

A comparison of laparoscopic and open surgery for early stage endometrial cancer with analysis of prognostic factors: a propensity score matching study

Hao Lin¹, Hung-Chun Fu¹, Fu-Tsai Kung¹, Yu-Jen Chen², Chan-Chao Chang Chien¹, Chen-Hsuan Wu¹, Ching-Chou Tsai¹, Yu-Che Ou^{2,*}

¹Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, 833 Kaohsiung, Taiwan

²Department of Obstetrics and Gynecology, Chia-Yi Chang Gung Memorial Hospital, 613 Chia-Yi, Taiwan

*Correspondence: tedycou@gmail.com (Yu-Che Ou)

DOI: [10.31083/j.ejgo4204107](https://doi.org/10.31083/j.ejgo4204107)

This is an open access article under the CC BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/>).

Submitted: 8 February 2021 Revised: 28 March 2021 Accepted: 20 April 2021 Published: 15 August 2021

Objective: We aimed to compare the short- and long-term outcomes of a laparoscopic approach with those of laparotomy for early stage endometrial cancer and attempted to identify factors predicting survival. **Methods:** Between 2007 and 2014, patients with clinical early stage endometrial cancer and a uterine size less than 10 cm receiving surgical treatment were reviewed. Kaplan-Meier and multivariate Cox regression model were used for survival analysis. Short- and long-term outcomes were compared between the two groups before and after 1 : 1 propensity score matching (PSM). **Results:** Finally 255 patients were enrolled, 177 received laparotomy and 78 received laparoscopic surgery. The patients receiving laparoscopic surgery had significant less blood loss and shorter hospital stay, but longer operative time. Before PSM, the 5-year disease-free survival (DFS) and overall survival (OS) rates were in favor of laparoscopic group (94.4 vs. 84.1%, $p = 0.022$; 97 vs. 90.5%, $p = 0.060$). Cox regression analysis showed that high-grade lesion (HR 11.35, 95% CI 4.06–31.07), non-endometrioid histology (HR 3.99, 95% CI 1.52–10.44), and age >60 (HR 3.35, 95% CI 1.60–7.00) were independent factors predicting recurrence while high-grade lesion (HR 10.38, 95% CI 2.44–44.15) and CA125 >35 (HR 3.02, 95% CI 1.07–8.55) were independent factors predicting death. After PSM, two comparable groups of 59 patients each were obtained. There were no significant differences in 5-year DFS and OS between the two groups. **Conclusion:** Our results showed that compared with laparotomy, laparoscopic surgery improved short-term outcomes, with similar survival results. Factors predicting survival were high-grade tumor, non-endometrioid histology, age >60, and CA125 >35.

Keywords

Endometrial cancer; Laparoscopy; Laparotomy

1. Introduction

From 1991 to 2010, the total number of uterine corpus cancer increased by 5.7-fold in Taiwan. In addition, the annual age-specific rate nearly doubled during 2001 to 2010 when compared with 1991 to 2000 [1]. In Taiwan, there has been a noticeable increase in the number of women adopting

a Western-style diet and not having children in recent years, and thus changes in reproductive behavior and an increased rate of obesity may partially be responsible for the increase in endometrial cancer.

The standard treatment for endometrial cancer is staging surgery with total hysterectomy, bilateral salpingo-oophorectomy and pelvic/para-aortic lymph node dissection followed by tailored adjuvant therapy. Surgery is traditionally performed via laparotomy. Since Childers and Surwit first described laparoscopic surgical staging for early endometrial cancer in 1992, many subsequent studies have shown that this approach is an effective alternative to open surgery with a much faster recovery and fewer complications [2–5]. However, these studies lack well-designed randomization, and most of them are retrospective in nature. In 2009, Walker *et al.* [6] published the initial results of a large randomized controlled trial (LAP2) by the Gynecologic Oncology Group (GOG). With a longer follow-up period, they concluded that laparoscopic staging surgery is an acceptable alternative for patients with presumed early-stage endometrial cancer for better short-term benefits including shorter hospital stay, fewer moderate-to-severe postoperative adverse events, and improved body image. They also demonstrated that this approach improved the patients' quality of life, and, more importantly, did not compromise overall survival (OS) compared to those treated with laparotomy [7]. In a subsequent randomized controlled trial (Laparoscopic Approach to Cancer of the Endometrium, LACE), the results also demonstrated equivalent disease-free survival at 4.5 years and no difference in OS [8].

In Taiwan, there was only one previous study described the results of head-to-head comparison between laparoscopic and laparotomy surgery for endometrial cancer with limited case number. We started to treat some patients with early endometrial cancer laparoscopically at our department since 2007. Therefore, in this study, we aimed to evaluate whether

this surgical approach could be the preferred procedure for these patients compared with conventional open surgery at our institute. We used propensity score matching (PSM) analysis to eliminate the imbalance between groups and reduce the effects of confounding to achieve a random effect in this observational study. Furthermore, we attempted to analyze factors predicting prognosis.

