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Postsurgical urodynamic study of total laparoscopic nerve-sparing radical hysterectomy for uterine cervical cancer

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Short running title: Urodynamic study of radical surgery

Abstract

Aim: To evaluate the impact on urodyamic results between the laparoscopic nerve-sparing radical hysterectomy following a step-by-step procedure (LRH) and abdominal nerve-sparing hysterectomy (ARH) for patients with uterine cervical cancer.

Methods: This retrospective study enrolled 76 patients with cervical cancer: 35 in the LRH group and 41 in the ARH group. We analyzed their post-operative bladder function in a urodynamics study and examined the volume of resected pelvic nerves contained in parametrial sections using S-100 antibody staining.

Results: Estimated blood loss and hospital stay after operation for the LRH group were significant better than those in the ARH group ($p<0.0001$). As well, the number of harvested lymph nodes was significantly higher in the LRH group ($p=0.044$). There was no difference in perioperative complications between the two groups in this study. The 5-year disease-free survival rates and overall survival rates were 91.2% and 94.0% in the LRH group and 87.8% and 95.1% in the ARH group, both respectively. Although the median residual urine volume were no statistical differences between the LRH group and the ARH group, the recovery of post-operative bladder function (uroflowmetry) in the LRH group rapidly reached pre-surgery levels at 1 month, and the LRH group had a smaller number of s-100 antibody stained nerves contained the parametrial sections.

Conclusion: We demonstrated that laparoscopic nerve-sparing radical hysterectomy following a step-by-step procedure could achieve a higher level of prevention of damage to the bladder branch of the pelvic splanchnic nerve plexus and thus restore bladder function more rapidly.

Keywords: cervical cancer, urodynamics study, laparoscopic radical hysterectomy, laparoscopic nerve-sparing radical hysterectomy, S-100, minimally invasive surgery,

Introduction

The standard surgical approach for stage 1B and 2A cervical cancer is radical hysterectomy, and 63-65% of patients undergo surgery as the main treatment[1]. Radical abdominal hysterectomy for cervical cancer was firmly established in Japan by Okabayashi [2], with an efficacy equal to that of radiation therapy. It is well known that radical hysterectomy can be complicated by postoperative morbidities such as dysfunction of the lower urinary tract and loss of bladder function and sensation[3] [4] [5]. In order to prevent damage to the bladder branch from the inferior hypogastric nerve and the pelvic splanchnic nerve plexus during radical hysterectomy, a nerve sparing radical

hysterectomy has been developed by various surgeons [6-8] [9-11].

In 1992, the laparoscopic radical hysterectomy was first reported for the treatment of cervical cancer [12]. Compared to open surgery, LRH can reduce surgical morbidities such as intraoperative blood loss and lower the risk of postoperative complications [12-16]. Recently, some authors have reported on laparoscopic nerve sparing radical hysterectomy for patients with stage IA2 to IIA cervical cancer [17-21]. However, there have been few reports on urinary function where urodynamics *and* immunohistochemical of the pelvic nerves using the S-100 antibody are compared between LRH and ARH for cervical cancer. In this study, we assessed urodynamic analysis results from both procedures.

Materials and Methods

From May 2013 to April 2018, 76 patients with International Federation of Gynecology and Obstetrics (FIGO)(FIGO 2008) stage IB1, stage IB2, stage IIA1, stage IIA2, or stage IIB cervical cancer underwent a class C1 laparoscopic nerve sparing radical hysterectomy or a class C1 abdominal nerve sparing radical hysterectomy [22]. We explained the methods, merits, and risks of both surgeries (laparoscopic radical hysterectomy and abdominal radical hysterectomy) for the patients, and they chose either

of the two procedures. Informed consent was obtained from each patient before surgery, and all subjects in this study had their initial pathologic diagnosis confirmed at our institution. The consecutive medical charts of these 76 patients were retrospectively reviewed. Thirty-five patients underwent a laparoscopic nerve sparing radical hysterectomy (LRH group) by a single gynecologic expert surgeon (YT), and 41 patients underwent an abdominal nerve sparing radical hysterectomy (ARH group) by two expert surgeons (YT or MO).

We perform the laparoscopic nerve sparing radical hysterectomy with a pelvic lymphadenectomy under general anesthesia with the patient in the doesolithotomy position. The uterus is pulled-up using 5 mm grasping forceps that are inserted under the left costal arch; however, a uterine manipulator is not used in order to prevent the transmission of cancer cells into the abdominal cavity. In this way, we detect several vesiouterine vessels which are then isolated, ligated, and cut following a step-by-step procedure [9, 23]. After we isolate the bladder branch and the uterine branch from the inferior hypogastric nerve and the pelvic splanchnic nerve plexus, we then cut only the uterine branch. Afterwards, we form the tumor-covering vaginal cuff closer via a transvaginal procedure to resect a 2-4cm vaginal cuff. A circumferential colpotomy is then performed on the rim of the Vagi-pipe® (Hakko CO, Japan) with monopolar scissors.

