Original Article

Safety of laparoscopic surgery in the management of endometrioid endometrial cancer

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Abstract

Background: Laparoscopic surgery has increasingly been preferred in recent years. However, data regarding the safety of laparoscopy in endometrial cancer are not sufficient. The aim of this study was to compare perioperative and oncologic outcomes of laparoscopic and laparotomic staging surgery in patients with endometrioid endometrial cancer and to evaluate the safety and efficacy of laparoscopic surgery in this population.

Methods: Data of 278 patients, who underwent surgical staging for endometrioid endometrial cancer at the gynecologic oncology department of a university hospital between 2012 and 2019, were analyzed retrospectively. Demographic, histopathologic, perioperative, and oncologic characteristics were compared between laparoscopy and laparotomy groups. A subgroup of patients with a body mass index (BMI) >30 was further evaluated.

Results: Demographic and histopathologic characteristics were similar between the two groups, while laparoscopic surgery was seen to be significantly superior in terms of perioperative outcomes. The number of removed and metastatic lymph nodes was significantly higher in the laparotomy group; however, this difference did not affect the oncologic outcomes, including recurrence and survival rates, and the two groups had similar results in this aspect. The outcomes of the subgroup with BMI >30 were also in accordance with the whole population. Intraoperative complications in laparoscopy were managed successfully.

Conclusions: Laparoscopic surgery appears to be advantageous over laparotomy, and depending on the surgical experience, it may be performed safely for surgical staging of endometrioid endometrial cancer.

Keywords:
Endometrial cancer, laparoscopy, laparotomy, lymphadenectomy, surgical staging

Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries.[1-3] Because most of the cases are elderly, obese patients with significant comorbidities, it is important to reduce the intraoperative and postoperative complications.[4] Laparoscopic surgery has become an increasingly preferred method in recent years because of better perioperative results and faster postoperative recovery periods in comparison with traditional open surgery.[2,5]

Several studies have reported laparoscopy (L/S) to be a safe and efficacious procedure in the management of endometrial cancer, with similar disease-free

Access this article online	
Website: www.indianjcancer.com	Quick Response Code:
DOI: 10.4103/ijc.IJC_206_21	

How to cite this article: Durdağ GD, Alemdaroğlu S, Baran ŞY, Şimşek SY, Yetkinel S, Çelik H. Safety of laparoscopic surgery in the management of endometrioid endometrial cancer. Indian J Cancer 2023;60:366-72.
Submitted: 20-Feb-2021 **Revised:** 12-May-2021
Accepted: 28-Aug-2021 **Published:** 30-Nov-2022

survival (DFS) and overall survival (OS) periods of the cases, when compared with laparotomy (L/T).[3,6-8] Although the safety of laparoscopic surgery is questioned after the LACC (Laparoscopic Approach to Cervical Cancer) trial in cervical cancer,[9] data regarding this issue in endometrial cancer are not sufficient. Therefore, homogeneous data of different centers may be valuable, as far as varying clinical conditions and setups are considered.

The aim of this study was to compare the intraoperative, postoperative, and oncologic outcomes of laparoscopic and laparotomic staging surgery in patients with endometrioid endometrial cancer, as a homogenous population, in a single center, and also to evaluate the efficacy and safety of laparoscopic surgery in this population.

Materials and Methods

Data of patients, who underwent surgical staging for endometrioid endometrial cancer at the gynecologic oncology department of a university hospital between 2012 and 2019, were analyzed retrospectively. A total of 278 patients who were diagnosed with intermediate- or high-risk endometrioid endometrial cancer due to preoperative evaluation or intraoperative frozen assessment and who underwent a laparoscopic or laparotomic hysterectomy, bilateral salpingo-oophorectomy and bilateral pelvic and para-aortic lymphadenectomy for treatment during this period were included in the study. Patients with histopathologic results other than endometrioid type, patients who received chemotherapy or radiotherapy for treatment of endometrial cancer preoperatively, patients who needed a second operation for complementary surgery after hysterectomy, and patients who were not performed a complete pelvic and para-aortic lymph node dissection were excluded.

