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Original article

Surgical and oncological outcome of laparoscopic surgery, compared to laparotomy, for Japanese patients with endometrial cancer

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ABSTRACT

Study objective: The purpose of this study was to elucidate the surgical and oncological outcomes after laparoscopic surgery for endometrial cancer at our hospital.
Materials and methods: Surgical outcomes, complications rates, 2-year survival rates, and recurrence rates were evaluated in 44 patients who underwent total laparoscopic hysterectomy (TLH) and 57 patients who underwent total abdominal hysterectomy (TAH) for endometrial cancer at our hospital between August 2010 and November 2013.
Results: There was no significant difference between the two groups with respect to age or body mass index. More than 80% of patients in both groups had stage I cancer. In the TLH group, the histological types were endometrioid adenocarcinoma in 42 of 44 patients, carcinosarcoma in one patient, and serous adenocarcinoma in one patient. Operative times were significantly longer in the TLH group, but patients in this group had less intraoperative blood loss, shorter hospital stays, and reduced levels of postoperative pain, compared to patients in the TAH group. There were four cases of postoperative infection and one case of vessel injury in the TLH group. No patient in this group required blood transfusion or conversion to open surgery. There were recurrences in two (4.7%) patients in the TLH group (i.e., carcinosarcoma and serous adenocarcinoma) and in five (8.6%) patients in the TAH group.
Conclusion: Laparoscopic surgery is safe and feasible for patients with early-stage endometrial cancer. However, patients with carcinosarcoma and other histologic types of endometrioid adenocarcinoma require special attention because of the high risk of recurrence and poor prognosis.

Introduction

In recent years, the incidence of endometrial cancer has been increasing in Japan. In 1990, 3574 cases were reported; in 2000, the number had increased to 5609 cases; and in 2011, 14,763 new cases were reported.[1] Surgery is the initial treatment in 95% of all new cases. Radiation therapy or chemotherapy is recommended for patients who are not surgical candidates because of advanced age, comorbidities, or stage IVB cancer with peritoneal or distant metastasis.[2] The standard operating procedures for endometrial cancer are hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy. Thus, the main treatment option for patients with endometrial cancer is surgery. However, laparoscopic surgery for endometrial cancer was not covered by insurance in Japan until March 2014; before that point, an open abdominal approach was the standard technique.

In 2005, a randomized controlled trial reported the analysis of survival after laparoscopy versus laparotomy in women with endometrial cancer.[3] In 2009, the results of three other randomized controlled trials were also reported.[4–6] In 2010, the results of two more randomized controlled trials were also reported.[7,8] In all trials, intraoperative bleeding was significantly less and the length of hospitalization was significantly shorter in laparoscopic surgery than in abdominal surgery. There was no difference in organ injury or intraoperative complications. Postoperative complications such as ileus were significantly fewer in laparoscopic surgery. There was no difference in the recurrence rate. However, no difference in

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recurrence rate was found, although it should be noted that the majority of patients (77.5 to 93.2%) in all of the trials had endometrioid adenocarcinomas, which have inherently lower recurrence rates among early-stage endometrial cancers.

Based on the results of these randomized controlled trials, insurance coverage has been extended to laparoscopic surgery for endometrial cancer since April 2014 in Japan. Therefore, the number of cases in Japan is expected to rise in the future. However, the number of cases in Japan is small; therefore, the complication rates, surgical outcomes, and oncological outcomes after laparoscopic surgery for endometrial cancer are unknown. The surgical outcomes, complications rates, 2-year survival rates, and recurrence were retrospectively evaluated for laparoscopic surgeries performed for endometrial cancer at our hospital.