After removal of the bag holding the uterus and adnexa through the vagina, the vaginal cuff is then closed laparoscopically with running absorbable sutures.

For the abdominal nerve sparing radical hysterectomy, we perform a basic class C1 nerve sparing radical hysterectomy using our original two-point pull-up technique [24].

In this study, we evaluated residual urine volume, maximum flow rate (Qmax in ml/sec), and average flow rate (Qave in ml/sec) using the Flowsky® uroflowmetry device (TOTO) and according to the manufacturer's instructions at one week, one month, three months and six months postoperatively, as previously reported [25]. The Foley catheter was kept for seven days for the prevention of injury to both the bladder and urethra, and routinely removed on post-operative day 7. This was done in both the LRH and ARH group. Residual urine volume was then measured after the first trial of voiding. The patients' self-catheterizations had been kept until the residual urine volume was less than 100ml. One month after surgery, if the residual urine volume was over 100 ml, medication for urinary dysfunction was started. The drugs administered were distigmine bromide (Ubretid®) and urapidil (Ebrantil®), and dosing was discontinued when the residual urine volume fell below 100ml.

We also conducted an immunohistochemical study to analyze the volume of

resected pelvic nerves contained in the parametrial sections of the removed uterus using a polyclonal rabbit antihuman S-100 antibody (Spring Bioscience, Pleasanton, CA, USA). S-100 immunoreactivity was observed in both the cytoplasm the nucleus. All counting was done by two observers (ST and YT) and without any knowledge of the clinical data. All positive cells were counted in at least five high-power fields (X100 objective) chosen at random using light microscopy (Nikon Eclipse 50i, Nikon, Tokyo, Japan). The number of S-100 positive cells was given as an average for both sides of the parametrial section for each case.

Postoperative adjuvant therapy was determined by evaluating the prognostic risk factors for recurrence including lymph node metastasis, parametrial invasion, deep stromal invasion, lymph-vascular space invasion and bulky tumor (tumor diameter > 4cm). Those patients with prognostic risk factors for recurrence received concurrent cheomradiotherapy or chemotherapy (paclitaxel and carboplatin).

Statistical analysis

Statistical analyses were performed using the JMP® 14 software program (SAS Institute Inc., NC, USA), and categorical variables were analyzed using the Chi-square test. Median values of the continuous variables were compared by the Student' t test. For

the post-operative bladder function analysis, the comparison of the difference between surgical methods at each time point used multiple regression analyses adjusted for pre-operative data, and the mean differences between pre- and post-operative data were estimated, with the mean differences assessed with the paired t-test. Disease-free survival was defined as the period from surgery until the date of the first recurrence of the disease, and overall survival was defined as the period from surgery until the last date of the follow-up visit to the hospital. Disease-free survival and overall survival were calculated according to the Kaplan-Meier method, and survival curves were compared by the log rank test. Differences were considered statistically significant if the p-value was less than 0.05.

Results

During the study period, 35 patients had received a laparoscopic nerve sparing radical hysterectomy, and 41 patients had undertaken an abdominal nerve sparing radical hysterectomy. The clinical characteristics are detailed in Table 1. The distribution of FIGO stage (FIGO 2008) was 34 patients in stage IB1 and one patient in stage IIA1 in the LRH group. As well, there were 27 patients in stage IB1, three in stage IB2, 10 in stage IIA1, and one in stage IIB in the ARH group. There was significant difference

between the two groups (p=0.0002). The average tumor size was 19.4±10.2 mm in the LRH group and 26.6±18.8 mm in the ARH group, and there was significant different between the LRH and ARH groups (p=0.046).

Table 2 shows the details regarding operative outcomes. The mean operating time for the LRH group was similar to that of the ARH group (431.5 vs 460.9 minutes, p=0.11). However, the estimated blood loss for the LRH group was significantly less than that for the ARH group (153.7 vs 448.6 ml, p<0.0001). Hospital stay after operation for the LRH group was also significantly shorter than that for the ARH group (15.3 vs 20.4, p<0.0001). Gross specimens from the LRH and ARH groups showed an adequate amount of parametrial width and length of the vaginal cuff, and there were no significant differences between the two groups. The number of harvested lymph nodes was 39.1 in the LRH group and 33.3 in the ARH group, and there was a significant difference between the two groups (p=0.044). In the ARH group, there was one noted case of vesiocovaginal fistula and one case of ureter injury. Moreover, there was no conversion to open surgery in this study. The median follow-up time was 74.0 months in the LRH group and 64.0 months in the ARH group, and there was no significant difference between two groups. There were 4 noted cases of recurrence and one case of death from disease in the LRH group, along with 5 cases of recurrence and one case of death from disease in the ARH