Diagnosis of intermediate-/high-risk endometrioid endometrial cancer, as well as the decision of surgery and adjuvant treatment, was made according to the recommendations of oncology guidelines.[10] Based on the routine practice of our department, all patients with any of the findings of tumor Grade 2–3, tumor diameter above 2 cm, or myometrial invasion depth higher than 50% were performed staging surgery.[11] All operations were performed by the same experienced surgical team that has been performing endoscopic gynecologic oncological surgery for about 20 years. All patients were informed about the advantages and disadvantages of both laparoscopic and laparotomic surgery. Considering the patient's request, L/S was preferred when laparoscopic setup was appropriate, and L/T was performed in other cases. L/S was preferred provided the decision was left to the surgeon. Laparoscopic-assisted vaginal hysterectomy was not performed in any of the patients and in any circumstances. This approach did not change throughout the study period; therefore, the applications of both surgical routes were homogeneous during this time, and the L/S percentage did not increase over the years. Routine bowel preparation was not made in any of the patients. This study included the patients who were performed underwent complete surgical staging for endometrial cancer. Uterine manipulator Clermont-Ferrand (Karl Storz Gmbh&Co., Tuttlingen, Germany) was utilized at hysterectomy and salpingo-oophorectomy part. In all patients who underwent complete surgical staging, six trocars (one 10 mm umbilical/supraumbilical trocar, two 5 mm trocars on both sides at the lateral of the rectus muscle, and one 10 mm suprapubic trocar) were used as demonstrated in our previous study.[12] While the uterus was removed through the vaginal route, lymph nodes were taken out of the abdominal cavity via the trocar ports in separate endobags. Pelvic lymph node dissection was performed in the area encircled by the bifurcation of common iliac vessels superiorly, psoas muscle laterally, ureter medially, circumflex iliac vein inferiorly, and obturator nerve posteriorly, whereas the para-aortic lymph node dissection was performed including lymph nodes adjacent to the aorta and vena cava up to the level of renal vein superiorly.[2] Oral alimentation was started subsequent to the beginning of bowel passage postoperatively. The surgical drain, which was placed in each patient during the operation, was withdrawn following the end of apparent chylous or hemorrhagic drainage. The staging was performed according to the FIGO (International Federation of Gynecology and Obstetrics) classification.[13] All patients were followed up every 3 months for the first 2 years, every 6 months for the next 3 years, and annually afterward. While DFS was defined as the time from surgery to recurrence or last control, OS was defined as the time from surgery to death or last control.[3]

The patients were classified into two groups according to their surgical intervention being L/T or L/S. Sociodemographic features such as age, body mass index (BMI), smoking, parity, comorbidities, the American Society of Anesthesiologists (ASA) score, presence of previous abdominal surgery, and menopausal status; histopathologic data including tumor diameter, grade, myometrial invasion, peritoneal cytology, FIGO stage, and removed and metastatic pelvic and para-aortic lymph node numbers; perioperative data such as operation duration, intraoperative complications including bladder/ureter/bowel or vascular injuries, rate of

Key Message

Depending on the surgical experience, laparoscopic surgery may be performed safely in the management of endometrioid endometrial cancer.

conversion from L/S to L/T, the difference between postoperative and preoperative hemoglobin (Hb) values as an indicator of blood loss, postoperative first flatus and oral alimentation time, time of drain withdrawal, time of hospitalization; and also oncologic data including adjuvant treatment rates, recurrence rates, and DFS and OS outcomes of the two groups were compared.

SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis of the data. Categorical measurements were defined as numbers and percentages, and continuous measurements were summarized as mean and standard deviation or median and range when necessary. Chi-square or Fisher exact tests were used to assess the relationship between categorical measurements and surgical technique. In comparing continuous measurements between groups, distributions were evaluated. Student *t*-test was used for variables with parametric distribution, and Mann–Whitney *U* test was used for variables without parametric distribution. Kaplan–Meier survival analysis and log-rank test were used to compare survival rates. Statistical significance was taken as 0.05 in all tests.

This study was approved by the Institutional Review Board of our university (Project No. KA20/183, 21/05/2020). The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients prior to their treatment.

Results

It was observed that 132 (47.48%) of 278 patients who underwent staging surgery with the diagnosis of intermediate- or high-risk endometrioid endometrial cancer had laparotomic surgery, whereas 146 (52.52%) had laparoscopic surgery. The mean age of the patients was 62.23 ± 9.05 years, mean BMI was 35.85 ± 8.30. The ASA score of the groups was similar. Demographic features of both groups are demonstrated in Table 1; these parameters were similar between the groups ($P > 0.05$).

As for histopathologic features, there was no significant difference in terms of tumor diameter, grade, myometrial invasion, and FIGO stage between the groups who were performed L/T and L/S. Peritoneal cytology was also negative for all patients [Table 1].

When perioperative features of the patients were compared, the duration of operation was significantly longer in the L/S group, whereas the time of postoperative flatus, drain removal, and hospital stay were significantly higher in patients who underwent L/T ($P = 0.000$ for all parameters). The difference between postoperative and preoperative hemoglobin (Hb) values was also higher in the L/T group ($P = 0.066$).

