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Original Article

Long-term survival outcomes of laparoscopic staging surgery in treating endometrial cancer: 20 years of follow-up

Chyi-Long Lee [a, 1], Soshi Kusunoki [b, 1], Kuan-Gen Huang [a], Kai-Yun Wu [a], Chen-Yin Huang [a], Chih-Feng Yen [a, c, *]

[a] Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital at Linkou and Chang Gung University College of Medicine, Taoyuan, Taiwan
[b] Department of Obstetrics and Gynecology, Faculty of Medicine, Juntendo University, Hongo, Bunkyo-ku, Japan
[c] Graduate Institute of Clinical Medical Sciences, Chang Gung University College of Medicine, Tao-Yuan, Taiwan

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ABSTRACT

Objective: To assess the long-term outcomes of laparoscopic staging surgery (LSS) in treating patients with endometrial carcinoma.
Materials and Methods: Patients with endometrial cancer who underwent LSS between June 1995 and June 2014 were prospectively registered. Perioperative data, complications, disease recurrence, and long-term survival were measured.
Results: The study included 287 consecutive patients [mean age (± standard deviation), 53 ± 10.4 years; mean body mass index, 27.3 ± 6.7 kg/m^2] with a median follow-up ranging from 1 to 216 months. No laparotomy conversion was recorded for any patient. The mean operative time was 207 ± 63.5 minutes, and the mean blood loss was 183 ± 166.7 mL. The mean numbers of pelvic nodes and para-aortic nodes removed were 18 ± 4.8 and 8 ± 5, respectively. More than 80% of the patients had an International Federation of Gynecology and Obstetrics (FIGO) Stage 1 disease. The overall complication rate was 3.1%, including two patients of bladder injuries and one with bowel injury intraoperatively, and post-operatively one patient with pelvic abscess, three with urinary tract infection, one with voiding difficulty, and one with bowel perforation. The overall survival rates were 94% in 5 years and 92.7% in 20 years. No port-site metastasis was recorded in this study.
Conclusions: Patients with endometrial carcinoma treated by LSS had compatible or even better long-term survival outcomes and less complication in comparison with the published data, in addition to the benefits of its minimally invasive characteristics. LSS should be the treatment of choice for endometrial cancer.

Introduction

Endometrial cancer is the most common gynecologic cancer of the female genital tract in developed and developing countries, and it occurs in postmenopausal women, with a peak incidence between 55 and 60 years of age. The incidence of endometrial cancer increases in patients with diabetes mellitus or hypertension and notably in recent decades in Taiwan, probably because of lifestyle changes among its citizens.

Most patients with endometrial cancer are diagnosed at an early stage and treated surgically with good outcomes [1]. Complete surgical staging for endometrial cancer includes peritoneal cytology, exploration of the peritoneal cavity, extrafascial total hysterectomy, bilateral salpingo-oophorectomy, and systematic pelvic and para-aortic lymphadenectomy [2]. The idea of laparoscopic lymphadenectomy first originated in combination with Schauta's vaginal hysterectomy by Dargent [3,4]; however, Querleu et al [5] first reported laparoscopic pelvic lymphadenectomy in the staging of early carcinoma of the cervix, and Childers et al [6] were the first to report the laparoscopic para-aortic lymph node dissection. Childers et al [7] were also the first to report the laparoscopic treatment of endometrial cancer.

* Corresponding author. Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital at Linkou, 5, Fu-Hsin Street, Kwei-Shan, Tao-Yuan 33305, Taiwan.
E-mail address: chihfeng.yen@outlook.com (C.-F. Yen).
[1] C.-L. Lee and S. Kusunoki contributed equally to this work.

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Over the past two decades, there have been many reports on the efficacy and safety of laparoscopic oncologic surgery with at least equivalent outcomes, including disease-free survival and overall survival rates [8,9]. However, the results of long-term follow-up are still few. We have been performing laparoscopic staging surgery (LSS) for patients with endometrial cancer since 1993, and published a preliminary report of 105 patients with good results in 2012 [10]. In this study, we extended our follow-up to 288 patients for a period of >20 years, with the aim of evaluating the long-term outcomes.