2. Methods

2.1 Patients

We conducted this retrospective review to identify all cases of uterine cancer between January 2007 and December 2014 at our hospital. Four hundred and thirty-two patients were identified during this period. All of the patients received imaging studies with computed tomography or magnetic resonance imaging for preoperative evaluations of disease burden and extent once the diagnosis had been established. In order to maintain uterine intactness and prevent cancer cell spillage during its removal from vagina, in our clinical practice the selection criteria for laparoscopic surgery were clinical stage I disease with a uterine size less than 10 cm in maximal diameter based on imaging findings. In order to match the patient background properly in the laparotomic group, we excluded patients who received open surgery with a clinical stage of II or higher, and/or a uterine size more than 10 cm. Patients who did not receive surgery as the initial treatment and those with sarcoma histology were also excluded. Finally, 255 patients fulfilled the criteria and were enrolled in this study.

2.2 Method of operation

Surgical procedures including peritoneal washing cytology, total hysterectomy, bilateral salpingo-oophorectomy, and pelvic/para-aortic lymphadenectomy were performed via a laparotomic or laparoscopic route. The choice of surgical route was determined according to the patients' or physicians' preference. However, laparoscopic surgery was performed by only two well-trained laparoscopic oncologists (HL and YCO). The postoperative adjuvant therapy was arranged according to clinical guidelines based on surgical pathological findings. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital.

2.3 Basic information of the patient

Age, gravidity, parity, body mass index (BMI), levels of the pretreatment tumor marker cancer antigen-125 (CA125), and co-morbid medical conditions were recorded for each patient.

2.4 Perioperative outcome

The intraoperative complications included vascular injuries, intestinal injuries, bladder or urologic injuries, and conversion to open laparotomy. Peri- and post-operative data collected included operative time (defined as Veres needle insertion/skin incision to skin closure), estimated blood loss, pre- and post-operative hemoglobin values, need for transfusion, length of hospital stay, and re-operation or re-

admission. Pathologic data were collected including the total number of lymph nodes retrieved, FIGO stage of the tumor, and the histology and grade of the tumor. Disease-free survival (DFS) and OS were estimated as the interval from the date of diagnosis to the first evidence of recurrence or death, respectively. Recurrent disease was defined as proof from a biopsy, image findings, and/or persistent elevation of tumor markers.

2.5 Statistical analysis

Comparisons of median and mean values were performed using the two-sample *t*-test. Frequency distributions between categorical variables were compared using the chi-square test. A Cox regression model was used for multivariate analyses using DFS and OS as end points. DFS and OS curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Because some baseline characteristics were statistically different between patients received laparoscopic and laparotomic surgery, one-to-one PSM was performed with the nearest available neighbor matching to eliminate the imbalance using a 0.2 caliper. Propensity scores were calculated using a multivariable logistic regression model to estimate the conditional probability of a patient receiving a surgery approach. The degree of covariate imbalance in the unmatched and matched samples was measured using the standardized difference. A standardized mean difference (SMD) of less than 0.1 indicates very small differences; values between 0.1 and 0.3 indicate small differences; values between 0.3 and 0.5 indicate moderate differences; values above 0.5 indicate considerable differences. Data management and analysis were performed using MedCalc and SPSS software for Windows version 22 (SPSS Inc., Chicago, IL, USA). A *p* value less than 0.05 was taken to indicate statistical significance, and a *p* value between 0.05 and 0.1 was taken to indicate a statistical trend.

3. Results

3.1 Basic characteristics of the patients

A total of 255 patients were finally enrolled for this retrospective study. The basic characteristics of the patients are listed in Table 1. The median age at diagnosis was 57 years old (interquartile range (IQR) 50–61 years), and the median follow-up time was 56.0 months (IQR 42–71 months). Among the 255 patients analyzed, 30 had recurrent disease and 17 died. The 5-year DFS and OS rates were 87.3% and 92.5%, respectively (not shown). Eighty-three (32.6%) patients received post-operative adjuvant therapy, including 45 (17.7%) with radiotherapy, 28 (11.0%) with chemotherapy, and 10 (3.9%) with radiation and chemotherapy.