Total removed pelvic and para-aortic lymph node numbers as well as metastatic pelvic and para-aortic lymph node numbers were significantly higher in patients who underwent laparotomic surgery (*P* values 0.000, 0.000, 0.017, and 0.033 respectively) [Table 2].

BMI was above 30 in 204 (73.4%) patients. Perioperative features of this subgroup were further evaluated; duration of operation was significantly longer in the L/S group, whereas the time of postoperative flatus and hospital stay were found to be significantly higher in the L/T group. The difference in Hb values and drain removal time were also higher in the L/T group; however, statistical significance was not detected for these parameters. The total removed and metastatic lymph node numbers were significantly higher in patients who underwent L/T in this subgroup as well [Table 2].

In all patients, intraoperative complications were found to be recorded in two (1.5%) patients in the L/T group, and eight (5.5%) patients in the L/S group. However, the difference between the complication rates was not statistically significant ($P = 0.108$). All the complications were found to be vascular injuries. It was observed that L/T decision was made for complication intervention in four patients in the L/S group, whereas three patients did not require L/T for the management of complications. (Vena cava injury in two patients and left external iliac vein laceration in one patient were found to be repaired laparoscopically.)

In the L/S group, 22 (15.1%) of 146 patients were seen to have a conversion from L/S to L/T. It was seen that 18 of these procedures were performed for technical feasibility, whereas four were performed for

Table 1: Demographic and histopathologic characteristics

	Laparotomy (*n*=132)	Laparoscopy (*n*=146)	*P*
Age (Mean±SD)	62.67±8.67	61.84±9.38	0.441
BMI (Mean±SD)	35.74±8.33	35.91±8.31	0.913
Parity (Median, range)	3.0 (0-9)	3.0 (0-10)	0.398
Smoking (%)	16.9	14.5	0.616
Menopausal status (postmenopausal %)	88.6	82.2	0.175
Comorbidity (%)	70.5	72.6	0.789
Previous abdominal surgery (%)	39.2	39.6	1.000
ASA Score			
I-II (%)	64.3	68.2	0.308
III-IV (%)	35.7	31.8	
Tumor size (cm) (Median, range)	4.0 (0-12)	4.0 (0-8)	0.468
Grade 1 (%)	42.5	45.5	0.249
Grade 2 (%)	41.7	45.5	
Grade 3 (%)	15.7	9.1	
Myometrial invasion (%)			
<50%	73.3	82.9	0.154
≥50%	26.7	17.1	
FIGO stage (%)			
Ia	59.8	76.6	0.120
Ib	16.7	11.7	
II	5.3	2.8	
IIIa	3.8	2.8	
IIIc1	3.8	2.1	
IIIc2	7.6	2.8	
IV	3.0	1.4	

BMI=Body mass index; SD=Standard deviation; ASA=American Society of Anesthesiologists; FIGO=International Federation of Gynecology and Obstetrics

Table 2: Perioperative outcomes for all patients and for the cases with BMI >30

All patients (*n*=278)	Laparotomy (*n*=132) (Median, range)	Laparoscopy (*n*=146) (Median, range)	*P*
Operation duration (minutes)	120 (60-300)	180 (60-360)	***0.000****
Hb difference (g/dL)	1.90 (0.8-5.2)	1.79 (0.4-3.3)	0.066
First flatus time (day)	2 (1-5)	1 (1-3)	***0.000****
Drain removal (day)	4 (2-17)	3 (1-11)	***0.000****
Duration of hospitalization (day)	6 (3-20)	4 (2-15)	***0.000****
Total pelvic LN numbers	34 (6-65)	26 (9-52)	***0.000****
Total para-aortic LN numbers	32 (3-94)	19 (3-63)	***0.000****
Metastatic pelvic LN numbers	0 (0-20)	0 (0-3)	***0.017****
Metastatic para-aortic LN numbers	0 (0-45)	0 (0-2)	***0.033****
Patients with BMI >30 (*n*=204)	**Laparotomy (*n*=78, 38.2%) (Median, range)**	**Laparoscopy (*n*=126, 61.8%) (Median, range)**	***P***
Operation duration (minute)	150 (80-240)	185 (60-315)	***0.000****
Hb difference (g/dL)	2.0 (0.9-3.6)	1.74 (0.4-3.3)	0.123
First flatus time (day)	2 (1-4)	1 (1-3)	***0.001****
Drain removal (day)	4 (2-8)	3 (1-9)	0.069
Duration of hospitalization (day)	5 (3-15)	4 (3-15)	***0.000****
Total pelvic LN numbers	33 (20-65)	24 (12-45)	***0.000****
Total para-aortic LN numbers	31 (3-77)	16 (3-63)	***0.001****
Metastatic pelvic LN numbers	0 (0-20)	0 (0-3)	***0.004****
Metastatic para-aortic LN numbers	0 (0-45)	0 (0-1)	***0.009****