Materials and methods

Between June 1995 and June 2014, we investigated 287 consecutive patients with endometrial cancer who underwent LSS at Chang Gung Memorial Hospital, Tao-Yuan, Taiwan. Preoperatively, these patients were all histologically proven to have endometrial cancer and assumed to be in the early stage based on clinical assessment.

As reported previously, two experienced surgeons (C.L.L. and K.G.H.) performed most of the surgeries, including procedures of peritoneal lavage, hysterectomy with bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, as well as omentectomy for patients of serous papillary carcinoma and clear cell carcinoma. The operation was performed with five trocars, including two 12-mm and three 5-mm trocars, using a 10-mm laparoscope via a skin incision at the midpoint of the umbilicus and xiphoid process (Lee–Huang point), and all other ancillary ports laterally, as described previously [11–13]. Laparoscopic hysterectomy (LH) was performed via a laparoscopically assisted vaginal approach or a total laparoscopic approach and the uterus was removed vaginally without breaking into the endometrial cavity. Since the revised International Federation of Gynecology and Obstetrics (FIGO) staging criteria of 2009 [14], the current policy at our institution is to perform pelvic and para-aortic lymphadenectomy in all patients with endometrial cancer.

Patients with FIGO Stage IB Grades 2–3 and FIGO Stage IC Grades 1–2 were clinically observed or received whole-pelvic radiation and vaginal brachytherapy or chemotherapy, according to the adverse risk factors. Furthermore, those with FIGO Stages IIA and IIB received whole-pelvic radiation and/or vaginal brachytherapy. Patients with advanced stages of endometrial cancer received adjuvant therapy with radiotherapy, chemotherapy, or concurrent chemoradiotherapy.

Data collection and statistical analysis

Perioperative data including the operation time, number of retrieved lymph nodes, intraoperative blood loss, length of hospitalization stay, and the occurrence of intra- and postoperative complications including blood transfusion, and febrile status were recorded, and also the pathological data including the histological type, presence of lymphovascular space invasion, cytological findings, and the number of lymph nodes in the pelvic and para-aortic areas. At the end of the study, the patterns of recurrence, disease-free survival, and overall survival were analyzed.

All the data were analyzed using SPSS for Windows release 19.0.0/2010 (IBM-SPSS Inc., Chicago, IL, USA). Continuous variables such as age and body mass index (BMI) values are presented as mean ± standard deviation, whereas parity is presented as median value and range. The cumulative event rates (recurrence and death) were calculated using the Kaplan–Meier method, with the time to the first event as the variable.

Results

The characteristics of the study population are shown in Table 1. The mean age (± standard deviation) of the patients was 53 ± 10.4 years. The mean BMI was 27.3 ± 6.7 kg/m^2. Fourteen patients had a history of other cancers: six with breast cancer, five with colon cancer, one with nasopharyngeal carcinoma, one with a molar pregnancy, and one with liver cancer. Of 287 patients, 126 (43.7%) underwent hysteroscopic examination. Of these, one (0.79%) was positive for peritoneal cytology. More than 80% of the patients had FIGO Stage 1 cancer. As for the final pathological findings, there were 161 patients (56.3%) with Grade 1, 71 (24.7%) with Grade 2, and 47 (16.2%) with Grade 3 cancer.

The intra- and postoperative characteristics are shown in Table 2. The mean operation time was 207 ± 63.5 minutes, and the mean blood loss was 183 ± 166.7 mL. The type of hysterectomy was generally simple hysterectomy (84.7%), whereas some had modified radical hysterectomy (10.1%) for the suspicion of cervical involvement preoperatively. However, 15 (5.2%) patients underwent LH and bilateral salpingo-oophorectomy only and did not undergo other staging surgery procedures because of the very early stage or superficial involvement of the disease and the well-differentiated characteristics (Table 2), and among young patients oophorectomy could also be spared. None of the patients received an autologous blood transfusion or required conversion to laparotomy. The mean numbers of pelvic lymph nodes and para-aortic nodes removed were 18 ± 4.8 and 8 ± 5, respectively. Para-aortic lymph node dissection was performed in 76 patients (26.4%) who had known risk factors. The mean hospital length of stay was 6 ± 4.4 days. In total, 71 patients (24.7%) received adjuvant therapy according to their final surgical stage and adverse risk factors. Nineteen patients (6.6%) underwent adjuvant chemotherapy, 12 (4.1%) radiotherapy, and 40 (13.9%) concurrent chemoradiotherapy.

