Original Article

Laparoscopic Systemic Retroperitoneal Lymphadenectomy for Women with Low-Risk Early Endometrial Cancer

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Abstract

Introduction: There is no consensus on the extent of lymphadenectomy and the appropriate patients for lymphadenectomy in low-risk patients with endometrial cancer. This study aimed to evaluate the feasibility and effectiveness of laparoscopic lymphadenectomy for low-risk patients with endometrial cancer. Materials and Methods: From January 2004 to May 2008, we reviewed the medical records of 28 patients with low-risk, endometrial cancer; endometrioid type, grade 1 or 2, and with a depth of myometrial invasion of less than one-half of the myometrium. All patients underwent laparoscopically-assisted staging surgery. Results: The median age and body mass index were 56 years (range, 28 to 75) and 25.5 kg/m^2 (range, 21.3 to 37.2). The median operating time, estimated blood loss, and length of hospital stay were 142 minutes (range, 110 to 410), 215 mL (range, 100 to 700), and 7 days (range, 3 to 19), respectively. No conversion to laparotomy was noted. The median number of harvested lymph nodes was 21 (range, 10 to 48) pelvic nodes and 12 (range, 4 to 21) para-aortic nodes. One (3.6%) patient presented pelvic lymph node metastasis and 2 (7.1%) presented isolated para-aortic lymph node metastasis. The complication rate was 14.3%. No recurrence in the vaginal vault, distant metastasis, port site metastasis was noted up to the last follow-up. Conclusion: Systemic pelvic and para-aortic lymphadenectomy should be considered in all low-risk patients with endometrial cancer until it is concluded to be clinically insignificant through large-scale prospective research in the future. However, it will be difficult to explain statistical differences in survival rates according to lymphadenectomy, because the increase of the survival rate resulting from lymphadenectomy will fall within the margin of statistical error.

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Key words: Endometrial cancer, Laparoscopy, Lymphadenectomy

Introduction

Endometrial cancer is the third most frequent gynaecologic cancer in Korea, following cervical cancer and ovarian cancer. With the increasingly Westernised lifestyles of Korean women – including exposure to oestrogen hormones, the number of pregnancies, the age of menarche and the age of menopause – the number of reported endometrial cancers has rapidly increased, up from 132 in 1991 when the gynaecological cancer registration programme was started, to 862 in 2004, a 6-fold increase.[1] Because of this rapid increase in the incidence of endometrial cancer, there is increasing concern over and research on endometrial cancer in Korean women.[2]

Since being recommended by FIGO (International Federation of Gynecology and Obstetrics) in 1988, surgical staging of endometrial cancer has been performed. Surgical staging includes total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO), peritoneal washing cytology, and selective pelvic and para-aortic lymph node biopsy or lymphadenectomy through a midline incision.[3,4] However, there is no consensus on the extent of lymphadenectomy and the appropriate patients for lymphadenectomy. In particular, controversies are focused on FIGO stage Ia or Ib endometroid adenocarcinoma with grade 1 or 2.

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Thus, we conducted laparoscopic surgical staging including systemic pelvic and para-aortic lymphadenectomy for patients with clinical stage Ia or Ib endometroid endometrial cancer with grade 1 or 2, and produce a preliminary report on the feasibility, safety and effectiveness of pelvic and paraaortic lymphadenectomy in low-risk, early endometrial cancer.

Materials and Methods

Of the patients with endometrial cancer who underwent laparoscopic surgical staging between January 2004 and May 2008, 28 patients who were diagnosed with clinical stage Ia or Ib endometroid adenocarcinoma with grade 1 or 2 were enrolled in the present study. We retrospectively reviewed their medical records, anaesthesia records, and histopathological reports. Preoperative work-up included medical history, physical examination, pelvic examination, gynaecological ultrasonography, Pap smear, endometrial biopsy and MRI. After being informed of the necessity and advantages of pelvic or para-aortic lymphadenectomy as well as their disadvantages (such as extended operating time and the increase of blood loss, etc), each patient gave an informed consent. Only laparoscopic pelvic lymphadenectomy (LPL) was performed in 6 patients diagnosed with early endometrial cancer before the American College of Obstetrical and Gynecologists announced their clinical guidelines for endometrial cancer in August 2005; in 22 patients diagnosed after the announcement, LPL and laparoscopic para-aortic lymphadenectomy (LPAL) were performed.

Operative Techniques

Operative technique is equivalent to the previously published journal, which is simply stated below.[2] Intravenous preoperative prophylactic antibiotics were administered: 2 g cefminox or 1 g flomoxef if the patient was allergic to cephalosporins. Preoperative bowel preparation with Fleet Phospho-soda was done in all cases. Patients were placed in a modified dorsal lithotomy position under general anaesthesia with endotracheal intubation, and surgical preparation was performed aseptically using povidone-iodine.