BMI=Body mass index; Hb=Hemoglobin; LN=Lymph node; *significant

urgent management of complications. (Conversion to L/T was decided due to left renal vein injury in two patients and internal iliac vein injury in two patients.) One of the 18 patients in whom the operation was

continued as L/T for technical difficulty was reported to have vena cava injury and repair after conversion to L/T.

Adjuvant treatments including brachytherapy (BRT), external beam radiation (EBRT) + BRT, chemotherapy (CT), CT + EBRT, CT + BRT, CT + EBRT + BRT as well as follow-up without treatment were not significantly different between the two groups (P = 0.122).

Although the recurrence rate was higher in the L/T group, a significant difference was not found between the groups (P = 0.074). One-year, 3-year, and 5-year OS rates were not significantly different between the two groups (P = 0.315) [Tables 3 and 4].

Discussion

In our study, laparoscopic surgery was seen to be significantly superior to laparotomic surgery in terms of perioperative outcomes. Although the number of removed and metastatic lymph nodes was found to be significantly higher in the L/T group, this difference did not affect the oncologic outcomes, and the two groups had similar results in this aspect. While a significant difference was not found between the intraoperative complication rates of the two groups, it was observed that intraoperative complications that were encountered in laparoscopic surgery could be managed successfully either laparoscopically or by conversion to laparotomic surgery.

Table 3: Oncologic outcomes

	Laparotomy (n=132)	Laparoscopy (n=146)
Adjuvant therapy (%)		
None	51.9	64.4
BRT	23.3	21.9
EBRT and BRT	1.6	3.4
CT	8.5	3.4
CT and BRT	3.9	1.4
CT and EBRT	2.3	1.4
CT, BRT, and EBRT	8.5	4.1
Recurrence (%)	6.9	2.1

P>0.05 for all parameters. BRT=Brachytherapy; EBRT=External beam radiation; CT=Chemotherapy

The absence of significant difference between the demographic characteristics of both groups in our study makes the comparison of surgical techniques more reliable. Besides, it demonstrates that these features are not prioritized in patient selection for surgical techniques. Although demographic features between the groups are found similar in many studies,[1,14] there are also reports with differences. Manchana *et al*.,[3] in their study population, found that the mean age of the patients was significantly higher in the L/T group whereas BMI was significantly lower in the L/S group in the study of Pulman *et al*.[2]

The superiority of perioperative outcomes in the L/S group in our study is similar to previous reports in the literature. The LAP2 study compared the results of L/S and L/T in endometrial cancer in a randomized controlled study for the first time and demonstrated that intraoperative and postoperative negative effects were fewer in laparoscopic staging, also the recurrence and survival rates were found to be similar in the ancillary data of the study.[15,16] In subsequent studies, it has also been reported that the operation time is longer; however, blood loss is less and hospital stay is shorter by laparoscopic surgery.[1,3,5,6] On the other hand, there are studies reporting similar operation times between the groups, and they associate this with surgical experience.[7,14] It was previously reported that the learning phase of pelvic lymphadenectomy included about 20 operations, whereas para-aortic lymphadenectomy necessitated more than 100 operations.[17] In the literature, open surgery has been reported to increase perioperative complications in obese patients.[18] However, it is reported that the rate of conversion to L/T has also increased with increasing BMI owing to reasons such as limited access to pelvic organs and inadequate lymphadenectomy.[4] Therefore, perioperative outcomes of the subgroup with BMI >30 were further compared in the L/S and L/T groups in our study. In this subgroup, unlike the whole population, the drain removal time of the two groups was found to be similar. Postoperative and preoperative Hb differences were similar between the two groups, and other outcomes were significantly superior in the L/S

Table 4: Survival rates

	Estimated Mean	Standard Error	95% Confidence Interval		1-year survivor %	3-year survivor %	5-year survivor %	P
			Lower Bound	Upper Bound				
OS	91.7	1.1	89.5	94.0	97.8	96.2	93.8	-
DFS	91.2	1.3	88.5	93.8	98.4	97.4	94.9	-
L/T (OS)	90.6	1.7	87.2	94.1	97.7	94.5	92.5	0.315
L/S (OS)	72.9	1.0	70.8	74.9	97.9	97.9	95.1	