The surgery-related complications are shown in Table 3. The perioperative complications included two bladder injuries and one bowel injury, and the postoperative complications within 30 days included one pelvic abscess, three urinary tract infections, one bowel perforation, and one difficulty voiding.

Table 1
Patient characteristics (n = 287).

	Mean ± SD
Age (y)	53 ± 10.4
BMI (kg/m^2)	27.3 ± 6.7
Cancer history (n)	
Breast cancer	6
Colon cancer	5
Nasopharyngeal carcinoma	1
Molar pregnancy	1
Liver cancer	1
Hysteroscopic examination (n = 126), n (%)	
Positive cytology after hysteroscopy,	1 (0.79)
FIGO (2008) stage, n (%)	No (%)
IA	210 (73.1)
IB	28 (9.7)
II	9 (3.1)
IIIA	9 (3.1)
IIIB	4 (1.3)
IIIC1	22 (7.6)
IIIC2	4 (1.4)
IV	1 (0.3)
Grading, n (%)	
G1	161 (56.3)
G2	71 (24.7)
G3	47 (16.2)
Unknown	8 (2.8)

BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics; SD = standard deviation.

Table 2
Intraoperative characteristics ($n = 287$).

	Mean ± SD or *n* (%)
Duration of surgery (min)	207 ± 63.5
Estimated blood loss (mL)	183 ± 166.7
Surgical methods	
Simple LH + staging procedures	243 (84.7)
Modified radical LH + staging procedures	29 (10.1)
Simple LAVH + BS(O) only	15 (5.2)
Number of lymph nodes removed ($n = 272$)	
Pelvic lymph nodes	18 ± 4.8
Para-aortic lymph nodes	8 ± 5
Hospital stay (d)	6 ± 4.4
Final pathology, *n*	
Endometrioid adenocarcinoma	271 (94.4)
Adenosquamous carcinoma	2 (0.7)
Serous carcinoma	2 (0.7)
Clear cell adenocarcinoma	8 (2.8)
Carcinosarcoma	4 (1.4)
Conversion to laparotomy, *n*	0
Adjuvant treatment	
Chemotherapy	19 (6.6)
Radiation therapy	12 (4.1)
Chemotherapy and radiation therapy	40 (13.9)

BS(O) = bilateral salpingectomy, with or without oophorectomy; LAVH = laparoscopic assisted vaginal hysterectomy; LH = laparoscopic hysterectomy; SD = standard deviation.

Table 3
Postoperative outcomes.

	No.
Intraoperative complication	
Bladder injury	2
Bowel injury	1
Postoperative complication (<30 d)	
Pelvic abscess/hematoma	1
Urinary tract infection	3
Bowel perforation	1
Voiding dysfunction	1
Postoperative (>30 d, <180 d)	
Wound infection	1
Deep vein thrombosis	1
Ileus	2
Urinary tract infection	1
Voiding dysfunction	1
Follow-up, mo; median (range)	46 (1–216)
Recurrence (*n*)	22
Follow-up (*n*)	241
Lost to follow-up (*n*)	24
Recurrence, mo; median (range)	12.1 (2.9–100)
Death (*n*)	
Death from endometrial cancer	12
Death from other disease	12
Death, mo; median (range)	25.5 (2–180)

Of 287 patients, 24 patients were lost to follow-up and 22 patients experienced recurrence after a median follow-up duration of 46 months (Table 3). The total recurrence rate was 7.6%. Recurrent disease was treated with radiotherapy or a combination of radiotherapy and chemotherapy. No port-site metastasis occurred in this study.

Table 4 provides an overview of the characteristics of 12 patients who died of disease, in which seven patients were in advanced stage and another five patients were in Stage 1. Stage 1A cases had poorly differentiated histology with endometrioid adenocarcinoma, and mixed endometrioid and clear cell adenocarcinoma, whereas Stage 1B cases had deeply myometrial invasion. All recurrent patients had high-risk tumors.