Of the 255 patients, 177 (69.4%) received open laparotomy and 78 (30.6%) received laparoscopy. None of the patients selected for laparoscopic surgery were converted to laparotomy. There were no significant differences between the two groups in terms of median age at diagnosis, number of gravidity and parity, percentage of menopause, hypertension and diabetes mellitus, and FIGO stage distribution. How-

Table 1. Basic characteristics of the patients enrolled.

| Variables | |
|--|------------------|
| Patients, n | 255 |
| Age at diagnosis, median (IQR), years | 57 (50–61) |
| Gravidity, median (IQR) | 3 (2–4) |
| Parity, median (IQR) | 2 (1–3) |
| BMI, median (IQR), kg/m ² | 25.1 (22.5–29.4) |
| Menopause, n (%) | 173 (67.8) |
| HTN, n (%) | 82 (32.2) |
| DM, n (%) | 41 (16.1) |
| CA125 level, median (IQR), U/mL | 17.4 (11.2–30.4) |
| Surgical method, n (%) | |
| Laparotomy | 177 (69.4) |
| Laparoscopy | 78 (30.6) |
| Follow-up time, median (IQR), months | 56 (42–71) |
| Disease-free survival time, median (IQR), months | 53 (41–70) |

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; IQR, interquartile rang.

ever, moderate to considerable differences (SMD >0.3) were observed in percentage of age older than 60 year-old, mean BMI and CA125 level, histologic type and grade, and adjuvant therapy between the two groups (Table 2).

3.2 Comparison of perioperative outcomes

The peri- and post-operative events of both groups are shown in Table 3. The patients who received laparoscopic surgery had significantly less blood loss (150.0 versus 180.0 cc, $p = 0.015$), shorter hospital stay (7.0 versus 8.0 days, $p < 0.001$), but longer operative time (278.5 versus 220.0 minutes, $p < 0.001$) compared with the laparotomic group. The median lymph node yield was similar in both groups. Pelvic lymphadenectomy was performed in all of the patients, but para-aortic lymphadenectomy was omitted in 71 (27.8%) patients (54 (30.5%) in the laparotomy group and 17 (21.8%) in the laparoscopic group). The complication rates were low in both groups (9.1% and 5.1% in laparotomy and laparoscopic group, respectively) and only two major complications occurred, including one patient who died on postoperative day 6 due to acute myocardial infarction, and one patient with a great vessel injury during surgery which resulted in massive blood loss. Both of these patients received open surgery. Detailed descriptions of complications were shown in Table 3.

3.3 Prognostic factors analysis and survival outcomes in all patients

A significant better 5-year DFS (94.4 vs. 84.1%, $p = 0.022$) and a trend towards better 5-year OS (97 vs. 90.5%, $p = 0.060$) were observed for the patients receiving laparoscopic surgery (Fig. 1A,B). Although more patients in laparotomic group had recurrent disease, the recurrent pattern was similar for both groups. The first recurrent site in our study occurred mostly in the local sites, including vagina and pelvis, and distant lung was the second most common site (Table 3). To clarify the impact of the type of surgery on DFS and OS, we used multivariate Cox regression analysis to identify in-

dependent factors that were probably associated with DFS and OS. After adjusting for multiple prognostic covariates, grade III tumor (HR 11.35, 95% CI 4.06–31.70, $p < 0.001$), non-endometrioid histology (HR 3.99, 95% CI 1.52–10.44, $p = 0.005$), and age older than 60 year-old (HR 3.35, 95% CI 1.60–7.00, $p = 0.001$) were the independent factors to estimate the relative risk of recurrence. Grade III tumor (HR 10.38, 95% CI 2.44–44.15, $p = 0.002$) and CA125 > 35 U/mL (HR 3.02, 95% CI 1.07–8.55, $p = 0.037$) were the independent factors to estimate the relative risk of death (Tables 4 and 5).

3.4 Survival outcomes analysis after propensity score matching

Patients treated with different surgical approached were matched one-to-one using PSM to eliminate confounding factors. Seven covariates entered in the propensity model, including age, BMI, CA125, FIGO stage, pathologic type and grade, and adjuvant therapy. In total, 59 pair patients were matched in both groups. There were only small differences (SMD <0.2) in the clinicopathological variables between the 2 matched groups indicating a good matching outcome of the propensity model (Table 2). Comparisons of the DFS and OS curves between both groups after PSM are shown in Fig. 2A,B. There were no significant differences in 5-year DFS (95 vs. 92.5%) and OS (100 vs. 97.5%) between the two groups.

3. Discussion

In the present study, we demonstrated the safety and feasibility of laparoscopic surgery for the management of presumed early-stage endometrial cancer. In addition, this surgical approach provided better peri- and post-operative outcomes, and, most importantly, did not compromise survival outcomes. The major factors predicting poor survival for clinical early stage disease were high-grade tumor, non-endometrioid histology, age >60, and CA125 >35 U/mL but not surgical type. Although our results are similar to previous reports, there are some issues needed to be addressed.

The question of whether to perform pelvic lymphadenectomy routinely has been debated. Similar to LAP2 trial, we performed pelvic lymphadenectomy in all patients during the study period. However in LACE trial, only half of patients had lymphadenectomy. When we looked at the pathological findings, 23% of ours and 12% of LAP2 patients had deep myometrial invasion while none in LACE trial [6, 8]. Furthermore, as high as 70% of patients in LACE trial had disease limited to endometrium [8]. That's why surgeons in LACE trial aborted lymphadenectomy in some patients. Caution should still be made because it is difficult to preoperatively identify these low-risk patients based on gross observation and frozen section results. Studies had demonstrated the uncontrollable variables of change in grade and depth of myometrial invasion on final pathology [9].

