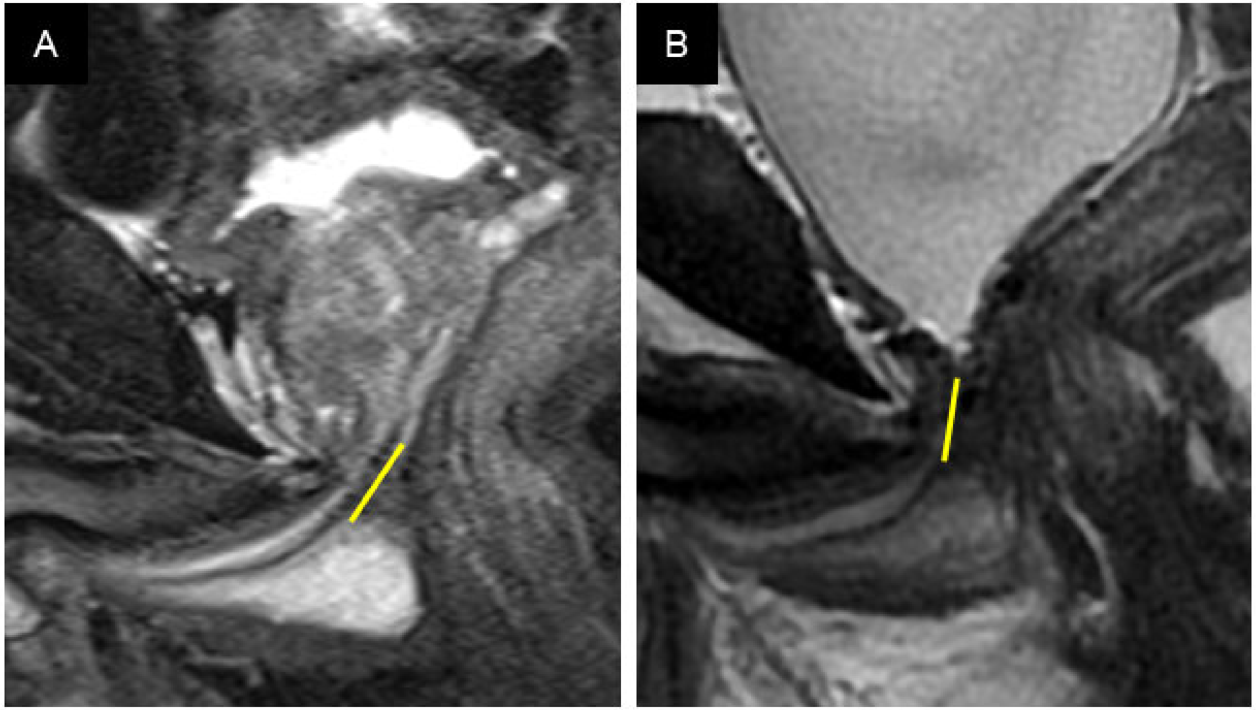


