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Feasibility of Laparoscopic Para-Aortic Lymphadenectomy for Locally Advanced Cervical Cancer

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ABSTRACT

Background: Radiological evaluation of para-aortic lymph node metastasis in patients with locally advanced cervical cancer (LACC) possess the risk of missing microscopic metastasis. We commenced laparoscopic para-aortic lymphadenectomy (Lap-PAN) on patients with LACC for surgical staging in 2016. We assessed the feasibility of Lap-PAN in patients with LACC.

Methods: We retrospectively reviewed the records of 31 patients with LACC who were staged at International Federation of Gynecology and Obstetrics (FIGO) 2009 IIB to IVA without enlargement of the para-aortic lymph nodes who underwent radiation therapy in our hospital between January 1, 2011 and December 31, 2018. The postoperative outcomes of Lap-PAN were analyzed, and distinct parameters for each patient, including sites of recurrence and disease-free survival, were compared between the Lap-PAN (n = 12) and no surgery (n = 19) groups.

Results: The average operation time for Lap-PAN was 167 min, and the estimated blood loss was less than 50 ml in all patients. There were no perioperative complications. The average number of excised lymph nodes was 25, and no pathological metastases were observed. There was no difference in disease-free survival rates between the Lap-PAN and no surgery groups (p = 0.42). During the follow-up period, there were two cases of recurrence in the cervix in the Lap-PAN group, and three and four cases of lung and para-aortic lymph node recurrence, respectively in the no-surgery group.

Conclusions: Lap-PAN was safely performed as a pretherapeutic staging method for LACC without worsening patient prognosis. Although Lap-PAN requires a high level of skill, it may be a method to avoid excessive radiation for LACC.

Key Words: Cervical cancer, Laparoscopic para-aortic lymphadenectomy, Radiation therapy, Recurrence.

INTRODUCTION

The spread of vaccination and cytology screening has decreased the prevalence of cervical cancer in developed countries;[1] however, there is a trend of increase in cervical cancer patients in Japan especially in their 30s to 40s due to the lack of vaccination.[2] Concomitant chemoradiation therapy is the current standard therapy for locally advanced cervical cancer (LACC), which does not indicate the laparoscopic approach to cervical cancer in this study. The irradiation field should extend to include the area of para-aortic lymph nodes (PALN), if metastasis of PALN is determined by radiological or surgical evaluation.[3] Radiological diagnosis of PALN metastasis was reported to have a sensitivity of 50% and a specificity of 92%, using contrast enhanced computed tomography (CT), and a sensitivity of 82% and a specificity of 95% using positron emission tomography (PET)-CT.[4] The false-negative rate of PET-CT was reported to be 5% – 17%, and the false-positive rate was 5% – 10%.[4, 5] Similar to radiological evaluation, surgical staging by laparoscopic para-aortic lymphadenectomy (Lap-PAN) for LACC patients is also

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recommended in National Comprehensive Cancer Network (NCCN) guidelines to prevent overlooking the PALN metastasis.[3] However, in Japan, surgical staging of the Lap-PAN is less common than radiologic evaluation due to the difficulty of the technique and the uncertainty of its necessity. Additionally, the impact of Lap-PAN on patient survival and the site of recurrence remains unclear.

This study aimed to analyze the treatment outcomes of Lap-PAN in our hospital, the impact of Lap-PAN on the patients' disease-free survival, and the difference in the site of recurrence.