Regarding para-aortic lymph node (PAN) retrieval, we performed this procedure in about 70% of patients while over 90% of patients in LAP2 trial had PAN lymphadenectomy. Previous studies have reported that para-aortic lym-

Table 2. Patient characteristics and group comparisons before and after propensity score matching (PSM).

| | Before PSM | | SMD§ | After PSM | | SMD§ |
|-----------------------------------|--------------------|--------------------|-------|-------------------|--------------------|-------|
| | Laparotomy N = 177 | Laparoscopy N = 78 | | Laparotomy N = 59 | Laparoscopy N = 59 | |
| Age (years) ≥60, n (%) | 65.0 (36.7) | 18.0 (23.1) | 0.301 | 17 (28.8) | 15 (25.4) | 0.076 |
| BMI kg/m ² , mean (SD) | 27.0 (5.4) | 24.9 (4.0) | 0.441 | 25.6 (4.9) | 25.1 (4.3) | 0.100 |
| CA125 U/mL, mean (SD) | 38.9 (58.3) | 21.5 (26.4) | 0.385 | 19.4 (15.7) | 19.7 (16.6) | 0.018 |
| FIGO stage, n (%) | | | 0.086 | | | 0.163 |
| Stage I | 149 (84.2) | 68 (87.2) | | 54 (91.5) | 51 (86.4) | |
| Stage II–IV | 28 (15.8) | 9 (12.8) | | 5 (8.5) | 8 (13.6) | |
| Histology, n (%) | | | 0.404 | | | 0.135 |
| Endometrioid | 142 (80.2) | 73 (93.6) | | 56 (94.9) | 54 (91.5) | |
| Non-endometrioid | 35 (19.8) | 5 (6.4) | | 3 (5.1) | 5 (8.5) | |
| WHO grade, n (%)‡ | | | 0.465 | | | 0.073 |
| G1 | 94 (53.1) | 54 (69.2) | | 41 (69.5) | 39 (66.1) | |
| Non-G1 | 83 (46.9) | 24 (30.8) | | 18 (30.5) | 20 (33.9) | |
| Adjuvant therapy, n (%) | | | 0.484 | | | 0.193 |
| No | 108 (61.0) | 64 (82.1) | | 50 (84.7) | 47 (79.7) | |
| Radiotherapy (RT) | 37 (20.9) | 8 (10.3) | | 6 (10.2) | 6 (10.2) | |
| Chemotherapy (CT) | 24 (13.6) | 4 (5.1) | | 2 (3.4) | 4 (6.8) | |
| Both CT and RT | 8 (4.5) | 2 (2.6) | | 1 (1.7) | 2 (3.4) | |

§A standardized mean difference (SMD) of less than 0.1 indicates very small differences; values between 0.1 and 0.3 indicate small differences; values between 0.3 and 0.5 indicate moderate differences; values above 0.5 indicate considerable differences. ‡ Serous and clear cell carcinoma are considered as high-grade lesions.

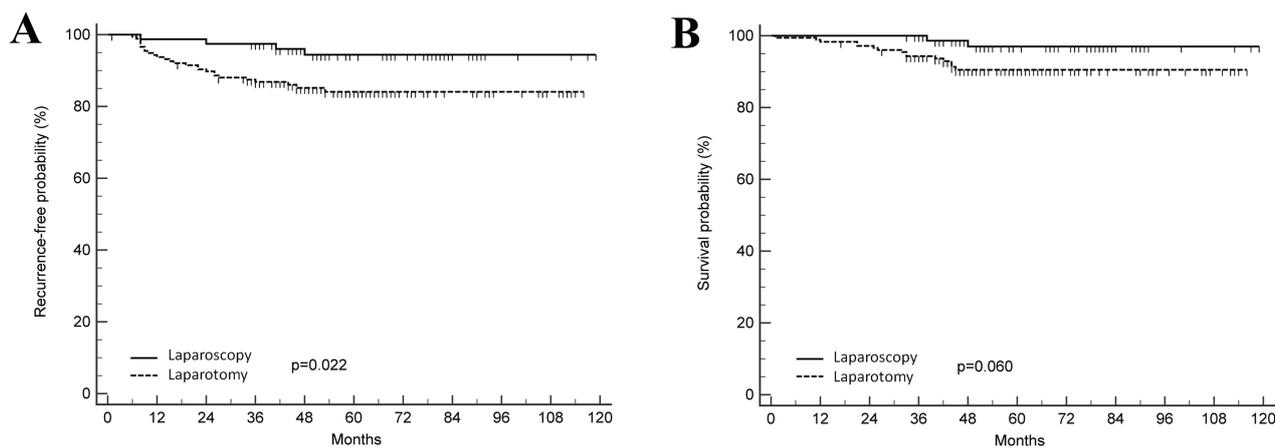


Fig. 1. Kaplan-Meier survival curves. Disease-free survival (A) and overall survival (B) curves before propensity score matching according to different surgical approaches.