Materials and Methods

This study was approved by the in-hospital ethics committee. Fifty-three laparoscopic surgeries for endometrial cancer were performed from August 2010 to November 2013. Forty-four patients (i.e., the TLH group) had laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy, and nine patients had laparoscopic hysterectomy and bilateral salpingo-oophorectomy. The main eligibility criterion for laparoscopic surgery for endometrial cancer at our hospital is International Federation of Gynecology and Obstetrics (FIGO) 2008 stage IA grades 1 and 2 endometrioid adenocarcinoma diagnosed by endometrial aspiration or curettage before major surgery. Patients who met the eligibility criteria were offered laparoscopic surgery. Pelvic lymphadenectomy was recommended for all patients with endometrioid adenocarcinoma; however, not all patients consented. Pelvic magnetic resonance imaging (MRI) and positron emission tomography–computed tomography were performed preoperatively in all patients to check for muscle and cervical invasion and lymph node or ovarian metastasis or other cancers. If the MRI findings suggested stage IB disease, then TLH was contraindicated and we performed open surgery with pelvic lymphadenectomy. The exclusion criteria were patients who could not be placed in a lithotomy position or patients who had a large uterine fibroid that would have been difficult to remove from the vagina. Patients who had other than FIGO stage IA disease and endometrioid adenocarcinoma grades 1 or 2 were treated by adjuvant chemotherapy.

In the present study, surgical outcomes, complications, recurrence, death, length of hospitalization, pain score (based on the visual analog scale), and hemoglobin level on postoperative Day 1, C-reactive protein (CRP) on postoperative Day 3, and 2-year survival rates between the TLH group and the 57 patients (i.e., the TAH group) in whom open abdominal surgery for endometrial cancer (e.g., hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy) were compared during the same period.

Laparoscopic surgical technique

Laparoscopic surgery for endometrial cancer was performed, as follows: intermittent pneumatic compression was applied to the lower extremities to prevent thrombosis. Prophylactic antibiotics were administered before the beginning of the surgery. After general anesthesia was induced, the patient was placed in the lithotomy position with the operator standing on the left side of the patient. After carbon dioxide insufflation of the abdominopelvic cavity, an 11-mm camera trocar was placed at the umbilical region, followed by the placement of bilateral 5-mm trocars at 3 cm inside the right and left anterior superior iliac spines, a 12-mm trocar at the left upper quadrant, and a 5-mm trocar at the right upper quadrant. A 10-mm 30° laparoscope was used. No uterine manipulator was used. After the laparoscopic survey of the abdominal cavity, peritoneal cytology or a washing cytology was collected. After sealing both oviducts, the round ligament was sealed and divided, and the broad ligament of the uterus was opened. After identifying the ureter at the crossing of the uterine artery, the uterine artery was skeletonized, ligated, and divided. The infundibulopelvic ligament was ligated and divided. The uterosacral ligament was sealed and divided. After the preparation of the bladder off the vagina, the cardinal ligament was sutured and ligated and divided. A Vagi-Pipe (Hakko Medical, Nagano, Japan) was inserted to localize the vaginal vault, and the vaginal wall was incised with an electric scalpel. The uterus was placed in a EZ-Purse (Hakko Medical) and removed through the vagina. The vaginal stump was washed with saline and sutured. In patients who received pelvic lymphadenectomy, both lateral umbilical ligaments were lifted toward the abdomen to ensure a sufficient field of view. The right and left common iliac, external and internal iliac, and obturator lymph nodes were resected using sterile probe covers and removed. An absorbable adhesion barrier (Gynecare Interceed; Ethicon, Somerville, NJ, USA) was placed over the peritoneum. A drain was inserted through the left port. All laparoscopic surgeries were performed by a laparoscopist and gynecologic oncologist team. The same team performed all laparoscopic surgeries that were included in this study.

Statistical analysis

Statistical analysis was performed using GraphPad Prism, version 6.0 for Windows (GraphPad Software, Inc., San Diego, CA, USA). The Student t test was used to analyze the results. All calculated p values were two-sided and $p < 0.05$ was considered statistically significant. The disease-free and overall survival rates were calculated by the Kaplan–Meier method. Differences between survival curves were analyzed using the log-rank test and $p < 0.05$ was considered statistically significant.