The disease-free survival rate was 89.3%. Of 287 patients, 24 (8.3%) died, 12 of whom (12/287, 4.1%) died from other diseases. The 5-year overall survival was 94%, and the 10-, 15- and 20-year overall survival rates were each 92.7% (Figure 1).

Discussion

The present study evaluated 288 patients with endometrial cancer undergoing LSS and with a follow-up period of 20 years, which—to our knowledge—is the largest study performed in a single institution. Our results of 94% in the 5-year overall survival rates and no laparotomy conversion needed in any patient are apparently better than those of the previous landmark study of LAP2 delivered by the Gynecologic Oncology Group and published in 2009.

There has been an increasing trend to perform the surgical treatment laparoscopically for endometrial cancer over the past 20 years [1,15,16]. We reviewed the literature for studies that enrolled more than 100 endometrial carcinoma patients who underwent long-term follow-up after laparoscopic surgery (Table 5) [15,17–21]. Most of these studies compared the overall outcomes of total LH or laparoscopically assisted vaginal hysterectomy with those of abdominal hysterectomy for early-stage endometrial carcinoma. The largest study performed was the Gynecologic Oncology Group Study LAP2 in 2009 [22], which compared laparoscopy in 1682 patients and laparotomy in 920 patients. The authors concluded that, with the incidence of 10% for intraoperative complications, and 14% for the postoperatively moderate to severe complications in the laparoscopic group, LSS for endometrial cancer is feasible and safe, despite a high rate of conversion to laparotomy (25.8%) [22]. Furthermore, in 2012 they reported a 5-year overall survival rate of 89.8% in the study group [15].

The current study found a 92.7% 20-year overall survival rate. As shown in Table 5, Malzoni et al [23] performed a prospective randomized study that enrolled 81 patients who underwent total LH with lymphadenectomy for early-stage endometrial cancer. After a median follow-up duration of 38.5 months, the disease-free and overall survival rates were 91.4% and 91.1%, respectively. Kalogiannidis et al [24] conducted a prospective, nonrandomized cohort study of consecutive patients with clinical Stage I endometrial adenocarcinoma. Of 169 patients, 69 underwent laparoscopic vaginal hysterectomy with lymphadenectomy. At the median follow-up of 51 months, the recurrence rate was 8.7%, and the actuarial overall survival and disease-free survival rates were 93% and 91%, respectively. Zullo et al [25] reported a prospective long-term extension study for a randomized controlled study that included 84 patients with clinical Stage I endometrial carcinoma. Of those 84 patients, 40 were included in the laparoscopy group, with a follow-up period of 78 months, and 38 comprised the laparotomy group, with a 79-month follow-up period [25]. Seven of 40 (17.5%) and six of 38 (15.8%) patients died in the laparoscopy and laparotomy groups, respectively, of whom six (15%) and five (13.2%) respective patients died of the disease. Among these studies, our study is the largest series in the literature, and it also indicated the feasibility and safety of LSS for endometrial cancer.

In the present study, the complication rate was extremely low compared with those reported in other studies, as shown in Table 5. Since 2008, an additional intraoperative complication experienced was bladder injury, seen in one case. As for the complication rate, surgeons who have performed more than 30 laparoscopic hysterectomies were associated with a significantly lower rate of bladder, ureteral, and bowel complications [26], and more than one-third of the ureteral injuries that did occur were caused by surgeons who had performed fewer than 30 laparoscopic hysterectomies [27]. These reports indicate that the surgeon's experience with laparoscopic surgery has an impact on the surgical outcome.

Table 4
Patients who died of endometrial cancers.