For port placement, the four-trocar method was performed.[5] After the entire abdominal and pelvic cavities were thoroughly examined, peritoneal washing cytology was performed and multiple biopsies were performed for any suspected area in the abdominal cavity. To prevent the retrograde spread of cancer cells through fallopian tubes, the tube including both the round and ovarian ligament were ligated using the extracorporeal endosuture technique (Suture LapLoop®, Sejong Medical, Seoul, Korea). Subsequently, an uterine elevator (Sairges uterine grasping forcep, WOLF, Germany) was inserted. Before performing laparoscopically assisted vaginal hysterectomy (LAVH) with BSO, we completed LPL and LPAL from the deep circumflex iliac vein level to the left renal vein level using a dissector with monopolar coagulator and harmonic shears (Ultracision Harmonic Scalpel®, Ethicon Endo-Surgery, Cincinnati, OH). Dissected lymphatic tissues were safely removed through the opened vaginal vault after LAVH with BSO. Laparoscopic incidental appendectomy was performed in all patients. Following the completion of all surgical procedures, a drainage tube (Evacuator Barovac®, Sewoon Medical, Seoul, Korea) was inserted after confirming ureteral peristalsis and the absence of trocar site and intra-abdominal cavity bleeding.

Statistical Analysis

Data are expressed as the median and range. Student's *t*-test was used to compare the numbers of left and right harvested pelvic lymph nodes. $P < 0.05$ was taken to indicate a significant difference. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

The median age of the patients was 56 years (range, 28 to 75) and the median body mass index was 25.5 kg/m^2 (range, 21.3 to 37.2). The clinical characteristics of the patients are presented in Table 1. Fifteen patients (53.6%) had 1 or more concomitant medical diseases such as hypertension,

Table 1. Clinical Characteristics of Patients

Characteristics	Median (range)/Number (%)
Number of patients	28
Age (y)	56 (28-75)
Body mass index (kg/m2)	25.5 (21.3-37.2)
Number of patients with concomitant medical disease	15 (53.6)
Hypertension	10 (35.7)
Diabetes mellitus	6 (21.4)
Ischaemic heart disease	1 (3.6)
Number of patients with previous abdominal surgery	12 (42.9)
Laparoscopic tubal ligation	5 (17.9)
Cesarean section	6 (21.5)
Appendectomy	1 (3.6)
Tubal reversal	1 (3.6)
Cholecystectomy	1 (3.6)
Follow-up (months)	23 (3-51)

Table 2. Operative Data

Performed procedures	**Number (%)**
LAVH with BSO + LPL	5 (17.9)
LAVH with BSO + LPL + LPAL	22 (78.6)
Hysteroscopic tumourectomy + LPL	1 (3.6)
Operative results	**Median (range)**
Operating time (min)	142 (110-410)
Estimated blood loss (mL)	215 (100-700)
Hospital stay (days)	7 (3-19)
Number of harvested lymph nodes	
Pelvic lymph nodes	21 (10-48)
Para-aortic lymph nodes	12 (4-21)
Complications	**Number (%)**
Number of total complications	4 (14.3)
Transfusion	2 (7.1)
Lymphocyst formation	1 (3.6)
Fever (>38˚C within postoperative 48 hours)	1 (3.6)
Histopathological results	**Number (%)**
FIGO surgical stage	
Ia	21 (75.0)
Ib	4 (14.3)
IIIc	3 (10.7)
Histologic grade	
G1	23 (82.1)
G2	5 (17.9)

* BSO: bilateral salpingo-oophorectomy, LAVH: laparoscopically assisted vaginal hysterectomy, LPL: laparoscopic pelvic lymphadenectomy, LPAL: laparoscopic para-aortic lymphadenectomy

diabetes mellitus and ischaemic heart disease. Twelve patients (42.9%) had 1 or more history of previous abdominal surgery as follows: laparoscopic tubal ligation, cesarean section, appendectomy, tubal reversal and cholecystectomy. Table 2 shows the operative data. Operative techniques included LAVH with BSO combined with LPL in 5 patients (17.9%), LAVH with BSO combined with LPL and LPAL in 22 patients (78.6%), and hysteroscopic tumourectomy with LPL in 1 patient (3.6%) for fertility conservation.[6,7] Median operating time was 142 minutes (range, 110 to 410). Median estimated blood loss was 215 mL (range, 100 to 700). No cases of conversion to laparotomy were noted. Intraoperative complications included 2 cases of transfusion. Postoperative complications were noted in 2 patients: a symptomatic lymphocyst in one and a high fever (>38°C) within postoperative 48 hours in another. In these cases, the symptoms improved with conservative treatment. Median length of hospital stay was 7 days (range, 3 to 19). Peritoneal washing cytology was negative in all patients. The median number of harvested lymph nodes was 21 (range, 10 to 48) in pelvic lymph nodes, 12 (range, 5 to 32) in right pelvic lymph nodes, 11 (range, 4 to 21) in left pelvic lymph nodes and 12 (range, 4 to 21) in para-aortic lymph nodes. There was no statistical difference between the numbers of right and left harvested pelvic lymph nodes (P = 0.93). From histopathological reports, 1 patient had pelvic lymph node metastases (Patient No. 1) and 2 had isolated para-aortic lymph node metastases (Patient No. 7 and 12). No patient had both pelvic and para-aortic lymph node metastases.