MATERIALS AND METHODS

Patients

This was a retrospective, case-control study. The clinical records of LACC FIGO (2009) stage IIB – IVA patients with radiologically negative result of PALN metastasis who received radiation therapy from January 1, 2011 to December 31, 2018 were retrospectively reviewed. Lap-PAN was started in 2016, when the procedure was approved by the evaluating committee for highly difficult new medical technology evaluation in our hospital. The patients were divided into two groups: the no-surgery group (January 1, 2011 – December 31, 2015) and the Lap-PAN group (January 1, 2016 – December 31, 2018). Radiological diagnosis of lymph node metastasis was defined as a lymph node short axis diameter >10 mm based on multidetector CT and fluorodeoxyglucose uptake on lymph nodes by PET-CT. Lap-PAN was performed in patients without radiological PALN metastases. All radiological studies were performed by several diagnostic radiology experts. The quality of radiological studies did not change during the study period. All surgeries were performed by an experienced gynecologic oncology team consisting of experts with licenses in gynecologic oncology and gynecologic endoscopy. Surgical outcome parameters such as operative time, intraoperative blood loss, postoperative length of hospital stay, interval between operation and radiation therapy, number of excised lymph nodes, and operative complications were collected. The standard treatment was pelvic chemoradiation therapy (CRT) using a four fields technique at a dose of 45 – 50.4 Gy in daily 1.8 – 2.0 Gy fractions following intracavitary brachytherapy in combination with weekly administration of cisplatin at a dose of 40 mg/m^2. The patients with renal or heart failure did not undergo chemotherapy. The radiation field was extended if the PALN was pathologically positive. An external beam boost in pelvic lymph node (PELN) field to a dose of 10 Gy was added when obvious enlargement of the lymph nodes was confirmed after standard external beam therapy. In the pathological evaluation, the lymph nodes were submitted for routine sectioning and evaluation using hematoxylin-eosin slides. This study was reviewed and approved by the Institutional Review Board in Kyoto University Hospital. (Approval number: R2711).

Statistical Analysis

Fisher's exact test or the χ^2 test was used to evaluate the association between qualitative variables, as appropriate. Continuous variables were compared using the Mann-Whitney U test. Continuous variables were reported as medians and ranges. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Differences were considered statistically significant at a two-sided P-value ≤ 0.05. All data were analyzed using GraphPad PRISM version 60.0.

Standardized Laparoscopic Para-Aortic Transperitoneal Lymphadenectomy

All surgeries were performed under general anesthesia. The patients were placed in the head-down lithotomy position with the operator on the right side, the first assistant on the left side, and the camera assistant between the legs. The monitor is set on the head side. Six trocars are used as follows: First 12-mm trocar is inserted through umbilical site and CO_2 gas is insufflated. Two 5-mm trocars inserted in the right upper and lower quadrant, respectively. The other two 5-mm trocars were symmetrically arranged. One trocar inserted at the midline in the suprapubic region, which is also used as camera trocar (**Figure 1**).

The procedure of para-aortic lymphadenectomy was commenced by cutting the peritoneum 4 cm transversely 2 cm above the level of the aortic bifurcation and, lifting the peritoneum using sutures in the direction of the abdominal wall to keep the retroperitoneal cavity open. The abdominal aorta and vena cava were exposed from the bifurcation level to the level of renal vein. Both the left and right ureters were identified, and lymphadenectomy was performed.

The order of lymphadenectomy was as follows: between the aorta and vena cava, left side of the aorta, and right side of the vena cava in the head–foot direction (**Figure 2**). Ultrasonic dissector harmonic devices (Harmonic®; Ethicon Inc., Cincinnati, OH, USA) were mainly used during lymphadenectomy which enables the precise dissection of a layer

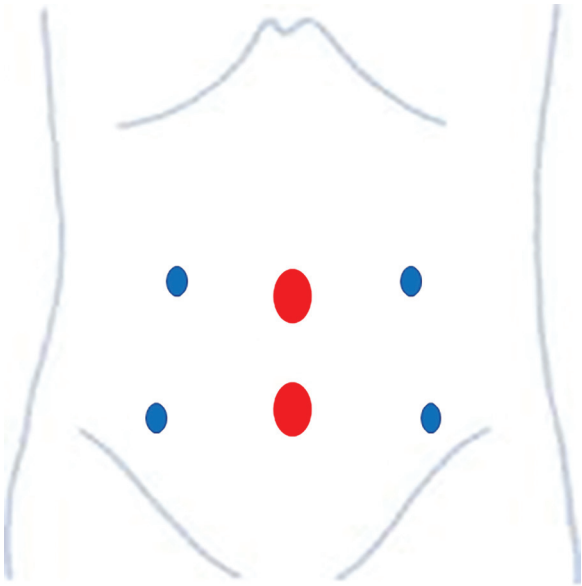

Figure 1. Trocar positioning of Lap-PAN Red circle: 12 Millimeter trocar, Blue circle: 5 Millimeter trocar.

of tissue without bleeding, rather than the vessel sealing system, which is commonly used for lymphadenectomy. The lymphatic vessels were sealed separately using a titanium LigaClip® to avoid lymphatic leakage.