	Age (y)	Pathology	Stage	pTNM	Adjuvant treatment	Recurrent	Disease-free interval (mo)	Overall survival (mo)
1	63	Endometrioid adenocarcinoma, Grade 3	IIIC1	pT1bN1M0	EP 6 cycles	Peritoneal carcinomatosis	19	23
2	54	Endometrioid adenocarcinoma, Grade 3	IVB	pT1bN0M1	EP 6 cycles, RT	Liver	18	21
3	53	Serous adenocarcinoma	IIIC2	pT3aN1M0	EP 4 cycles	Adrenal gland, vaginal stump	6	8
4	55	Endometrioid adenocarcinoma, Grade 3	IIIC1	pT1bN1M0	CCRT	Sigmoid colon	24	25
5	80	Endometrioid adenocarcinoma, Grade 3	IB	pT1bN0M0	RT	Peritoneal carcinomatosis	12	13
6	76	Endometrioid adenocarcinoma, Grade 3	IIIA	pT3aN0M0	RT	Lung, Axilla	3	4
7	55	Endometrioid adenocarcinoma, Grade 1	IB	pT1bN0M0	CCRT	Vaginal stump	11	50
8	77	Endometrioid adenocarcinoma, Grade 3 Clear cell carcinoma	IA	pT1aN0M0	—	Pelvic lymph nodes	12	31
9	63	Endometrioid adenocarcinoma, Grade 2	IIIA	pT3aN0M0	n/a	n/a	n/a	50
10	38	Endometrioid adenocarcinoma, Grade 3	IA	pT1aN0M0	—	Kidney	13	29
11	53	Endometrioid adenocarcinoma, Grade 1	IIIA	pT3aN0M0	—	Lung, brain, liver	11	22
12	63	Endometrioid adenocarcinoma, Grade 1	IB	pT1bN0M0	CCRT	Peritoneal carcinomatosis	3	4

CCRT = concurrent chemoradiation therapy; EP = etoposide and cisplatin chemotherapy; pTNM = pathological tumor-node-metastasis staging; RT = radiation therapy.