Results

Laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy were performed in 44 patients (i.e., the TLH group), and laparoscopic hysterectomy and bilateral salpingo-oophorectomy were performed in nine patients. Fifty-seven patients (i.e., TAH group) received abdominal hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy during the same period.

The median age of the TLH group was 56 years (range, 39–78 years), and the median body mass index (BMI) value was 23.0 kg/m^2 (range, 17.2–37.3 kg/m^2). The median age of the TAH group was 56 years (range, 31–80 years), and the median BMI of the TAH group was 22.5 kg/m^2 (range, 16.9–40.5 kg/m^2). Therefore, no differences were observed between the TLH and TAH groups (Table 1). In the TLH group, the postoperative histological diagnosis for all patients was endometrioid adenocarcinoma, except for one patient with carcinosarcoma and one patient with serous adenocarcinoma. Eighty-five percent or more of both groups had FIGO stage I cancer. Patients with other than FIGO stage IA disease or endometrioid adenocarcinoma grades 1 or 2 were treated with chemotherapy. Nine (20.5%) patients in the TLH group and 18 (31.6%) patients in the TAH group also received chemotherapy (i.e., paclitaxel + carboplatin, or paclitaxel + epirubicin + carboplatin).

The TLH group had significantly longer operative times than the TAH group (310.1 ± 67.1 minutes vs. 237.1 ± 67.6 minutes, $p < 0.05$; Table 2). However, the TLH group had significantly less

Table 1
Characteristics of patients with endometrial cancer by type of surgery.

	Laparoscopy ($n = 44$)	Laparotomy ($n = 57$)	p
Age (y), median (range)	56 (39–78)	56 (31–80)	N.S.
BMI kg/m^2 median (range)	23.0 (17.2–37.3)	22.5 (16.9–40.5)	N.S.
Histological subtype before surgery			
Endometrioid adenocarcinoma grade 1	41	46	
Endomertioid adenocarcinoma grade 2	3	11	
Histological subtype			
Endomertioid adenocarcinoma grade 1	39	42	
Endomertioid adenocarcinoma grade 2	3	13	
Endomertioid adenocarcinoma grade 3	0	2	
Carcinosarcoma	1	0	
Serous adenocarcinoma	1	0	
FIGO (2008) stage			
IA	35	39	
IB	4	10	
II	2	3	
IIIA	1	5	
IIIC1	1	0	
IVB	1	0	
Adjuvant chemotherapy			
TC therapy	7	13	
TEC therapy	2	5	

BMI = Body mass index; N.S. = not significant; TC = paclitaxel + carboplatin; TEC = paclitaxel + epirubicin + carboplatin.

Table 2
Surgical outcome of patients with endometrial cancer by type of surgery.

	Laparoscopy ($n = 44$)	Laparotomy ($n = 57$)	p
Duration of operation (min)	310.1 ± 67.1	237.1 ± 67.6	< 0.05
Estimated blood loss (mL)	100.3 ± 128.1	474.5 ± 362.0	< 0.05
Specimen (g)	162.5 ± 102.7	172.4 ± 124.0	N.S.
Lymph nodes yield	25.3 ± 8.3	23.9 ± 9.4	N.S.
Hospital stay (d)	7.9 ± 4.0	17.2 ± 6.9	< 0.05
Delta Hb (g/dL)[a]	1.8 ± 1.1	2.7 ± 1.0	< 0.05
Day 1 VAS	2.9 ± 1.2	4.0 ± 2.3	< 0.05
Day 3 CRP (mg/dL)	4.1 ± 3.1	4.9 ± 3.4	N.S.