In terms of adjuvant therapies, 3 patients diagnosed as FIGO stage IIIc were treated with chemoradiation therapy using paclitaxel and carboplatin according to the clinical experiment protocol of the Korean Gynecologic Oncology Group (KGOG 2001). Three patients diagnosed as FIGO stage Ib with grade 1 or 2 were treated with vaginal brachytherapy, depending on lymph-blood vessel invasion. For 1 patient who underwent hysteroscopic tumourectomy with LPL for fertility conservation, medroxyprogesterone acetate (500 mg/day) was prescribed for 16 months. The other patients are under follow-up observation without additional adjuvant therapy (Table 3).

The median period of follow-up was 23 months (range, 3 to 51), and there was no recurrence in the vaginal vault, distant metastasis, or port site metastasis up to the last follow-up.

Discussion

Since the recommendation of FIGO in 1988, surgical staging of endometrial cancers have been conducted, consisting of hysterectomy, BSO, peritoneal washing cytology, and selective pelvic and para-aortic lymph node biopsy or lymphadenectomy through a midline incision.[2,3] However, no agreement has been reached on the extent of and appropriate patients for lymphadenectomy.

The National Comprehensive Cancer Network,[8] the American College of Obstetrical and Gynecologists,[9] and the Korean Society of Gynaecologic Oncology and Colposcopy[10] recommend pelvic and para-aortic lymphadenectomy rather than lymph node biopsy in all endometrial cancer patients including patients with early endometrioid adenocarcinoma. However, the American National Cancer Institute[11] recommends selective lymph node biopsy for patients at FIGO stage I, and its omission for low-risk patients.

The grounds for the argument that pelvic and para-aortic lymphadenectomy should be performed for all patients are as follows. First, considering the current FIGO staging system, whether there is lymph node metastasis has a

Table 3. Clinical Data of Patients

No. of patients	Age	Histology	Grade	Preoperative stage	Pelvic LN metastasis	Paraaortic LN metastasis	Surgical stage	Adjuvant treatment
1	28	Endometrioid	G1	Ia	Negative	-	Ia	-
2	51	Endometrioid	G1	Ia	Negative	-	Ia	-
3	64	Endometrioid	G2	Ib	Positive	-	IIIc	CCRT
4	29	Endometrioid	G1	Ia	Negative	-	Ia	Hormone therapy
5	54	Endometrioid	G1	Ia	Negative	-	Ia	-
6	33	Endometrioid	G1	Ia	Negative	-	Ia	-
7	67	Endometrioid	G2	Ib	Negative	Positive	IIIc	CCRT
8	57	Endometrioid	G1	Ib	Negative	Negative	Ib	Vaginal brachytherapy
9	50	Endometrioid	G1	Ia	Negative	Negative	Ia	-
10	53	Endometrioid	G2	Ia	Negative	Negative	Ia	-
11	58	Endometrioid	G1	Ia	Negative	Negative	Ia	-
12	75	Endometrioid	G1	Ia	Negative	Positive	IIIc	CCRT
13	65	Endometrioid	G1	Ib	Negative	Negative	Ib	-
14	45	Endometrioid	G1	Ia	Negative	Negative	Ia	-
15	66	Endometrioid	G1	Ia	Negative	Negative	Ia	-
16	43	Endometrioid	G1	Ia	Negative	Negative	Ia	-
17	57	Endometrioid	G1	Ia	Negative	Negative	Ia	-
18	49	Endometrioid	G1	Ia	Negative	Negative	Ia	-
19	51	Endometrioid	G1	Ia	Negative	Negative	Ia	-
20	61	Endometrioid	G1	Ia	Negative	Negative	Ia	-
21	64	Endometrioid	G1	Ia	Negative	Negative	Ia	-
22	61	Endometrioid	G1	Ia	Negative	Negative	Ia	-
23	74	Endometrioid	G2	Ia	Negative	Negative	Ib	Vaginal brachytherapy
24	45	Endometrioid	G2	Ia	Negative	Negative	Ia	-
25	59	Endometrioid	G1	Ia	Negative	Negative	Ia	-
26	46	Endometrioid	G1	Ia	Negative	Negative	Ib	-
27	41	Endometrioid	G1	Ia	Negative	Negative	Ia	-
28	47	Endometrioid	G1	Ia	Negative	Negative	Ia	-