phadenectomy did not improve clinical outcomes, because the presence of PAN metastasis indicates systemic disease [10–12]. In a study from Northern Taiwan, reported by Chu *et al.* [5], PAN lymphadenectomy was performed in only 2.8% and 13.6% of patients in the laparoscopic and laparotomic group, respectively. Another single arm study from Taiwan reported by Lee *et al.* [13], 14.3% of patients had received PAN lymphadenectomy. However, the 5-year DFS and OS rates in both studies were not inferior to the LAP2 result. The potential risks of routine para-aortic lymphadenectomy include a considerably longer operative time, greater blood loss, and higher rate of post-operative ileus [14, 15]. Therefore, the NCCN (National Comprehensive Cancer Network) panel

has changed their recommendations on PAN lymphadenectomy since 2014. They recommend such a procedure for selective high-risk situations, including those with positive pelvic nodes [16] or high-risk histologic features [17].

Another interesting issue is the survival outcomes between laparoscopic and laparotomic groups. Most studies have shown equivalent DFS and OS rates between patients undergoing different surgical approaches. Initially, we found better DFS and OS rates in the laparoscopic group, the survival benefits disappeared after a PSM analysis to balance the baseline clinicopathological characteristics such as age, CA125, and histologic type and grade. An unfavorable histology such as serous or clear cell and high-grade endometri-

Table 3. Comparison of perioperative, postoperative events, and recurrent pattern in all patients (N = 255).

| | Laparotomy N = 177 | Laparoscopy N = 78 | p-value |
|---------------------------------------|---------------------|---------------------|---------|
| Operative time, minutes, median (IQR) | 220.0 (191.0–257.0) | 278.5 (239.3–309.0) | <0.001 |
| Blood loss, mL, median (IQR) | 180.0 (100.0–250.0) | 150.0 (100.0–200.0) | 0.015 |
| Hb changes, g/dL, median (IQR) | 1.20 (0.60–1.80) | 1.40 (1.00–2.00) | 0.116 |
| Hospitalization days, median (IQR) | 8.0 (7.0–11.0) | 7.0 (5.0–9.0) | <0.001 |
| Lymph node retrieval, n, median (IQR) | | | |
| Pelvic | 24.0 (18.0–31.0) | 23.0 (18.0–27.0) | 0.209 |
| Para-aortic | 4.0 (2.0–6.0) | 3.0 (2.0–5.0) | 0.261 |
| Complication rate, n (%) | 16 (9.1) | 4 (5.1) | |
| Intraoperative† | 1 (0.6) | 0 (0.0) | 1.000 |
| Postoperative‡ | 15 (8.5) | 4 (5.1) | 0.348 |
| Recurrence, n (%) | 26 (14.7) | 4 (5.1) | 0.029 |
| Vagina | 5 (2.8) | 0 (0.0) | |
| Pelvis | 0 (0.0) | 2 (2.6) | |
| Abdomen | 2 (1.1) | 0 (0.0) | |
| Liver | 0 (0.0) | 0 (0.0) | |
| Lung | 4 (2.3) | 1 (1.3) | |
| Bone | 1 (0.6) | 0 (0.0) | |
| Nodal | 2 (1.1) | 0 (0.0) | |
| Multiple | 12 (6.8) | 1 (1.3) | |

† Intraoperative complication: Laparotomy: internal iliac artery injury.

‡ Postoperative complications: Laparotomy: Four with urinary tract infections (one with septic shock), five with postoperative ileus, two with ICU stay for 1 day (one due to severe aortic stenosis for postoperative observation, one due to vessel injury and severe blood loss), three with wound infection, one died at day 6 postoperatively due to acute myocardial infarction. Laparoscopy: three with chylous ascites, one with postoperative fever with a suspected intraabdominal infection. IQR, interquartile range.