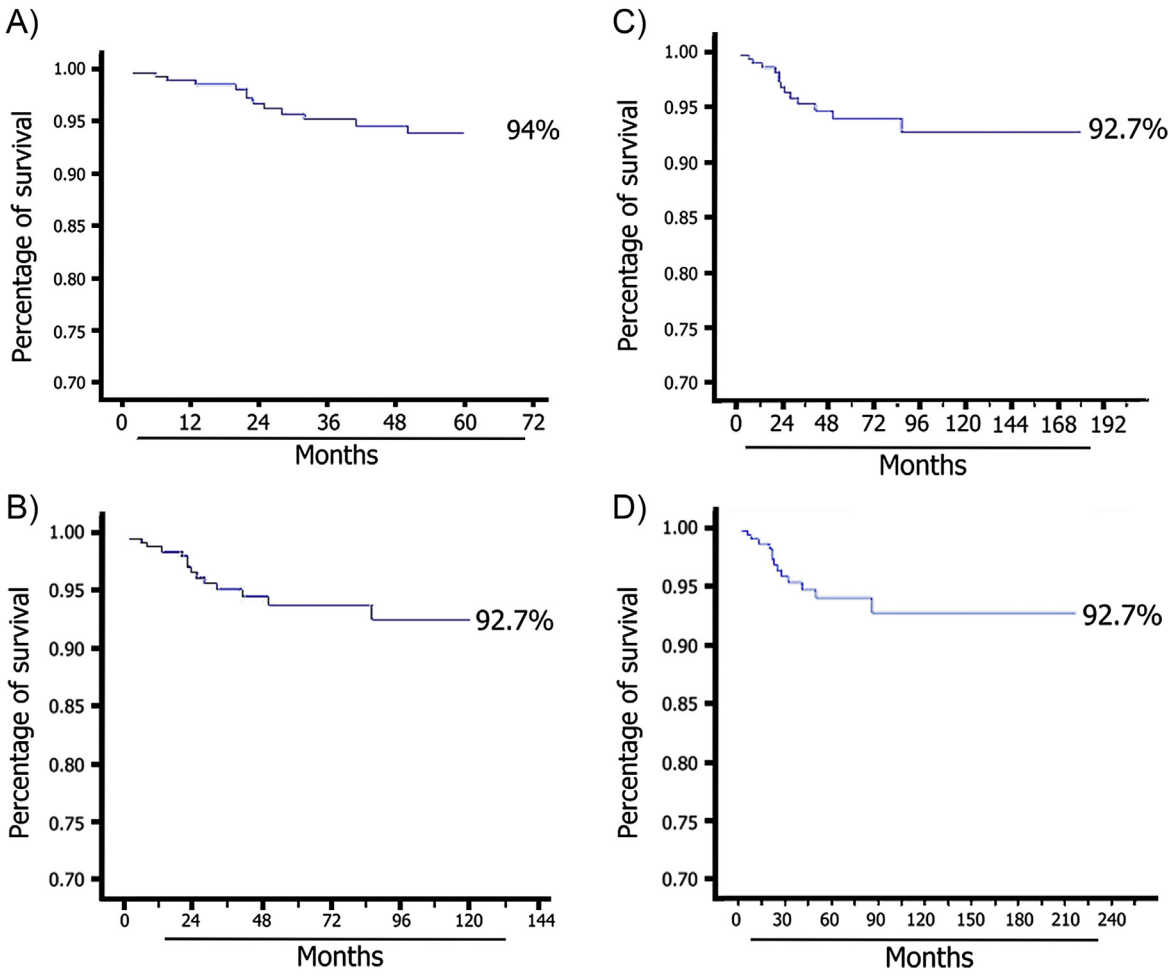

Figure 1. Kaplan–Meier plots showing percentage of (A) 5-year, (B) 10-year, (C) 15-year, and (D) 20-year overall survival. The 5-year overall survival rate was 94%, and 10-, 15-, and 20-year overall survival rates were each 92.7%.

Table 5
Literature reviews for the surgical outcomes for the LSS for endometrial cancer.

Study design	Eltabbakh 2002 [18]	Cho 2007 [19]	Tinelli 2011 [21]	Palomba 2012 [20]	Walker 2012 [15]	Lu 2013 [17]	Current study
	Retrospective	Retrospective	Retrospective, multicenter study	Retrospective, multicenter study	Prospective GOG study LAP2	Prospective	Retrospective
Study pt no. (*n*)	100	165	123	403	1696	151	287
Open pt no. (*n*)	86	144	103	609	920	121	
Age (y), mean ± SD (range)	62 ± 12.9 (16–89)	50 (26–77)	62 ± 13	53 ± 12	62.8 (23.9–92.8)	56.6 (27–82)	53 ± 10.4
BMI (kg/m^2), mean ± SD (range)	28.8 ± 7.1 (17.8–49.6)	25.6 (16.9–42.4)	27 ± 7.3	27 ± 4.5	28.4 (14.9–65.3)	26.4	27.3 ± 6.7
Surgical stage (%)							
Ia	42	32.7	30.8	12.9	69.6	39	73.1
Ib	31	55.8	29.2	61.5	12.6	36.4	9.7
Ic	10	6.1	18.6	17.4	—	15.2	—
IIa	3	2.4	4.8	3	4	6.6	3.1
IIb	5	3	2.4	1.2	—		—
III	7	0	12.7	3.7	11.5	2.6	13.5
IV	2	0	0	0.2	2.4	0	0.3
Grade (%)							
1	57	57	34.9	47.4	—	62.9	56.3
2	26	32.7	46	35.2	—	26.4	24.7
3	17	10.3	18.6	17.4	—	10.5	16.2
Lymph node removed							
Pelvic, *n* (mean)	11 ± 5.1	26.2 (1–70)	22.9 ± 6.3	16 ± 6	17 (12–23)		18 ± 4.8
Para-aorta, *n* (mean)	2.5 ± 1.9	4.9 (1–20)	9.8 ± 3.1	5 ± 3	7 (4–11)		8 ± 5
Total, LN (mean)		27.1 (1–70)				25 (10–41)	
Conversion to open (%)	6	5.30	0	13.2	25.8	—	0
Lymphadenectomy	PLA 86% PALA 24%	PLA 89.7% PALA 17.6%	PLA 100% PALA 21.1%	PLA 47.6% PALA 10.2%	PLA+PALA 95.8%	PLA 100%, PALA 15% (sampling 80%)	
Complication (%)	11%	9.1	7.3 (intraoperative), 33.3 (postoperative)		10 (intraoperative)	12	1.0 (intraoperative) 4.1 (postoperative)
Disease-free survival (%)	90 (5 y)	95.5 (5 y)	91.9	73.2			89.3
Overall survival (%)	92 (5 y)	98 (5 y)	94.4	77.9	89.8 (5 y)	94	94 (5 y)
Median follow-up, mo	27	28	49.5	49	59	68	46

BMI = body mass index; LSS = laparoscopic staging surgery; PALA = para-aortic lymphadenectomy; PLA = pelvic lymphadenectomy; pt = patient.