*CCRT: concurrent chemoradiation therapy

critical effect on postoperative adjuvant therapy and the prediction of prognosis. Second, cell differentiation grade and the depth of myometrial infiltration have been taken into account as predictors of lymph node metastasis, but 19% to 30% of patients diagnosed with preoperative cell differentiation grade 1 showed a rise in cell differentiation grade in postoperative histopathological testing,[12,13] and the depth of myometrial infiltration also showed an increase in postoperative cytohistopathologic testing when compared to that observed before or during operation in 16.3% to 23% of patients.[13,14] Accordingly, the omission of lymphadenectomy based on preoperative findings is likely to lead to under-diagnosis. Third, lymphadenectomy has not only a diagnostic effect but also a therapeutic effect. In addition, endometrial cancer patient survival rates increase according to the number of resected lymph nodes.[15-17] Fourth, if lymphadenectomy is conducted by skilful gynecologic oncologists, the incidence of complications resulting from the performance of lymphadenectomy does not increase significantly.[18,19] Fifth, para-aortic lymph node metastasis

cannot be predicted based on pelvic lymph node metastasis seen from pelvic lymph node biopsy or lymphadenectomy.[20] Sixth, in diagnosing lymph node metastasis, the sensitivity of CT and MRI is not so high (43% to 60% and 50% to 60%, respectively). Furthermore, although there have been several other diagnosis methods, including enhanced MRI and FDG-PET, satisfactory results have not yet been attained.[21-23]

In contrast, the grounds for opposition to the performance of pelvic and paraaortic lymphadenectomy for all endometrial cancer patients are as follows. First, the therapeutic effect of lymphadenectomy is not yet clear.[24,25] In addition, lymphadenectomy does not improve low-risk endometrial cancer patient survival rates significantly. [11,26] Moreover, para-aortic lymphadenectomy cannot control the paths of propagation to regions outside the uterus. Second, the performance of lymphadenectomy may increase perioperative complications significantly.[8]

Takeshima et al reported that 4% of endometrial cancer patients with no myometrial infiltration and at cell differentiation grade 1 showed lymph node metastasis,[27] and Creasman et al reported that 9% of endometrial cancer patients at clinical stage I or II showed pelvic lymph node metastasis and 6% of them showed para-aortic lymph node metastasis.[28] In this study, pelvic lymphadenectomy was conducted in all patients and para-aortic lymphadenectomy was performed in 22 (78.6%) of them. Three (10.7%) patients showed pelvic or para-aortic lymph node metastasis. In the patients who showed metastasis, there was no preoperative finding indicating metastasis except old age. The incidence of metastasis appeared to be the same as in previous research.

Because this is a preliminary report on the performance of pelvic and para-aortic lymphadenectomy in low-risk endometrial cancer patients, we cannot conclude whether pelvic and paraaortic lymphadenectomy must be conducted for low-risk endometrial cancer patients. However, in this study, if lymphadenectomy was not conducted, lymph node metastasis in the 3 patients would not have been found, and because they did not have any risk factor demanding postoperative adjuvant therapy, follow-up observation would have been made without adjuvant therapy. Consequently, there would have been serious errors in predicting their prognosis and applying adjuvant therapies. We expect a conclusion on whether to perform pelvic and para-aortic lymphadenectomy for low-risk endometrial cancer patients through large-scale prospective research, but because the 5-year survival rate of low-risk endometrial cancer patients is reported to be as high as 95% to 97%, it will be difficult to explain statistical differences in survival rates according to lymphadenectomy, because the increase of the survival rate resulting from lymphadenectomy will fall within the margin of statistical error. However, as explained above, we believe that pelvic and para-aortic lymphadenectomy for low-risk endometrial cancer patients must be considered in surgical staging in the current situation in which cell differentiation grade and the depth of myometrial infiltration, which are used as criteria for dividing the disease into low-risk and high-risk groups, are not absolutely reliable.

Conclusions

It is believed that pelvic and para-aortic lymphadenectomy should be considered in surgical staging for all low-risk endometrial cancer patients until it is concluded to be clinically insignificant through large-scale prospective research in the future. However, it will be difficult to explain statistical differences in survival rates according to lymphadenectomy, because the increase of the survival rate resulting from lymphadenectomy will fall within the margin of statistical error.

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