Figure 3

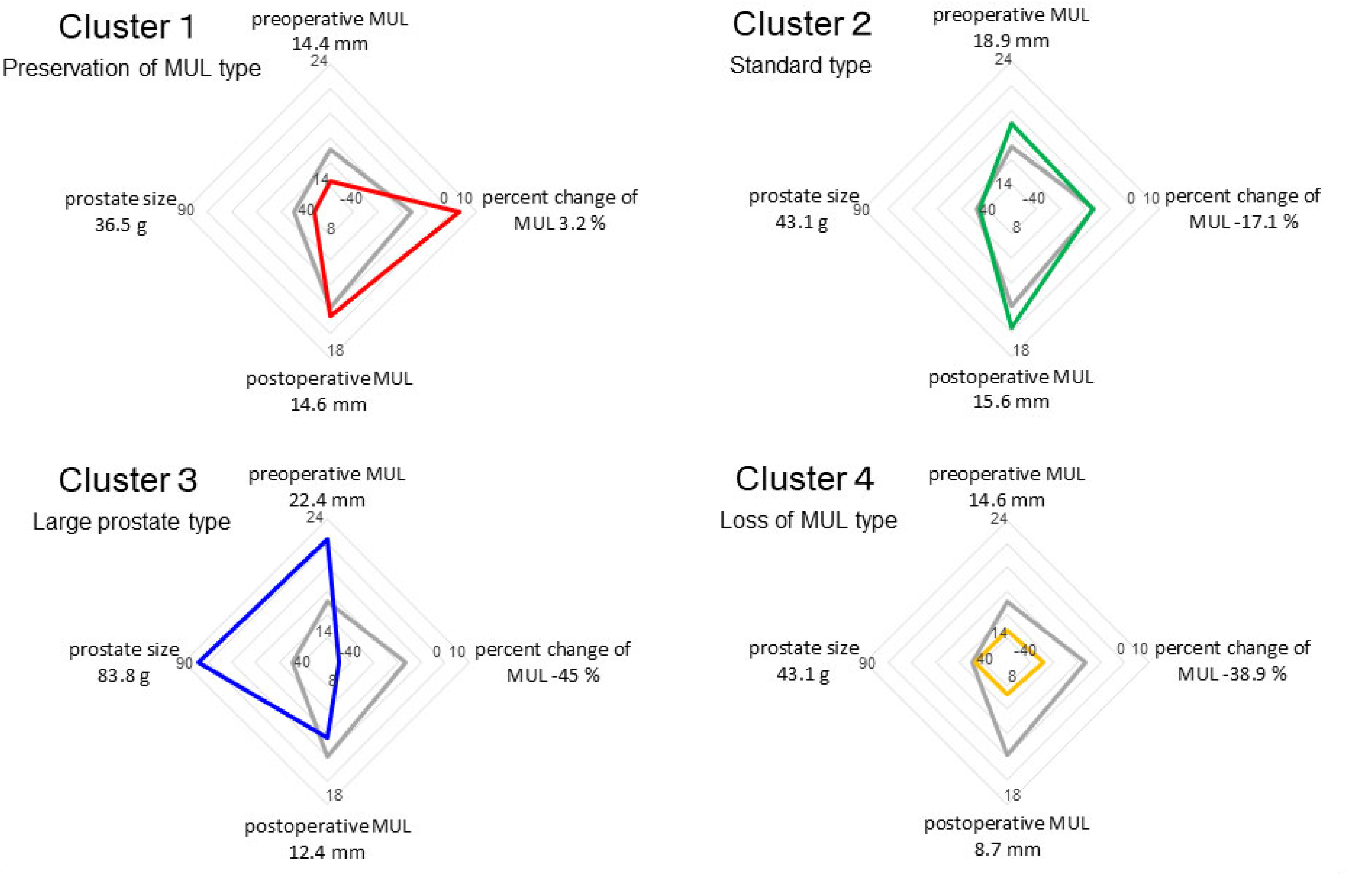