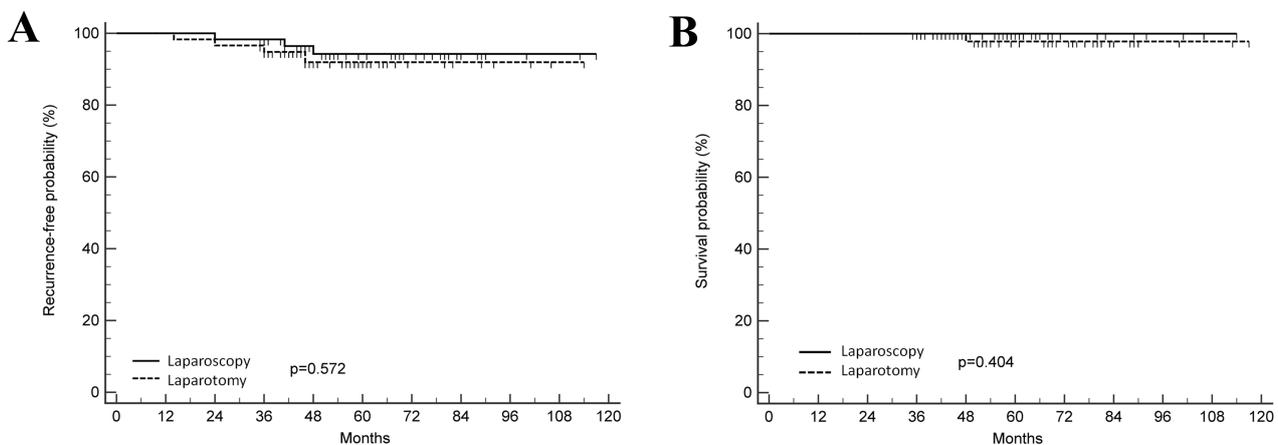


Fig. 2. Kaplan-Meier survival curves. Disease-free survival (A) and overall survival (B) curves after propensity score matching according to different surgical approaches.

oid carcinoma tend to enhance extra-uterine spreading in the early stage of the disease [18, 19]. The study reported by Chu *et al.* showed a better survival than ours could be explained by excluding non-dometrioid histology in their study. In addition, we previously found that a pretreatment CA125 level of more than 40 U/mL was a risk factor for lymph node metastasis [20]. For these reasons we prefer not to perform laparoscopic surgery for these high-risk patients at our hospital, and this may have led to the higher mean level of CA125 and higher proportion of unfavorable histology and grade, and

also higher rate of postoperative adjuvant therapy in the laparotomy group. Our multivariate analysis confirmed that the type of surgery did not have any impacts on DFS and OS independently after adjusting for histology, grade, CA125 level, FIGO stage and age.

It is generally believed that operating on obese patients can be challenging especially when a new surgical approach is introduced. Furthermore, the results of LAP2 trial showed that risk of conversion to laparotomy increased with increasing BMI. Based on these findings, we strictly selected our candi-

Table 4. Univariate and multivariate analyses to identify factors related to disease-free survival (DFS) in all patients (N = 255).

| | Univariate (Log rank) | | Multivariate (Cox regression) | | |
|------------------|-----------------------|---------|-------------------------------|------------|---------|
| | 5-year DFS (%) | p-value | HR | 95% CI | p-value |
| Age (years old) | | 0.001 | | | 0.001 |
| <60 | 92.9 | | 1 (Ref) | | |
| ≥60 | 75.6 | | 3.35 | 1.60–7.00 | |
| Grade | | <0.001 | | | <0.001 |
| I | 93.2 | | 1 (Ref) | | |
| II | 90.5 | | 1 (Ref) | | |
| III | 49.4 | | 11.35 | 4.06–31.70 | |
| Histology | | <0.001 | | | 0.005 |
| Endometrioid | 96.1 | | 1 (Ref) | | |
| Non-endometrioid | 76.7 | | 3.99 | 1.52–10.44 | |
| FIGO stage | | 0.002 | | | 0.052 |
| I | 89.8 | | 1 (Ref) | | |
| II–IV | 73.3 | | 2.154 | 0.99–4.67 | |
| CA125 (U/mL) | | 0.355 | | | NS |
| ≤35 | 87.7 | | | | |
| >35 | 83.1 | | | | |
| Surgical method | | 0.022 | | | NS |
| Laparoscopy | 94.4 | | | | |
| Laparotomy | 84.1 | | | | |

HR, hazard ratio; CI, confidence interval; NS, not significant; Ref, reference.

dates for laparoscopic approach surgery in our study resulting in a low mean BMI of 24.9 kg/m², and fortunately none had a conversion to laparotomy. Even though the mean BMI was higher in our laparotomic group, the value was still much lower than that of LAP2 and LACE trials (28–33 kg/m²). The exact reason is not clear but may be due to the difference of obese prevalence between Asian and White ethnicity [21]. In LAP2 and LACE trials, almost 90% of patients enrolled were White race. In a Japanese study investigating different surgical approaches for early endometrial cancer showed a median BMI of 23–24 kg/m² in 120 cases, which was much close to our patients [22].

Last but not least, the recurrence in our study occurred mostly in the local site, including vagina and pelvis, and distant lung metastasis took the second spot for both laparoscopic and laparotomic groups. These results were similar to the LAP2 study, but different from the Chu *et al.* which showed more lung metastasis in laparoscopic group. According to the explanation of Chu *et al.*, this difference might be related to the inconsistent criteria of receiving postoperative adjuvant brachytherapy between two different types of surgery. Because of the fear of vaginal stump recurrence in the laparoscopic group, more had brachytherapy and no had received chemotherapy although not significant. The real causative reason contributing to this different recurrent pattern in the Chu *et al.* maybe not clear, but one supposed mechanism is that increased intra-abdominal pressure during laparoscopic surgery may push tumor cells into the lymphovascular space and might cause distant spread of the tumor sequentially [23]. In our study, we had the same criteria of postoperative adjuvant brachytherapy for both groups.