Results

A total of 31 LACC patients with radiologically negative results for PALN metastasis who underwent radiation therapy from January 1, 2011 to April 30, 2018 at Kyoto University Hospital were enrolled. Of these, 12 underwent Lap-PAN (Lap-PAN group) from January 1, 2016 to December 31, 2018, whereas 19 did not (no-surgery group) from January 1, 2011 to December 31, 2015. All cases were histologically diagnosed as squamous cell carcinoma (SCC).

The clinical characteristics of the patients are summarized in **Table 1**. The age of the Lap-PAN group was significantly lower than that of the no-surgery group (53 vs. 67 years, P = .03). There was no statistical difference between the groups in the body mass index, and FIGO stage, although there were no stage IVA patients in the Lap-PAN group. There was no difference in the SCC values, proportion of PELN enlargement, maximum size of PELN and PALN based on CT findings, interval between the first visit and initiation of radiation therapy. All the patients in the Lap-PAN group received chemoradiation therapy (CRT), whereas 14 patients (73.7%) patients in the no-surgery group did, although there was no statistical difference. Four patients with renal failure and one patient with heart failure underwent radiation therapy without chemotherapy in the no-surgery group. The proportion of the patients who received additional boost radiation to the PELN region in the Lap-PAN group was fewer than the patients in the no-surgery group (41.6% vs. 63.1%, P = .29).

The surgical outcomes of Lap-PAN are shown in **Table 2**. The estimated blood loss was < 50 ml, and the operative time was 167 min. No patients in the Lap-PAN group or among those who received extended radiation therapy had pathological lymph node metastasis. The interval between the operation and initiation of radiation therapy was 15 days. None of the patients experienced intraoperative or postoperative complications. The intervals of confirmation of mobilization and bowel movement after surgery were 1 and 2 days, respectively.

In this study, the median follow-up time was 16 months (range, 3 – 50) in the no-surgery group and 12 months (range, 2 – 38) in the Lap-PAN group. The 3-year disease-free survival for the no-surgery group was 59.4% and, in the Lap-PAN group was 66.7%. There was no statistical difference between the groups in the disease-free survival (Figure 3a) (P = .37, hazard ratio 0.61, 95% confidence interval: 0.15 – 2.54). In the survival analysis for the patients with PELN enlargement, the 3-year disease-free survival for the no-surgery group was 50.8% and for the Lap-PAN group was 75% (Figure 3b) (P = .31, Hazard ratio 0.37, 95% confidential interval: 0.07 – 2.11). The disease-free survival rate of the Lap-PAN group was slightly higher than that of the no -surgery group; however, there was no statistically significant difference between the groups.

The recurrence sites are shown in **Table 3**. There were two patients (18%) with recurrence in the Lap-PAN group, and seven patients (37%) in the no-surgery group. The sites of recurrence in the no surgery group included three patients with lung metastasis and four patients with PALN involvement, whereas those in the Lap-PAN group included two patients with regional recurrence in the cervix. There were no sites of recurrence or distant metastasis in the Lap-PAN group. Four patients with PALN recurrence in the no surgery group had PELN enlargement before radiation therapy.

DISCUSSION

Thus far, lymph node involvement was not reflected in the staging of cervical cancer in FIGO 2009, but the