Data are presented as mean ± the standard deviation.
CRP = C-reactive protein; Hb = hemoglobin; N.S. = not significant; VAS = visual analog scale.
[a] Delta Hb = (preoperation hemoglobin level) − (hemoglobin level on postoperation Day 1).

intraoperative blood loss (100.3 ± 128.1 mL vs. 474.5 ± 362.0 mL, $p < 0.05$), a smaller postoperative change in the hemoglobin level (1.8 ± 1.1 g/dL vs. 2.7 ± 1.0 g/dL, $p < 0.05$), shorter hospital stays (7.9 ± 4.0 days vs. 17.2 ± 6.9 days, $p < 0.05$), and a lower level of postoperative pain (visual analog scale score, 2.9 ± 1.2 vs. 4.0 ± 2.3, $p < 0.05$; Table 2). No significant differences existed between the two groups in specimen weight and number of lymph nodes and CRP level on postoperative Day 3 (Table 2).

The overall rate of perioperative complications for all patients was 13.9%. The rate of complications in the TLH group was 15.9%. The complications in the TLH group were one case of vascular injury, two cases of vaginal lacerations, and four cases of postoperative infections. There were no cases of blood transfusion or conversion to open abdominal surgery (Table 3).

Table 3
Intra- and postoperative complications by type of surgery.

	Laparoscopy ($n = 44$)	Laparotomy ($n = 57$)
Bowel injury	0	0
Urinary injury	0	0
Vessel injury	1	0
Blood transfusion	0	3
Conversion	0	–
Vaginal cuff abscess	4	2
Vaginal wall laceration	2	0
Wound dehiscence	0	2

The annual changes in the operative times and the blood loss in the TLH group at our hospital from 2011 to 2013 were indicated. The operative times in 2013 was significantly shortened, compared to that in 2011 (Figure 1A). The blood loss in 2013 was not significantly different from that in 2011 (Figure 1B).

Two (4.5%) patients in the TLH group and five (8.8%) patients in the TAH group had a recurrence. The histopathology of the two patients in the TLH group was carcinosarcoma and serous adenocarcinoma. Both patients received adjuvant chemotherapy, but neither patient survived (Table 4).

The disease-free survival ($p = 0.317$) and overall survival ($p = 0.941$) were not statistically significant between the TLH group and TAH group (Figure 2).

Discussion

Laparoscopic surgery is safe and feasible for patients with early-stage endometrial cancer. However, patients with carcinosarcoma and other histologic types of endometrioid adenocarcinoma require special attention because of the high risk of recurrence and poor prognosis.

It was the first report of laparoscopic surgery for gynecological cancer that Nezhat et al[9] performed pelvic lymphadenectomy for locally advanced cervical cancer in 1989. Childers and Surwit[10] first reported laparoscopic surgery for endometrial cancer in 1992. Since that time, many studies have reported the efficacy of laparoscopic

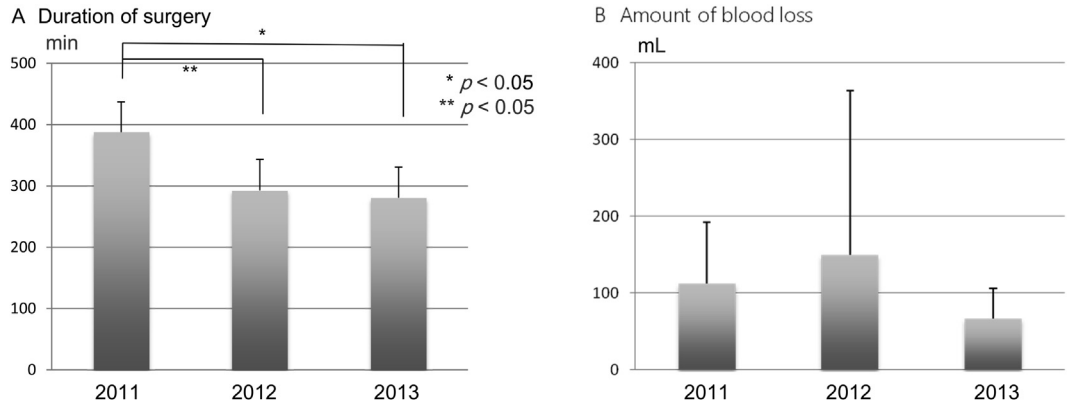

Figure 1. Annual changes in (A) the duration of surgery and (B) the amount of blood loss in the laparoscopic group. The duration of surgery in 2012 and 2013 was significantly shorter than in 2011. The amount of blood loss is not significantly different for each year.