group. In the first site of recurrence, there were two noted cases of pelvic lesion and two cases of lung metastasis in the LRH group. Furthermore, there were two noted cases of abdominal disseminations, one case of para-aortic lymphnode metastasis, and one case of mediastinum lymphnode metastasis in the ARH group. The 5-year disease-free survival rates was 91.2% in the LRH group and 87.8% in the ARH group (Logrank test: p=0.67) (Figure 1A). Additionally, the 5-year overall survival rates as 94.0% in the LRH group and 95.1% in the ARH group (Logrank test: p=0.87) (Figure 1B).

We evaluated post-operative bladder function at 1 week, 1 month, 3 months, and 6 months after operation. The median residual urine volume in the LRH group was 148.6ml after 1 week ($p<0.0001$), 72.6ml after 1 month ($p=0.004$), 3.31ml after 3 months ($p=0.89$), and 3.2ml after 6 months ($p=0.9$) (Figure 2). In the ARH group, the median residual urine volume was 171.8ml after 1 week ($p<0.0001$), 132.1ml after 1 month ($p<0.0001$), 77.9ml after 3 months ($p=0.3$), and 45.2ml after 6 months ($p=0.15$) (Figure 2). There were no statistical differences between the LRH group and the ARH group with regard to these measures. We then analyzed postoperative bladder function in a urodynamics study at 1 week, 1 month, 3 months, and 6 months after operation. In the LRH group, the differences in the postoperative max urinary flow rate (Qmax) compared with the Qmax before surgery were -13.1ml/sec after 1 week ($p<0.0001$), -5.27 ml/sec

after 1 month (p=0.073), -1.2 ml/sec after 3 months (p=0.714), and -3.5 ml/sec after 6 months (p=0.38) (Figure 3A). In the ARH group, the differences in the postoperative Qmax and the preoperative Qmax were -17.6 ml/sec after 1 week (p<0.0001), -11.9 ml/sec after 1 month (p=0.0002), -4.1 ml/sec after 3 months (p=0.19), and 0.24 ml/sec after 6 months (p=0.94) (Figure 3A). The differences in the postoperative average urinary flow rate (Qave) and the preoperative Qave in the LRH group were -8.53 ml/sec after 1 week (p<0.0001), -4.66 ml/sec after 1 month (p=0.028), -0.68 ml/sec after 3 months (p=0.77), and -0.44 ml/sec after 6 months (p=0.88) (Figure 3B). In the ARH group, the differences in the postoperative Qave and the preoperative Qave were -11.6 ml/sec after 1 week (p<0.0001), -8.4 ml/sec after 1 month (p=0.0001), -3.94 ml/sec after 3 months (p=0.067), and -0.2 ml/sec after 6 months (p=0.94) (Figure 3B). Using regression analysis, we also analyzed post-operative bladder function at 1 month and 3 months between the LRH group and the ARH group (Table 3), and bladder function in the LRH group rapidly recovered compared with that in the ARH group. These results suggest that laparoscopic nerve-sparing radical hysterectomy can achieve more precise isolations of the bladder and uterine branches from the inferior hypogastric nerve and the pelvic splanchnic nerve plexus, compared with those isolations during abdominal nerve-sparing radical hysterectomy. Regarding the supporting evidence, we examined the

199 volume of resected pelvic nerves contained in the parametrial sections of the removed
200 uterus using S-100 antibody staining (Figure 4). The number of pelvic nerves contained
201 these parametrial sections was 9.1 in the LRH group and 12.5 in the ARH group, although
202 an adequate amount of parametrial width was removed in both the LRH and ARH groups.
203 Moreover, the number of pelvic nerves contained in parametrial sections in the LRH
204 group was significantly less than that in the ARH group ($p= 0.019$).
205

206 ## Discussion

207 It is well known that the selective preservation of the bladder branch of the pelvic
208 splanchnic nerves and pelvic plexus during a radical hysterectomy is exceedingly difficult.
209 Fujii and Sekiyama indicated that a step-by-step procedure, which was originally
210 developed based on Okabayashi's radical hysterectomy, can be performed in a class C1
211 radical hysterectomy where the complete division of both the anterior and posterior leaf
212 of the vesicouterine ligament reveals the bladder branch from the inferior hypogastric
213 plexus and enables the selective division of the uterine branch from the inferior
214 hypogastric plexus [9, 23]. Previously published studies suggest that the primary
215 advantage of the nerve sparing method is reduced post-operative co-morbidities, without
216 it being inferior in terms of tumor control and overall survival. Furthermore, patients who