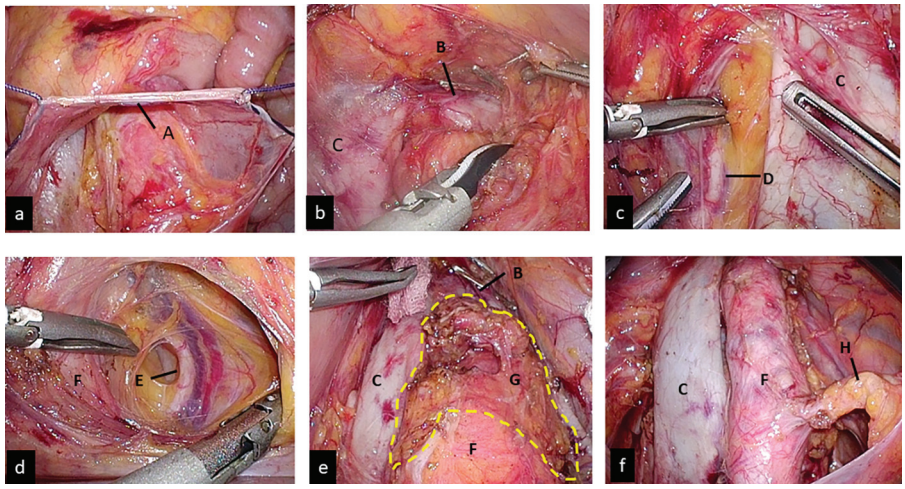

Figure 2. Procedures of transperitoneal para-aortic lymphadenectomy (**A**) elevation of the peritoneal membrane up to the abdominal wall; (**B**) Exposure of the renal vein (**C**) Identification of the right ureter, (**D**) Identification of the left ureter, (**E**) Determinant of outer frame of lymphadenectomy, (**F**) Completed lymphadenectomy A, peritoneum; B, left renal vein; C, inferior vena cava; D, right ureter; E, left ureter; F,aorta; G, regional lymph nodes; H, inferior mesenteric artery.

involvement of PELN and PALN was newly added to the classification in FIGO 2018 as stage IIIC1 and IIIC2, respectively,[6] which indicates the importance of a more accurate evaluation PALN involvement than ever before.

Although we performed Lap-PAN to avoid missing the radiologically diagnosed false-negative cases, there were no patient with pathological metastasis in PALN, and the diagnostic significance of surgical staging was not confirmed in this study. Gousy et al. reported that they performed Lap-PAN for the cases with negative findings on PET-CT and the false-negative rate was 12.2%, although when the maximum diameter of PALN was less than 5 mm, the false-negative rate decreased to 5.4%.[5] Yamanoi et al. also reported that the optimal cut-off value of lymph node size for the detection of metastasis of cervical cancer by multidetector CT was 5 mm. [7] There were only two cases with a PALN size > 5 mm in the Lap-PAN group (data not shown), which is considered to be one of the factors associated with negative findings of pathological metastasis.

Thus far, previous reports have shown that the similar number of excised lymph nodes (6 – 20.4)[8] as in our study (25). The completeness of lymphadenectomy in this study was satisfactory, and the operation is considered less likely to miss pathological metastasis.

Injuries to the blood vessels and ureter have been reported as intraoperative complications, and the formation of lymphocele, port site hernia and wound site hematoma have previously been reported as postoperative complications.[8] The standardization and stabilization of the procedures of Lap-PAN by the surgical team might have contributed to the lack of complications in this study.

Although para-aortic lymphadenectomy by laparotomy as surgical staging for cervical cancer was performed since the 1980s, the high rate of complications was reported as 10 to 19%.[9,10] Lap-PAN was commenced in the 1990s, with complication rate reported as 3%, which made it possible to start radiation therapy earlier.[11,12] Therefore, Lap-PAN has been mainly performed as surgical staging for LACC. The interval between the timing of Lap-PAN and initiation of radiation therapy was reported to be 2 to 15 days 8, which was similar to our result (15 days).

In this study, there was no statistical difference in the disease-free survival between the Lap-PAN and no-surgery groups, however a slight trend of therapeutic effect was confirmed in the patients with PELN enlargement in spite of the pathological metastasis which was not detected, and the proportion of PELN enlargement was slightly higher in the Lap-PAN group (66.7%) than in the no-surgery group (47.3%). One explanation for this result may be that selection bias favored the Lap-PAN group, which consisted of younger patients. Another likely explanation is the possibility of micro metastasis in PALN only in the no-surgery group because of the small size of the study. The therapeutic effect of para-aortic lymphadenectomy for LACC before radiation therapy remains controversial. In a single-center study by Lai et al., patients who