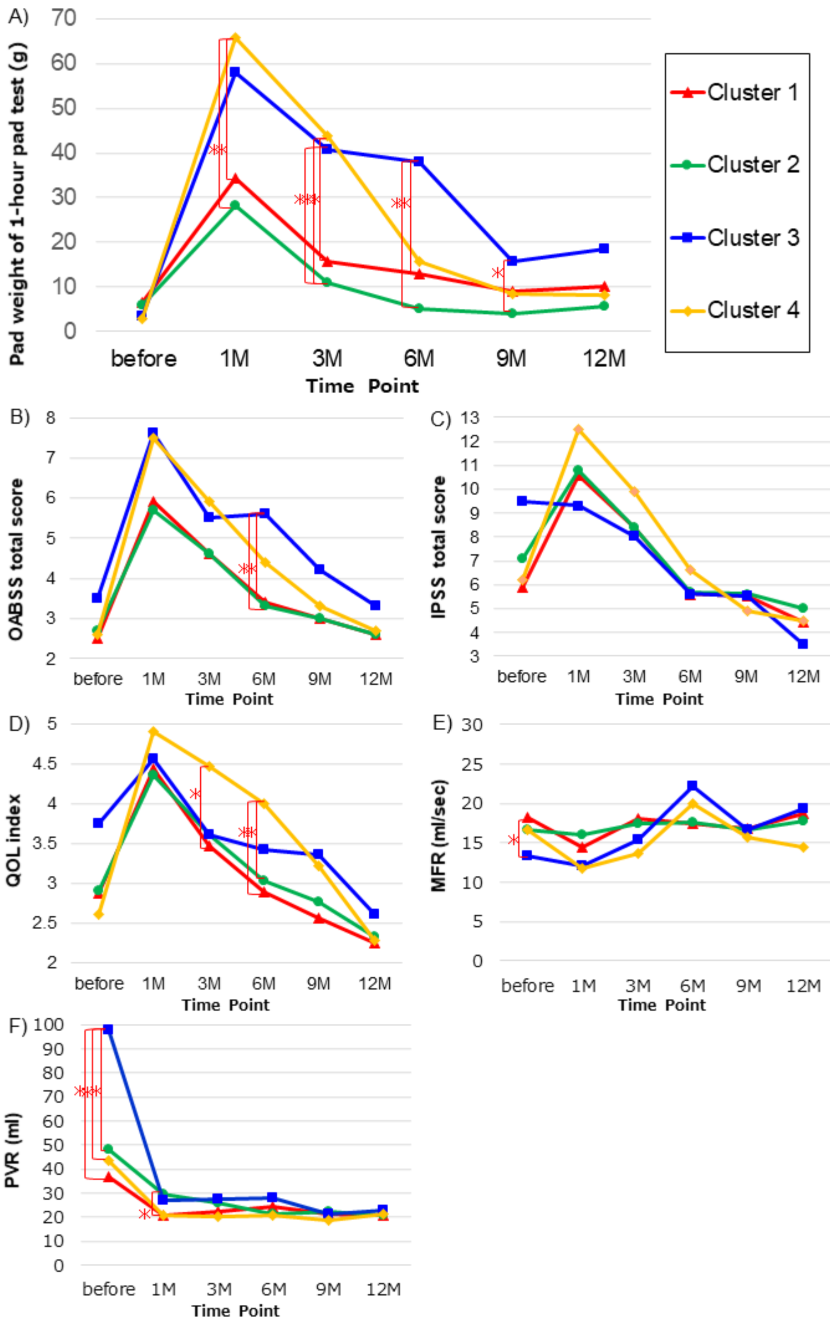