underwent a laparoscopic nerve-sparing radical hysterectomy experienced a shorter recovery time for bladder function than those who undertook open surgery. In these studies, however, a urodynamic assessment was not performed [26-30] [21]. In this study, we performed a laparoscopic nerve-sparing radical hysterectomy following a step-by-step procedure which was originally developed by Fujii [9]. The postoperative recovery of bladder function, including the Qmax and Qave status of uroflowmetry, reached pre-surgery levels at 1 month in the LRH group. These results suggest that the LRH group achieved better bladder function in a shorter period of time than the ARH group, as previous studies have reported [21, 30, 31]. In general, a magnified laparoscopic view has the potential of more precision and enhanced appreciation of the pelvic anatomical locations of the pelvic organs, vessels, and the pelvic splanchnic nerves and pelvic plexus. We showed a significantly smaller number of pelvic nerves plexus in the S-100 stained parametrial sections in the LRH group, and these results suggest that a laparoscopic nerve-sparing radical hysterectomy could be performed with more precise isolations of the bladder and uterine branches from the inferior hypogastric nerve and the pelvic splanchnic nerve plexus.

In this study, we observed a 74 months median follow-up time in the LRH group and 64 months in the ARH group. Although there was a slight difference in the

235 distribution of FIGO stage between the LRH and ARH groups, the 5-year disease-free
236 survival rate and the 5-year overall survival rate had no differences between the LRH and
237 ARH groups, which was similar to the disease-free survival rate (85-95%) and overall
238 survival rate (93-97%) in a previous meta-analysis [16, 32-35]. However, unexpectedly,
239 the Laparoscopic Approach to Cervical Cancer (LACC) trial has demonstrated that
240 minimally invasive radical hysterectomy was associated with a lower rate of 4.5-year
241 disease free survival than open surgery. There is no conclusive evidence as to why
242 minimally invasive surgery, including laparoscopic surgery, is associated with inferior
243 oncologic outcomes compared with open surgery. Several hypotheses for this argue that,
244 in laparoscopic surgery, the use of uterine manipulation potentially leads to tumor spillage,
245 especially when the vagina is opened and the tumor surface is exposed to circulating CO2
246 during the laparoscopic intracorporeal colpotomy [36]. In this study, a uterine
247 manipulator was not used, and we formed the tumor-covering vaginal cuff transvaginally
248 for all cases in order to prevent cancer cells transmission into the abdominal cavity. Köhler
249 demonstrated that the retrospective multicenter study of early cervical cancer patients who
250 underwent a laparoscopic radical hysterectomy combined both techniques [37]. We believe
251 that the procedure for laparoscopic radical hysterectomy, combined with both techniques (a
252 tumor-covering vaginal cuff and no uterine manipulator) is associated with better survival.

A further prospective study, however, would be required for positive proof.

The limitations of this study should be addressed. First, this was a single institution retrospective study. There was some selection bias in the patients enrolled in this study, accordingly, as this was not a prospective randomized control trial. Second, the study included a relatively small number of patients. Third, we did not investigate the influence of adjuvant radiation or chemotherapy on bladder function over a long period of time.

In conclusion, we have demonstrated that laparoscopic nerve-sparing radical hysterectomy following a step-by-step procedure could achieve a higher level of damage prevention to the inferior hypogastric nerve and the pelvic splanchnic nerve plexus and that bladder function recovers more rapidly compared with abdominal nerve-sparing radical hysterectomy.

Disclosure of Potential Conflicts of Interests

The authors declare that they have no competing interests.

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Authors' contributions

Yoshito Terai: Study conception and design, Manuscript writing

Shinichi Terada: Data Collection, Analyzed the data,

Yoshimichi Tanaka: Data Collection

Tomohito Tanaka: Data Collection

Ssatoshi Tsunetoh: Analyzed the Urodynamics data

Masahide Ohmichi: Data Collection

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Figure Legends:

Figure 1. Survival outcomes based on surgical procedure. Kaplan-Meier analysis of disease-free survival (A) and overall survival (B). Solid line and dotted line show the LRH group and the ARH group, respectively.

Figure 2. Post-operative median residual urine volume for pre-operation, 1 week, 1 month, 3 months, and 6 months after operation in the LRH group (black bars) and the ARH group (gray shaded bars), respectively. ** p-value <0.01, * p-value <0.05.

Figure 3. In a urodynamics study, post-operative bladder function of the max urinary flow rate (Qmax) (A) and the average urinary flow rate (Qave) (B) were demonstrated for pre-operation, 1 week after operation, 1 month after operation, 3 months after operation, and 6 months after operation. The LRH group is indicated by black bars and the ARH group by gray shaded bars. The differences between the postoperative Qmax and preoperative Qmax, as well as the difference between the postoperative Qave and the preoperative Qave, were analyzed using multiple regression analyses adjusted for pre-

389 operative data. ** p-value <0.01, * p-value <0.05.