OS=Overall survival; DFS=Disease-free survival; L/T=Laparotomy; L/S=Laparoscopy

group in accordance with the whole population. Consequently, depending on the surgical experience, it seems appropriate to prefer L/S for this subgroup as well.[3,4]

All the complications in our study were vascular injuries, and there was no significant difference between the two groups. Cochrane data also report no significant difference in terms of complications between laparoscopic and laparotomic procedures.[5] In the literature, there are studies that do not report complications[7,14] as well as studies reporting bladder injury[1] and vascular injuries.[3] The decision of conversion from L/S to L/T is not always made for the management of complications. Other reasons may be inadequate visualization due to lack of optimum Trendelenburg position or anatomic difficulties owing to dense adhesions or a large uterus, which prevent the completion of surgery.[4] In our study, conversion to L/T occurred in 22 (15.1%) patients in the L/S group, and only four of these procedures were due to complication intervention. In the LAP2 study, the conversion from L/S to L/T is reported in 23.7% of the cases, and this is associated with increased BMI, metastatic disease, and increased age.[15] However, the type of complication also affects the decision of L/T. Chu *et al.*,[1] in their study of 151 cases, reported that conversion to L/T was not performed in any of the patients; however, the rate of para-aortic lymphadenectomy (2.8% in the L/S group) was quite low in this study. Also, vascular injury was not reported, whereas bladder injury in two patients was repaired laparoscopically. Gao and Zhang[14] also reported no complications and no conversion to L/T in their L/S group. Manchana *et al.*[3] reported that 4.2% of their laparoscopic operations were converted to L/T due to vascular injury and ureter damage.

The number of removed and metastatic lymph nodes in our study was significantly higher in the L/T group in both the whole population and the subgroup with BMI >30. Although in many previous studies, a complete para-aortic lymph node dissection was not performed in all patients, and the evaluation was mostly done on pelvic lymph nodes, there are studies indicating removal of more lymph nodes by either L/T or L/S, as well as studies demonstrating no difference between the groups.[1-3,7] In previous studies, an average of eight to 23 pelvic lymph nodes in L/S and an average of six to 22 pelvic lymph nodes in the open surgery are reported to be collected.[1,3,6,14] Removed mean para-aortic lymph node numbers are denoted as 2.5 to 12 for L/S and 3 to 10 for L/T.[6] Many studies, which demonstrate that the number of removed pelvic and para-aortic lymph nodes in L/S are at least as much as those removed in L/T, have associated this with a better visualization.[6,8]

Similar to previous studies, statistical difference was not found between adjuvant treatments in both groups in our study. However, in patients who need adjuvant therapy, L/S may be more advantageous as fewer perioperative complications and a short recovery period may prevent a delay in further therapy.[8]

The absence of a significant difference regarding recurrence and survival times between our groups is also consistent with previous studies.[1,3,14,15] Also in Cochrane data, L/S results were reported to be similar to L/T in terms of DFS and OS in early-stage endometrioid endometrial cancer.[5] Although longer follow-up is recommended for assessment in this aspect, performing L/S in appropriate cases is supported.[1,3,14]

The main limitation of our study is its retrospective nature. This might cause bias in patient selection; nevertheless, the absence of significant difference between demographic characteristics such as BMI and previous abdominal surgery of two groups suggests that the results of the study were not significantly affected in this regard. Also, because the study included the cases of an experienced team, the outcomes may not be indicative of the safety of all the surgeons at different levels of experience and seniority. Furthermore, owing to the surgical dates, all the patients were not followed up for 5 years; therefore, the 1-year, 3-year, and 5-year OS rates for both groups were reported.

On the other hand, most studies in the literature have enrolled all histopathologic subtypes of endometrial cancer cases. However, the nature of non endometrioid endometrial cancer may resemble ovarian cancer rather than endometrial cancer in many aspects, which may affect the comparison of both perioperative and oncologic outcomes between the L/S and L/T groups. To prevent bias, we preferred a homogeneous population that could allow the assessment of the surgical techniques more properly. Therefore, conducting the study in a single center by the same surgical team with a homogeneous population as well as performing a complete pelvic and para-aortic lymph node dissection in all patients are the strengths of our study.

In conclusion, this study demonstrates that laparoscopic surgery appears to be advantageous over L/T in many aspects, and depending on the surgical experience, may safely be performed for surgical staging of endometrioid endometrial cancer

in both the general population and the subgroup of patients with high BMI.

Acknowledgments

The authors express their thanks for the help with statistical analysis provided by Çagla Sarıtürk, Başkent University, Department of Biostatistics.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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