Table 1.
Clinical Characteristics of Patients

	No-surgery (N = 19)	Lap-PAN (N = 12)	*P* value
Age (years)	67 (38–87)	53 (31–79)	0.03*
Body Mass Index (kg/m^2)	20.5 (15.6–26.9)	20.6 (14.9–28.2)	0.42*
Stage			
FIGO IIB	8	5	0.23**
FIGO IIIA	1	4	
FIGO IIIB	6	3	
FIGO VA	4	0	
SCC (ng/ml)	23.8 (1.9 – 13.4)	20.7 (2.2 – 55.9)	0.64*
PELN enlargement (n)	9 (47.3%)	8 (66.7%)	0.46***
PALN short axis diameter (mm)	3.8 (3.1 – 8.8)	4.6 (2.4 – 6.3)	0.14*
PELN short axis diameter (mm)	7.7 (2.5 – 14.7)	9.8 (2.9 – 28)	0.38*
Interval between first visit and radiation therapy (day)	26 (9 – 46)	30 (11 – 63)	0.42*
CRT (n, %)	14 (73.7%)	12 (100%)	0.13***
PELN boost (n, %)	12 (63.1%)	5 (41.6%)	0.29***

FIGO, Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; PELN, pelvic lymph node, PALN, para-aortic lymph node; CRT, chemoradiotherapy.
*Mann-Whitney U test, ** χ^2 test for trend, *** Fisher's exact test.

underwent para-aortic lymphadenectomy had poorer survival than those without PALN staging.[13] However, there were more advanced cases in the PALN staging group, and more patients with adenocarcinoma and adenosquamous carcinoma in the PALN staging group. Moreover, 50% of para-aortic lymphadenectomies were performed under laparotomy, and the complication rate was high, which might cause delay in radiation therapy. On the other hand, in the multicenter and retrospective study by Michael A et al., the patients in the surgical PALN sampling group with stage III and IV LACC had better progression-free survival and overall survival than those in the radiographic evaluation group.[14] They suggested that the radiographic evaluation group had potentially missed the micro metastasis in PALN. In the prospective multicenter study by Sebastien G et al., 12.2% of patients with para-aortic involvement underwent Lap-PAN with stage IB2 to IVA LACC and negative PET imaging in PALN field.

Table 2.
Treatment Outcome of Para-Aortic Lymphadenectomy

Outcome	
Estimated blood loss (ml)	< 50
Operative time (min, range)	167 (114 – 201)
Number of excised lymph nodes (n, range)	25 (14 – 42)
Metastatic lymph nodes (n)	0
Intraoperative complications (n)	0
Interval between operation and initiation of radiotherapy (day, range)	15 (8 – 26)
Mobilization after operation (day)	1
Bowel movement after operation (day)	2
Postoperative complications (n)	0

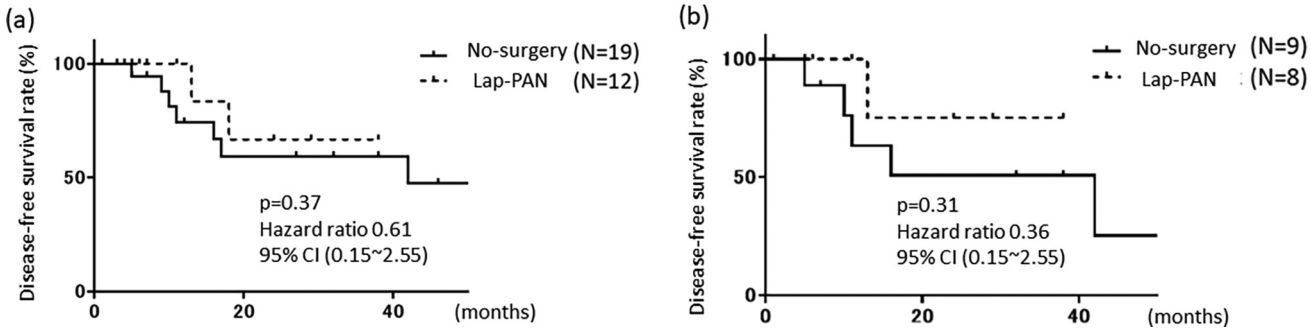

Figure 3. The comparison of disease-free survival between the groups (**A**) Disease-free survival in all patients (**B**) Disease-free survival in patients with pelvic lymph node enlargement.