Table 4
Recurrence and mortality cases in the laparoscopic group.

Patient	Age (y)	Pathology	Stage	pTNM	Adjuvant therapy	Site of recurrence	DFS (mo)	OS (mo)
1	62	Carcinosarcoma	IA	pT1aN0M0 (Peritoneal cytology positive)	TC (5 courses)	Pelvic	11	19
2	70	Serous adenocarcinoma	IVB	pT1aN0M1 (Peritoneal cytology positive)	TEC (2 courses)	Lung ascites	2	5

DFS = disease-free survival; OS = overall survival; TC = paclitaxel + carboplatin; TEC = paclitaxel + epirubicin + carboplatin.

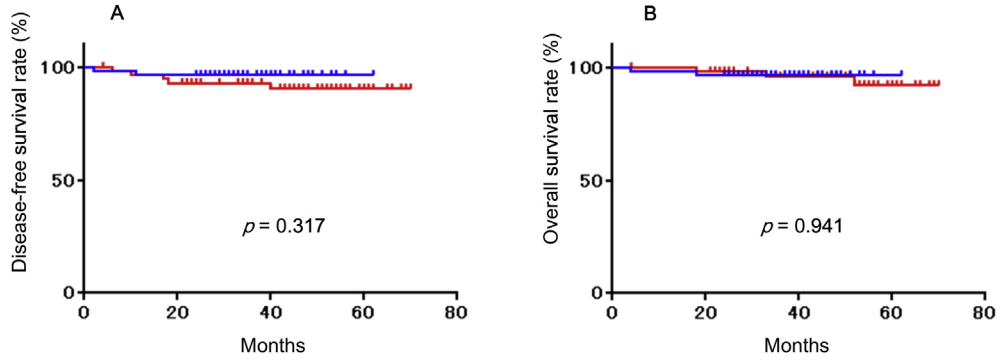

Figure 2. (A) The disease-free survival rate and (B) the overall survival rate show no statistically significant difference between laparoscopy and laparotomy.

surgery for endometrial cancer. The LAP2 study[4] in 2009 was a large-scale randomized controlled trial that compared 1682 patients in the laparoscopic group with 920 patients in the open abdominal group with early-stage endometrial cancer. There was no significant difference in the intraoperative complication rates between the two groups (10% in the laparoscopic group vs. 8% in the open group). The laparoscopic group had a significantly lower rate of postoperative complications than the open group (14% vs. 21%) and a significantly reduced length of hospital stay. These results proved the safety of laparoscopic surgery for endometrial cancer.

A prognostic analysis was also reported in 2012, and the expected 5-year survival rate was 89.9%.[11] Lu et al[12] also prospectively compared 151 cases of laparoscopic surgery for endometrial cancer with 121 cases of open abdominal surgery. They found that the rate of postoperative complications was significantly lower in the laparoscopic group (12%) than in the open group, whereas the recurrence rate (4.6%) and the 5-year survival rate (95%) was comparable to that of the open group. In our study, the rates of complication, recurrence, and 2-year survival were 15.9%, 4.5%, and 96.4%, respectively, which are in agreement with the findings of previous studies.[11] The number of resected lymph nodes was not different between groups in the present study, and the degree of completion was considered equivalent. A long-term convalescence survey will be required in the future.