Cluster 1
Preservation of MUL type
preoperative MUL
14.4 mm
percent change of
MUL 3.2 %
postoperative MUL
14.6 mm
prostate size
36.5 g
Cluster 2
Standard type
preoperative MUL
18.9 mm
percent change of
MUL -17.1 %
postoperative MUL
15.6 mm
prostate size
43.1 g
Cluster 3
Large prostate type
preoperative MUL
22.4 mm
percent change of
MUL -45 %
postoperative MUL
12.4 mm
prostate size
83.8 g
Cluster 4
Loss of MUL type
preoperative MUL
14.6 mm
percent change of
MUL -38.9 %
postoperative MUL
8.7 mm
prostate size
43.1 g

Figure 4



A)
Pad weight of 1-hour pad test (g)
70
60
50
40
30
20
10
0
before
1M
3M
6M
9M
12M
Time Point
Cluster 1
Cluster 2
Cluster 3
Cluster 4
B)
OABSS total score
Time Point
C)
IPSS total score
Time Point
D)
QOL index
Time Point
E)
MFR (ml/sec)
Time Point
F)
PVR (ml)
Time Point

Table 1.

A) Patient characteristics

Variables	Mean±SD or %
Number of patients	299
Age, years old	66.9±4.9
Preoperative PSA, ng/ml	10.2±10.4
Nerve preservation, %	24.2
Operation time, min	221.5±47.7
Estimated blood loss, ml	284.2±264.7
GS, %	
≦6	13.9
7	57.6
≧8	28.5
Pathologic stage ≧pT3, %	26.3
Preoperative MUL, mm	17.1±4.1
Percent change of MUL, %	-16.6±22
Postoperative MUL, mm	13.9±3.8
Prostate size, g	44.3±17.8

PSA, prostate specific antigen; GS, Gleason score; MUL, membranous urethral length.

B) Clinical characteristics of the patients in each clusters

Variables	Cluster 1	Cluster 2	Cluster 3	Cluster 4	p
Number of patients	92	137	23	47	
Percentage of patients, ％	30.8	45.8	7.7	15.7	
Age, years old	66.4±5.5	66.8±4.8	68.6±4.8	67.4±5.0	0.2324
Nerve preservation, ％	24.2	21.9	23.4	24.2	0.3603
Pathologic stage ≧pT3, ％	28.6	28.2	8.33	25.5	0.2127
Preoperative MUL, mm	14.4±2.9	18.9±3.1	22.4±4. 7	14.6±2.6	＜.0001
Percent change of MUL, ％	3.2±19.6	-17.1±12.1	-45.0±11.0	-38.9±14.0	＜.0001
Postoperative MUL, mm	14.6±2.9	15.6±3.1	12.4±4.4	8.7±1.8	＜.0001
Prostate size, g	36.5±10.2	43.1±13.2	83.8±24.7	43.1±9.5	＜.0001

MUL, membranous urethral length.

C) Tukey-Kramer HSD comparison of each parameter used in cluster analysis among each cluster

Preoperative MUL

Comparison among each Cluster	Preoperative MUL difference (mm)	95% CI (mm)	p
3 vs 1	8.2	6.3, 10	<.0001
3 vs 4	7.9	5.9, 9.9	<.0001
2 vs 1	4.6	3.5, 5.7	<.0001
2 vs 4	4.3	2.9, 5.6	<.0001
3 vs 2	3.6	1.8, 5.4	<.0001
4 vs 1	0.3	-1.1, 1,8	0.9441

Postopreative MUL

Comparison among each Cluster	Postoperative MUL difference (mm)	95% CI (mm)	p
2 vs 4	6.82	39.5, 55.1	<.0001
1 vs 4	5.83	32.1, 49.2	<.0001
3 vs 4	3.7	33.1, 48.2	<.0001
2 vs 3	3.11	2, 11.3	<.0001
1 vs 3	2.11	0.5, 12.8	<.0001
2 vs 1	0.99	-5.7, 5.8	1

Percent change of MUL

Comparison among each Cluster	Percent change of MUL difference (%)	95% CI (%)	p
1 vs 3	48.3	39.4, 57.2	<.0001
1 vs 4	42.1	35.1, 49.1	<.0001
2 vs 3	28	19.4, 36.5	<.0001
2 vs 4	21.8	15.3, 28.3	<.0001
1 vs 2	20.3	15.1, 25.5	<.0001
4 vs 3	6.2	-3.5, 15.9	0.3562

Prostate size

Comparison among each Cluster	Prostate size difference (g)	95% CI (g)	p
3 vs 1	47.3	39.5, 55.1	<.0001
3 vs 4	40.7	32.1, 49.2	<.0001
3 vs 2	40.6	33.1, 48.2	<.0001
2 vs 1	6.6	2, 11.3	<.0001
4 vs 1	6.6	0.5, 12.8	<.0001
2 vs 4	0	-5.7, 5.8	1

HSD, honestly significant difference. MUL, membranous urethral length. CI, confidence interval.