390

391 Figure 4. (A)The volume of resected pelvic nerves contained in parametrial sections of

392 the removed uterus using S-100 antibody staining. * p-value <0.05. (B) Images of specific

393 stainings of nerve tissues from the parametrial sections using the S-100 antibody.

394

Table 1: Clinicopathologic characteristics of patients

	LRH group (35)	ARH group (41)	p-value
Age, mean (SD),(y)	45.7±10.7	43.4±10.4	0.34
Body mass index (kg/m2)	21.2±3.9	22.7±3.7	0.1
FIGO stage (FIGO2008)			0.002
IB1	34	27	
IB2	0	3	
IIA1	1	10	
IIB	0	1	
Histological subtype			0.07
Squamous cell carcinoma	15	25	
Adenocarcinoma	15	8	
Adenosquamous	5	6	
others	0	2	
Average of tumor size (mm)	19.4±10.2	26.6±18.8	0.046
Risk factor			0.1
LVSI	5	14	
Deep stromal invasion	11	15	
Lymph node metastasis	7	6	
Adjuvant therapy	19	27	0.3
CCRT	4	6	
chemotherapy	15	21	
Prior conization	10	11	0.87

Table 2. The details regarding operative outcomes

	LRH group (35)	ARH group (41)	p-value
Operation time, (min)	431.5±73.2	460.9±85.0	0.11
Estimated blood loss (ml)	153.7±169.1	448.6±296.4	<0.0001
Length of vaginal cuff (mm)	25.6±10.3	26.2±8.1	0.79
Rt-Length of parametrial wide (mm)	17.8±4.7	17.8±4.4	0.97
lt-Length of parametrial wide (mm)	18.9±4.7	19.3±4.5	0.69
Harvested number of lymphnodes	39.1±12.0	33.3±12.4	0.044
Conversion to laparotomy	0		
Intraoperative complication, n(%)	0	0	
Postoperative complications, n(%)	0	2	
Hospital stay after operation (days)	15.3±2.3	20.4±3.6	<0.0001
Recurrences	4	5	0.92
First site of recurrences			
pelvic	2	1	0.38
abdomen	0	2	
Distant	2	2	
Patients died of disease	1	1	0.9
Follow-up, months	47.5±21.1	48.6±21.8	0.83

Table 3. Regression analysis of post-operative bladder function

	LRH group	ARH group	p-value
diff. Q max (m/sec) after 1 months	-6.65±1.99	-14.3±1.99	0.0326
diff.Q ave (ml/sec) after 1 months	-6.45±1.11	-10.997±1.13	0.0540
diff.Residual urine volume (ml) after 1 months	64.4±25.1	140.6±24.0	0.0337
diff.Q max (m/sec) after 3 months	-2.52±2.67	-6.97±2.29	0.4695
diff.Q ave (ml/sec) after 3 months	-2.79±1.25	-8.72±1.1	0.0301
diff.Residual urine volume (ml) after 3 months	2.6±23.0	84.4±21.3	0.012