However, more multiple recurrent sites in laparotomic group were noted, this could be explained by more unfavorable histology or high-grade lesions.

Although the patients enrolled were not assigned randomly to different surgical approaches which was a limitation of our study, we performed a PSM and successfully to eliminate a certain confounding factors. When randomized trial was limited by the objective conditions, PSM analysis could be applied to reduce selection bias. Another limitation of our study is a single institutional design; however, only 2 surgeons involved in laparoscopic surgery carried the strengths of unique operative procedures and maintaining sufficient experience during the period of patients' accrual.

4. Conclusions

This study demonstrated the feasibility of laparoscopic surgery in clinical early stage endometrial cancer patients with the benefits of shorter hospital stay and less blood loss. The survival outcomes were comparable to a laparotomic approach. Factors associated with survival were high-grade tumor, non-endometrioid histology, age >60, and CA125 >35 U/mL. In selected patients and under experienced surgeons, laparoscopic surgery can be performed safely considering both short-term and long-term outcomes.

Author contributions

HL, FTK, and YCO, design the study; HCF, CHW, CCC, and CCT, analysis or interpretation; FTK, CHW, YJC, CCT, and CCC, literature search; HL and YJC, writing manuscript; HL, HCF, and YCO, critical review. All authors read and approved the final manuscript.

Table 5. Univariate and multivariate analyses to identify factors related to overall survival (OS) in all patients (N = 255).

| | Univariate (Log rank) | | Multivariate (Cox regression) | | |
|------------------|-----------------------|---------|-------------------------------|------------|---------|
| | 5-year OS (%) | p-value | HR | 95% CI | p-value |
| Age (years old) | | 0.017 | | | NS |
| <60 | 95.3 | | | | |
| ≥60 | 87.1 | | | | |
| Grade | | <0.001 | | | 0.002 |
| I | 99.0 | | 1 (Ref) | | |
| II | 91.5 | | 1 (Ref) | | |
| III | 79.0 | | 10.376 | 2.44–44.15 | |
| Histology | | 0.012 | | | NS |
| Endometrioid | 89.3 | | | | |
| Non-endometrioid | 76.8 | | | | |
| FIGO stage | | 0.075 | | | NS |
| I | 93.8 | | | | |
| II–IV | 85.3 | | | | |
| CA125 (U/mL) | | 0.025 | | | 0.037 |
| ≤35 | 94.3 | | 1 (Ref) | | |
| >35 | 83.8 | | 3.02 | 1.07–8.55 | |
| Surgical method | | 0.060 | | | NS |
| Laparoscopy | 97.0 | | | | |
| Laparotomy | 90.5 | | | | |

HR, hazard ratio; CI, confidence interval; NS, not significant; Ref, reference.

Ethics approval and consent to participate

All clinical investigations are conducted according to the Declaration of Helsinki principles. The present study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (approval number: 105-4364C), and the requirement of written informed consent was waived.

Acknowledgment

This work was partly supported by the Chang Gung Memorial Hospital Research Grants CZRPG 880011, CDRPG 880012, and CDRPG 880013. We appreciated Miss Hsin-Yi Chien and Chih-Yun Lin from the Biostatistics Center of Kaohsiung Chang Gung Memorial Hospital for their assistant in statistic analysis.

Funding

This study has not received external funding.

Conflict of interest

The authors declare no conflict of interest.