Patients with pathological involvement with PALN less than 5 mm in size who underwent extrafield radiation had similar overall survival with those without PALN involvement, which implied the therapeutic and diagnostic effects of Lap-PAN before radiation therapy.[5]

Pedro et al. reported a correlation between surgical staging by Lap-PAN and PET-CT findings in patients with LACC. In the patients with negative PET-CT findings of PELN and PALN, 12% had micro metastasis in PALN, whereas in those with positive PET-CT findings of PELN and negative findings of PALN, 22% had micro metastasis in PALN.[15] This result suggests further efficacy of Lap-PAN in patients with PELN enlargement. Additionally, in the patients with positive PET-CT findings of PALN, as much as 29% of them did not have the metastasis, which implies the necessity of Lap-PAN for the patients with positive PET-CT findings in PALN as well as for the patients with negative PET-CT findings in PALN.

Extraperitoneal para-aortic lymph node dissection for the cervix, an ongoing multicenter prospective study, investigates the efficacy of surgical staging using Lap-PAN for patients with positive PET-CT findings in PELN and negative findings in PALN,[16] and the findings may support our data.

Table 3.
Site of Recurrence

Site	No-Surgery (n = 19)	Lap-PAN (n = 12)
Lung (n)	3 (16%)	0
Para-aortic lymph node (n)	4 (22%)	0
Uterine cervix (n)	0	2 (18%)
Total (n)	7 (37%)	2 (18%)

There was a difference in the sites of recurrence between the two groups in this study. Gold et al. reported that there were significantly more recurrences involving PALN in the radiographic group than in the surgery group, and there was a trend towards less recurrence out of the pelvis in the surgery group,[14] which is similar to our data. Micro metastasis in the PALN may have been missed in the radiographic group. In the NCCN guidelines for cervical cancer, prophylactic extended irradiation to the field of PALN for LACC patients without radiological PALN metastasis is not recommended because of the lack of a therapeutic effect and an increase in adverse events.[3,17] The efficacy of prophylactic irradiation in the PALN fields for LACC patients with PELN enlargement is yet to be determined. Thus, Lap-PAN may contribute to the prevention of PALN recurrence.

Lap-PAN in our institution has been performed via the transperitoneal approach since it was started. The extraperitoneal approach has been reported as an alternative method of Lap-PAN. Bruno et al. showed in the study about the difference of approach using animal laboratory that the surface area of adhesions was significantly lower in extraperitoneal group.[18] The operative time was shown to be longer in the extraperitoneal than in the transperitoneal group,[19] although extraperitoneal approach enables patient to maintain dorsal position, which is less harmful than the Trendelenburg position. Berta et al. reported on the use of the extraperitoneal Lap-PAN for LACC in a multicenter retrospective study in which the median length of hospitalization was only 2 days, and the median operative time was 150 min, which is shorter than that in our study.[20] However, the median number of excised lymph nodes was 13, which is less than that in our study. The interim report of the Uterus 11 trial, which is the study about the efficacy of transperitoneal Lap-PAN for LACC, showed longer disease-free survival and overall survival in the

surgical staging group than in the radiological group.[21] In the pathological evaluation, the detection of micro metastasis by slicing lymph nodes at thin intervals, although routine sectioning was performed in this study, may contribute to higher detection of pathological PALN involvement, which may improve patient prognosis.

The limitation of this study includes interpretation of the results regarding the impact of Lap-PAN on patient prognosis and recurrence due to its retrospective design, small sample size, selection bias, and short observation period. A multicenter prospective study is needed, especially considering the quality of Lap-PAN by experts.

CONCLUSION

In this study, transperitoneal Lap-PAN for LACC, which was performed by an experienced team, was shown to be safe and did not worsen the patient prognosis. Lap-PAN can be used to avoid excessive radiation in LACC.

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