difference to pre-data ±SE

Fig. 1

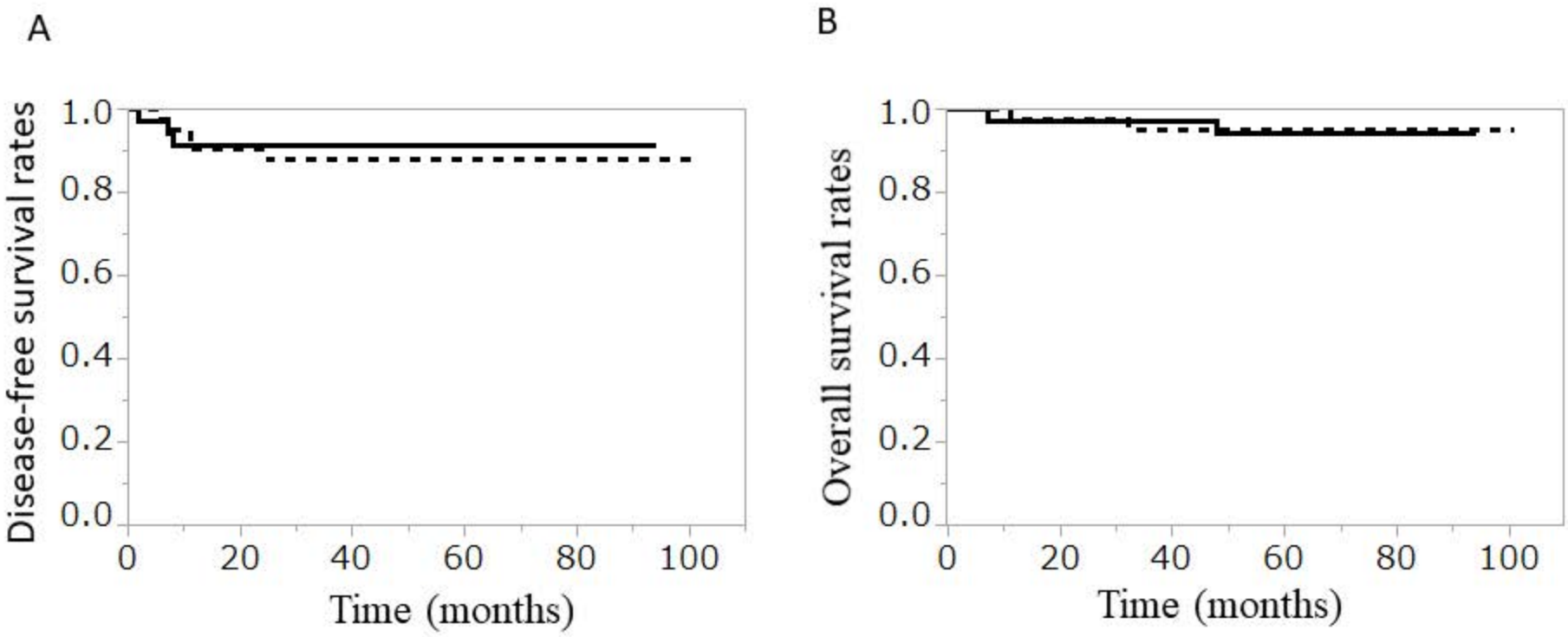

A
Disease-free survival rates
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
Time (months)
B
Overall survival rates
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
Time (months)