References

- [1] Lai JC, Weng C, Huang S, Huang N, Chou Y, Wang C, *et al.* Incidence and lifetime risk of uterine corpus cancer in Taiwanese women from 1991 to 2010. *Taiwanese Journal of Obstetrics and Gynecology.* 2017; 56: 68–72.
- [2] Childers JM, Surwit EA. Combined laparoscopic and vaginal surgery for the management of two cases of stage I endometrial cancer. *Gynecologic Oncology.* 1992; 45: 46–51.
- [3] Zullo F, Palomba S, Russo T, Falbo A, Costantino M, Tolino A, *et al.* A prospective randomized comparison between laparoscopic and laparotomic approaches in women with early stage endometrial cancer: a focus on the quality of life. *American Journal of Obstetrics and Gynecology.* 2005; 193: 1344–1352.
- [4] Tozzi R, Malur S, Koehler C, Schneider A. Laparoscopy versus laparotomy in endometrial cancer: first analysis of survival of a randomized prospective study. *Journal of Minimally Invasive Gynecology.* 2005; 12: 130–136.
- [5] Chu L, Chang W, Sheu B. Comparison of the laparoscopic versus conventional open method for surgical staging of endometrial carcinoma. *Taiwanese Journal of Obstetrics and Gynecology.* 2016; 55: 188–192.
- [6] Walker JL, Piedmonte MR, Spirtos NM, Eisenkop SM, Schlaerth JB, Mannel RS, *et al.* Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: gynecologic oncology group study LAP2. *Journal of Clinical Oncology.* 2009; 27: 5331–5336.
- [7] Walker JL, Piedmonte MR, Spirtos NM, Eisenkop SM, Schlaerth JB, Mannel RS, *et al.* Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: gynecologic oncology group LAP2 study. *Journal of Clinical Oncology.* 2012; 30: 695–700.
- [8] Janda M, GebSKI V, Davies LC, Forster P, Brand A, Hogg R, *et al.* Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with stage I endometrial cancer. *Journal of the American Medical Association.* 2017; 317: 1224–1233.
- [9] Kumar S, Bandyopadhyay S, Semaan A, Shah JP, Mahdi H, Morris R, *et al.* The role of frozen section in surgical staging of low risk endometrial cancer. *PLoS ONE.* 2011; 6: e21912.
- [10] Kyo S, Hashimoto M, Maida Y, Mizumoto Y, Nakamura M, Takakura M, *et al.* Analysis of outcome of stage I–III endometrial cancer treated with systematic operation omitting para-aortic lymphadenectomy. *European Journal of Gynaecological Oncology.* 2007; 28: 170–173.
- [11] Fujimoto T, Fukuda J, Tanaka T. Role of complete para-aortic lymphadenectomy in endometrial cancer. *Current Opinion in Obstetrics & Gynecology.* 2009; 21: 10–14.
- [12] Tong S, Lee J, Lee J, Kim JW, Cho C, Kim S, *et al.* Efficacy of para-aortic lymphadenectomy in early-stage endometrioid uterine corpus cancer. *Annals of Surgical Oncology.* 2011; 18: 1425–1430.

- [13] Lee C, Huang K, Wu P, Lee P, Yen C. Long-term survival outcome of laparoscopic staging surgery for endometrial cancer in Taiwanese experience. *Taiwanese Journal of Obstetrics and Gynecology*. 2014; 53: 57–61.
- [14] Fujita K, Nagano T, Suzuki A, Sakakibara A, Takahashi S, Hirano T, *et al*. Incidence of postoperative ileus after paraaortic lymph node dissection in patients with malignant gynecologic tumors. *International Journal of Clinical Oncology*. 2005; 10: 187–190.
- [15] Fagotti A, Fanfani F, Ercoli A, Giordano MA, Sallustio G, Scambia G. Postoperative ileus after para-aortic lymphadenectomy: a prospective study. *Gynecologic Oncology*. 2007; 104: 46–51.
- [16] Tanaka H, Sato H, Miura H, Sato N, Fujimoto T, Konishi Y, *et al*. Can we omit para-aorta lymph node dissection in endometrial cancer? *Japanese Journal of Clinical Oncology*. 2006; 36: 578–581.
- [17] Kumar S, Mariani A, Bakkum-Gamez JN, Weaver AL, McGree ME, Keeney GL, *et al*. Risk factors that mitigate the role of paraaortic lymphadenectomy in uterine endometrioid cancer. *Gynecologic Oncology*. 2013; 130: 441–445.
- [18] Snyder MJ, Bentley R, Robboy SJ. Transtubal spread of serous adenocarcinoma of the endometrium: an underrecognized mechanism of metastasis. *International Journal of Gynecological Pathology*. 2006; 25: 155–160.
- [19] Creasman WT, Ali S, Mutch DG, Zaino RJ, Powell MA, Mannel RS, *et al*. Surgical-pathological findings in type 1 and 2 endometrial cancer: an NRG Oncology/Gynecologic Oncology Group study on GOG-210 protocol. *Gynecologic Oncology*. 2017; 145: 519–525.
- [20] Hsieh C, ChangChien C, Lin H, Huang E, Huang C, Lan K, *et al*. Can a preoperative CA 125 level be a criterion for full pelvic lymphadenectomy in surgical staging of endometrial cancer? *Gynecologic Oncology*. 2002; 86: 28–33.
- [21] Anderson SE, Whitaker RC. Prevalence of obesity among us preschool children in different racial and ethnic groups. *Archives of Pediatrics & Adolescent Medicine*. 2009; 163: 344–348.
- [22] Deura I, Shimada M, Azuma Y, Komatsu H, Nagira K, Sawada M, *et al*. Comparison of laparoscopic surgery and conventional laparotomy for surgical staging of patients with presumed low-risk endometrial cancer: the current state of Japan. *Taiwanese Journal of Obstetrics and Gynecology*. 2019; 58: 99–104.
- [23] Wang P, Horng H, Chen C. Is it safe to use minimally invasive surgery in the management of endometrial cancer? *Taiwanese Journal of Obstetrics and Gynecology*. 2016; 55: 155–156.