All patients in our study had postoperative histological diagnoses of endometrioid adenocarcinoma grades 1 and 2, except for two patients (who had serous adenocarcinoma and carcinosarcoma) in the TLH group. The suitability of laparoscopic surgery for advanced endometrial cancer, other histologic types of endometrioid carcinoma, carcinosarcoma, or sarcoma has not been determined. It has been reported that the overall diagnostic accuracy of preoperative endometrial curettage was 35–96%, and the overall diagnostic accuracy of endometrioid adenocarcinoma grade 3, serous adenocarcinoma, and clear cell adenocarcinoma was 45–74%.[13–16] The cases of carcinosarcoma in this study were identified as adenocarcinoma in the preoperative diagnosis. However, the sarcomatous component could not be determined. The case of serous adenocarcinoma was endometrioid adenocarcinoma grade 1 in the preoperative diagnosis. Assessing the tumor grade by intraoperative frozen section may be useful.[14,17] If another histologic type of endometrioid adenocarcinoma or carcinosarcoma was diagnosed after laparoscopic surgery, an additional treatment may have been needed, based on the stage of advancement, and a strict follow-up observation would have been necessary.

The operative time was significantly longer in the TLH group than the TAH group. It has been significantly shortened on an annual basis since we began performing laparoscopic surgery for patients with endometrial cancer. There has not been a notable decrease in blood loss over subsequent years; however, one patient in 2012 had a blood loss of 838 g on account of severe adhesions accompanying endometriosis in combination with a vaginal wall laceration. There has not been a significant change, compared to the early experience, although there was a trend toward decreased blood loss by 2013. It is estimated that the improvement in skill becomes apparent after a surgeon performs ~10 laparoscopic surgeries for uterine cancer, as reflected by reduced operative times, blood loss, complication rates, and rates of conversion to open abdominal surgery.[18] The results of the present study support this finding.

One case of vascular injury and two (4.5%) cases of vaginal wall lacerations were the intraoperative complications and four (9.1%) cases of infections were the postoperative complications in the TLH group. These numbers are lower than those reported in the LAP2 study. The vascular injury was an injury to the left external iliac vein during lymphadenectomy. Hemostasis was achieved by applying pressure with a piece of gauze. All infections were vaginal cuff abscesses that resolved with antibiotic treatment. The rate of conversion to open abdominal surgery in the LAP2 study was very high at 25%. Advanced age, high BMI, and metastatic lesions were risk factors for conversion in the LAP2 study, and BMI was listed as a risk factor in the Life After Cancer Epidemiology (LACE) study.[19] In our study, the BMI tended to be lower than that in other reports.[3,4,6,7,11] Insufficient visual field, spreading of tumor cells, bleeding, and technical issues were also listed as direct causes of conversions to open abdominal surgery in the LAP2 study.

Laparoscopic surgery is a surgical procedure that can only be safely performed with sufficient technical skills. Laparoscopic surgery for endometrial cancer requires technical skills and anatomical knowledge. Because there are many obese patients, there is the risk of conversion to open abdominal surgery. Therefore, it is a rule that laparoscopists and gynecologic oncologists perform this operation in our hospital. We have been able to perform the surgery with lower rates of complications and conversion to open abdominal surgery. We recommend this system to facilitate a safe completion.

We found no difference in the recurrence rates between the laparoscopic group and the open abdominal group in our study. Despite the longer operative times, the benefits of reduced blood loss, postoperative pain, and length of hospital stay confirm that laparoscopic surgery for early-stage endometrial cancer is a procedure that can be safely performed in Japan and can contribute to improved quality of life for patients. However, the two deaths in the TLH group because of recurrent cancers emphasize the need for caution in patients with carcinosarcoma and other histologic types of endometrioid adenocarcinoma. Recurrences at the port sites and the vaginal stump can be attributed to laparoscopic surgery; therefore, both oviducts should be sealed immediately on starting the surgery, use of a uterine manipulator should be avoided, and specimen bags should be used to remove the uterus and lymph nodes to prevent intraperitoneal seeding of cancer cells.

We performed conventional multiport laparoscopic surgery in this study, Natural orifice transvaginal endoscopic surgery[20] or laparoendoscopic single site surgery[21] are other minimally invasive methods that may be safe and effective for select patients with endometrial carcinoma.

This study was not a randomized controlled trial. However, our results validate those of previous randomized controlled trials that have shown that laparoscopic surgery for early-stage endometrial cancer is a safe and feasible alternative.

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