Fig. 2

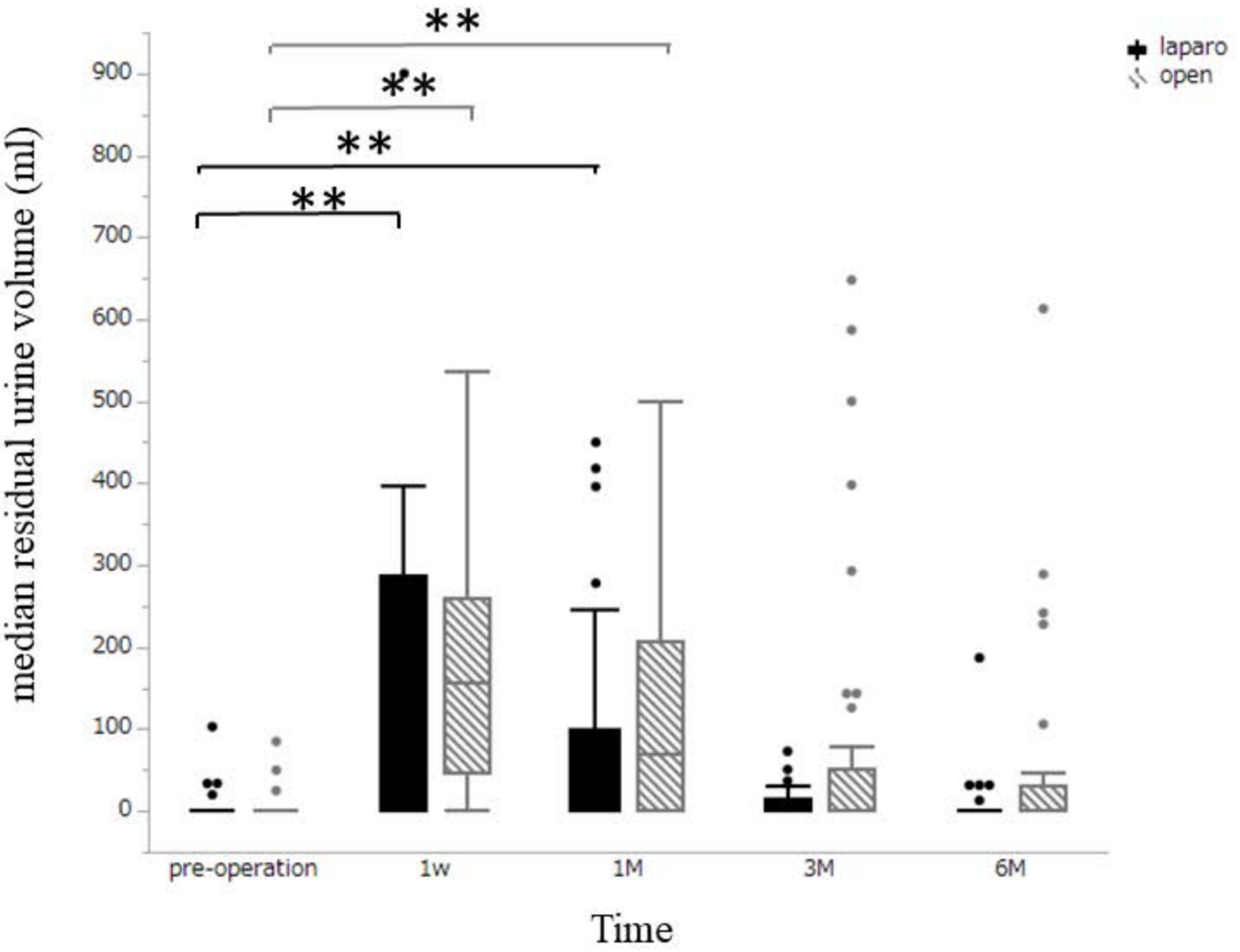

**
**
**
**
laparo
open
median residual urine volume (ml)
900
800
700
600
500
400
300
200
100
0
pre-operation
1w
1M
3M
6M
Time