There was no conversion to laparotomy in the present study. Risk factors for conversion to laparotomy included the patient's BMI and age in the Laparoscopic Approach to Cancer of the Endometrium (LACE) trial [28]. In the LAP2 trial, the failure to complete laparoscopy was greater with increasing age and BMI and with metastatic disease [22]. One of the reasons for our zero conversion could be a tendency toward a younger age and lower BMI among patients in our study compared with those in other reports, as shown in Table 5. Many studies have also supported such results [29,30]. We noted that a learning curve really existed, wherein operative time, hospital stay duration, and conversion rate to laparotomy associated with LSS would decrease with increasing operation experience [31], and the number of pelvic lymph nodes removed would also increase with increased surgeon experience [32], as we have experienced a high degree of familiarization for over two decades in practicing cancer laparoscopies, including laparoscopic radical trachelectomy [33], and natural orifice adnexal surgery and endometrial cancer [4,34]. Another reason for our zero conversion could be the incorporation of the Lee–Huang point, which enables a wider surgical field and safe performance of lymphadenectomy.

We routinely performed lymphadenectomy for patients with early-stage endometrial cancer, and this could be one of the possible reasons for a better survival prognosis in the present study. Todo et al [35] reported that among patients at an intermediate or high risk of recurrence, overall survival was significantly longer in the pelvic and para-aortic lymphadenectomy group than in the pelvic lymphadenectomy group. Cragun et al [36] found that after removing patients reported to have pelvic or aortic nodal metastasis from their analysis, more extensive lymphadenectomy was associated with improved survival. Although it is controversial to perform lymphadenectomy in all endometrial cancer patients, this procedure may have a therapeutic benefit selectively in patients with an intermediate or high-risk of recurrence [37]. Accordingly, the number of lymph node removal could not only be an issue of precise staging for pathologic diagnosis, but also regarding the radicality of cancer surgery. Therefore, we suggest that lymphadenectomy be routinely performed in LSS.

In the present study, 126 patients who underwent hysteroscopic examination preoperatively resulted in only one (0.79%) patient positive for peritoneal cytology detected intraoperatively, indicating that preoperative hysteroscopy does not increase the risk for spread of cancer cells and is not correlated with poor prognosis [38,39]. Hysteroscopy is a good—if not the best—diagnostic tool in some difficult cases to differentiate whether the tumor originates in the endometrium or in the endocervix.

Fourteen patients in the current study had five other associated malignancies, one of which was colon cancer, which is associated with the hereditary cancer, Lynch syndrome. Lynch syndrome, known as hereditary nonpolyposis colorectal cancer, is the most common form of hereditary colorectal cancer and hereditary endometrial cancer. The frequency of Lynch syndrome was reported to be approximately 1–2% in colorectal cancer patients [40,41], and we had five patients (1.7%) with colon cancer in our study. We need to pay more attention to

hereditary endometrial cancer by reviewing personal and family histories.

This study had the limitation of being a single-arm case series and in its retrospective nature, which pose potential threats to internal validity caused by confounding or bias. However, the patients usually come to Dr Lee and Huang's clinics seeking for laparoscopic operation, and none of them had given consent for laparotomy. Thus, the study can only be sequential, and it is difficult to have a counterpart of laparotomy to compare with.

In conclusion, few surgical complications and good survival outcomes were noted in the current series for LSS in treating patients with endometrial cancer. Hysteroscopic diagnosis and excisional biopsies for endometrial carcinoma did not seem to predispose the risk of intraperitoneal dispread or hamper the prognosis of treatment. As no laparotomy conversion happened herein, its incidence should be rare in the hands of experienced endoscopists. In addition to the benefits of its minimally invasive characteristics, patients treated by LSS in the current series had overall survival rates 94% in 5 years and 92.7% in 20 years, respectively, which is compatible or even better than the published data in the literature. Therefore, traditional laparotomy in staging surgery should be replaced with LSS in a move to push the progress of minimally invasive therapy into the next era.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Ethics approval

This clinical study has been reviewed and approved by the Human Investigation Review Board of Chang Gung Memorial Hospital, Taiwan (No. 104-9403B, date of approval: January 04, 2016).

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