Fig. 3

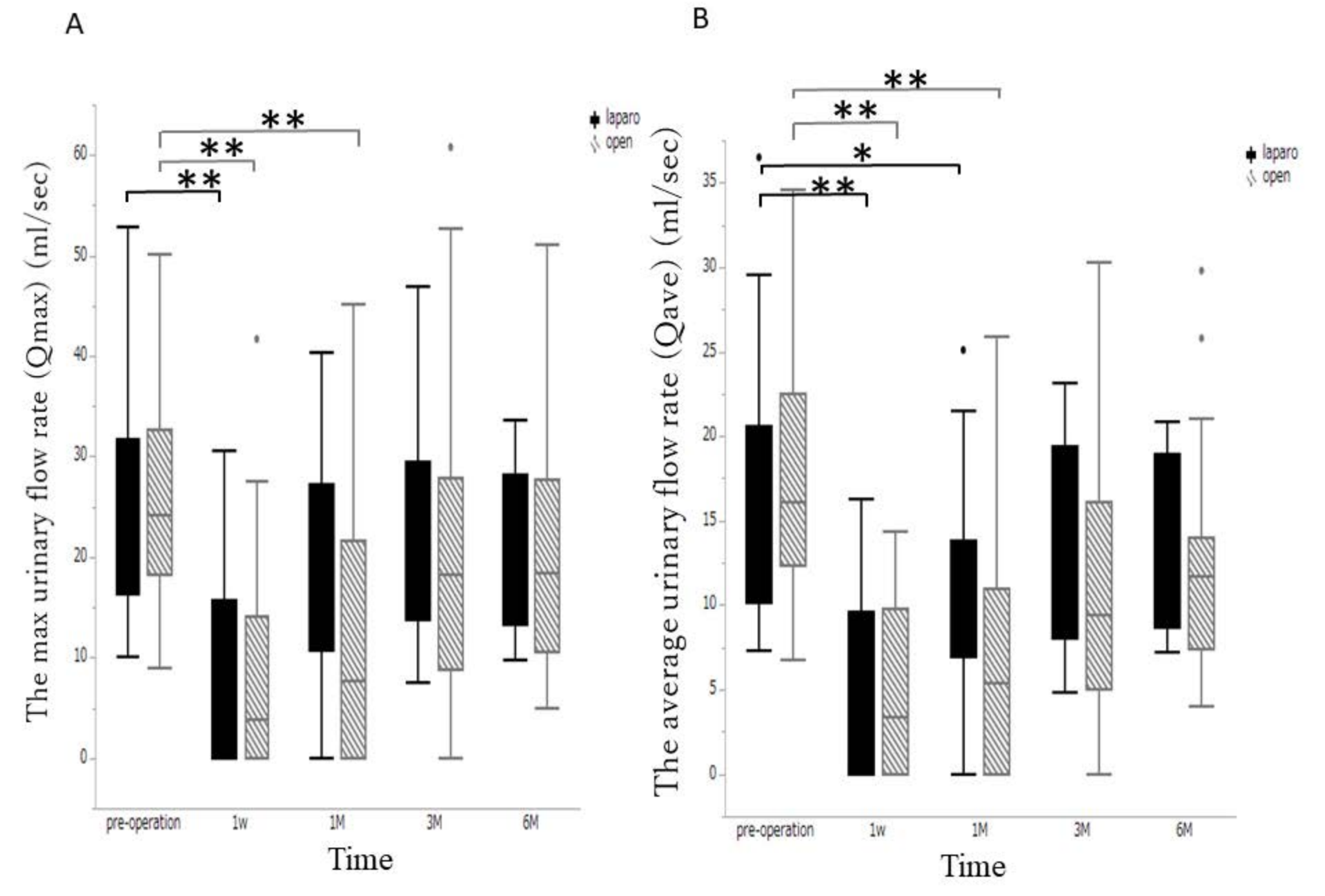
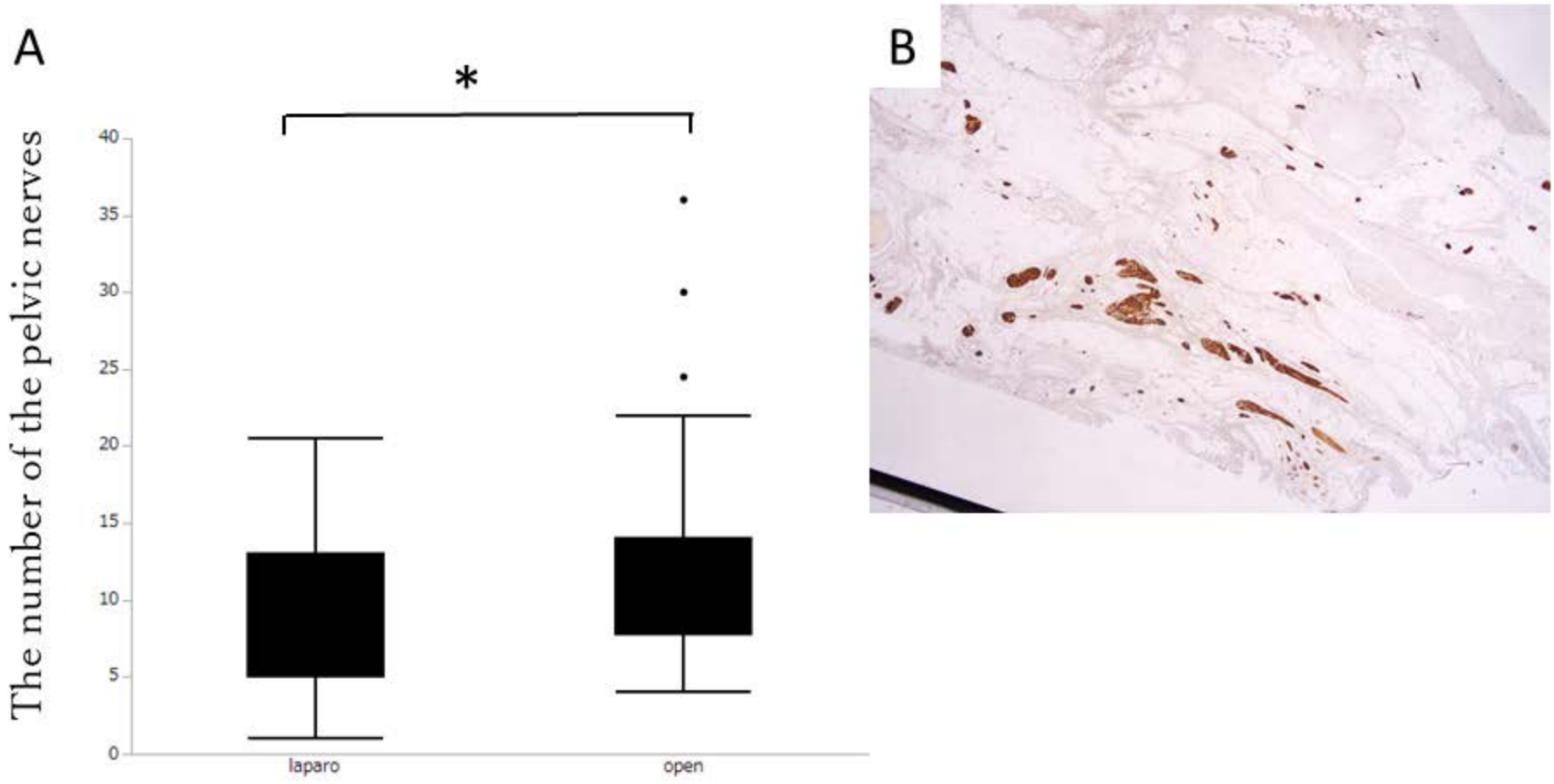

A
B
laparo
open
The max urinary flow rate (Qmax) (ml/sec)
The average urinary flow rate (Qave) (ml/sec)
pre-operation
1w
1M
3M
6M
Time
**
*

Fig. 4


A
B
*
The number of the pelvic nerves
40
35
30
25
20
15
10
5
0
laparo
open