OPEN

Comparison of Laparoscopy and Laparotomy in Surgical Staging of Apparent Early Ovarian Cancer

13-year Experience

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Abstract: The aim of this study was to compare the safety and morbidity of laparoscopic versus laparotomic comprehensive staging of apparent early stage ovarian cancer.

In this retrospective study, the outcomes of patients with apparent stage I ovarian cancer who underwent laparoscopic or laparotomic comprehensive surgical staging from January 2002 to January 2014 were evaluated. The long-term survival of patients with early ovarian cancer was compared.

Forty-two patients were treated by laparoscopy, and 50 were treated by laparotomy. The median operative time was 200 minutes in the laparoscopy group and 240 minutes in the laparotomy group ($P > 0.05$). The median length of hospital stay was 3 days in the laparoscopy group and 7 days in the laparotomy group ($P < 0.05$). Following laparoscopic and laparotomic staging, the cancer was upstaged for 9 (21.4%) and 10 (20.0%) women, respectively. The median follow-up time was 82 months in the laparoscopic and laparotomic groups, respectively. Excluding the upstaged patients, no recurrence was observed in the present study, and the overall survival and 5-year survival rates were 100% in both the laparoscopy and laparotomy groups.

Laparoscopic and laparotomic comprehensive staging of early ovarian cancer were similar in terms of staging adequacy, accuracy and survival rate. Laparoscopic staging was associated with a significantly reduced hospital stay. Prospective randomized trials are required to evaluate the overall oncologic outcomes.

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Abbreviations: BMI = body mass index, FIGO = International Federation of Gynecology and Obstetrics, RCT = randomized controlled trial.

INTRODUCTION

Ovarian cancer accounts for approximately a quarter of all genital tract malignancies. However, it is responsible for half of all deaths from gynecological cancer, primarily because of its insidious onset and late diagnosis. The prognosis of ovarian cancer is principally determined by its stage.[1] For patients with stage I cancer, the 5-year survival rate is optimal, approaching 90%.[2,3] In most patients with typical stage III disease, the 5-year survival rate is 46%.[4–6] International Federation of Gynecology and Obstetrics (FIGO) guidelines have stated that the standard management for apparent early stage disease is comprehensive surgical staging. Comprehensive surgical staging is defined by the Gynecology Oncology Group as the performance of exploratory laparotomy, peritoneal washings for cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, bilateral pelvic and para-aortic lymphadenectomy, and peritoneal biopsy.[7,8] With the rapidly growing availability of laparoscopy surgery in recent years, laparoscopic procedures are increasingly being accepted for the management of endometrial cancer and cervical cancer. However, whether laparoscopic comprehensive staging can be safely performed in patients with early stage ovarian cancer remains unclear. Only a few studies comparing laparoscopic and laparotomic comprehensive staging of ovarian cancer have been reported to date, with a median follow-up time of <5 years.[10–13] This has made evaluation of the long-term effects of laparoscopic staging of early stage ovarian cancer difficult. The purpose of this study was to compare the feasibility, accuracy, and safety of comprehensive laparoscopic with those of laparotomic surgical staging of apparent early ovarian cancer with a median follow-up time of >5 years.

Materials and Methods

The research protocol was approved by the Medical Ethics Committee of Capital Medical University Beijing Chao-Yang Hospital. A retrospective study of all of the patients who underwent comprehensive staging management for early stage ovarian cancer between January 2002 and January 2014 at the Capital Medical University Beijing Chao-Yang Hospital was performed. All of the patients underwent operations performed by the same 2 surgeons (Zhiqiang Zhang and Zhenyu Zhang), both of whom had extensive training and experience in gynecologic oncology and advanced laparoscopic procedures. The included criteria for our study are: (i) apparent FIGO stage I ovarian cancer; (ii) only epithelial ovarian cancers were included; (iii) no gross evidence of spread of the disease beyond the ovaries; (iv) no evidence of pelvic lymph node or distant metastasis; and (vi) no documented clinically important cardiopulmonary disease. The excluded criteria are: (i) patients with borderline ovarian malignancy, advanced ovarian cancer of

FIGO stage III or IV, or a concurrent malignancy of another organ and (ii) patients referred from other hospitals after staging surgery or who had a history of fertility-sparing surgery.

Preoperative Preparation

The preoperative work-up involved a pelvic examination, vaginal ultrasound examination, magnetic resonance imaging, chest x-ray, and blood sampling. Before surgery, all of the patients and their spouses were comprehensively counseled about the therapeutic options, risks of the procedure, and possibility of conversion to a laparotomic procedure.

Surgical Procedures

Early stage ovarian cancer was defined as an ovarian tumor grossly limited to 1 or both ovaries with no evidence of intraperitoneal disease (stage I according to the FIGO classification). The patients were staged according to the FIGO 2000 staging system. Intraoperative mass rupture was defined as any rupture, intentional or unintentional, that resulted in the release of cyst contents into the peritoneal cavity. If a mass was drained intentionally within a collection bag to facilitate removal without a resulting peritoneal spill, the mass was not considered to have ruptured. The operative times was defined as the skin-to-skin time. Postoperative complications were defined as procedure-related adverse events occurring within 30 days of surgery.

Laparoscopic Technique

The patient was placed in the lithotomy position and a general endotracheal tube anesthesia was placed. A self-made uterine manipulator was used. The laparoscopies were performed with CO_2 with an intraabdominal pressure of 12 mm Hg. After creating a pneumoperitoneum by a Verres needle inserted through the umbilicus, a 10-mm tracar was inserted through umbilical incision. After patients were placed in a Trendelenburg position, 3 ancillary trocars were inserted under direct vision. At first, procedures commenced with thorough exploration of all pelvic and abdominal organs and the peritoneal surface, including diaphragm, liver, gallbladder, small bowel and mesentery, recto-sigmoid colon, pouch of Douglas, and paracolic gutters. Pelvic washing was taken for cytological examination, and then ovarian tumor was removed in a capsule bag through the low left port for frozen section. The staging procedure included total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymph node dissection, omentectomy, and appendectomy. Surgical technique of lymphadenectomy has already been described.[11,12] The omentectomy was performed after dividing the omentum along its superior border adjacent to the transverse colon and stomach. Hemostasis was provided using harmonic. The resected omentum was extracted through the vaginal with the uterus after the hysterectomy. A 40-mm round needle was introduced through the 10-mm port, and we intracorporeally performed the closure of vaginal cuff with a 1−0 Vicryl continuous running suture.

Laparotomic Technique

The surgical procedures were essentially the same as for the laparoscopic approach, except that a midline vertical abdominal incision was made.

All of the patients received antibiotic prophylaxis (cefoxitin sodium 2 g intravenously) 30 minutes before the operation. Lower extremity sequential compression devices and graduated compression stockings for venous thrombosis prophylaxis were used intraoperatively. Low-molecular-weight enoxaparin was used postoperatively.

Postoperative Management

Patients with stage Ia and Ib grade1 cancer did not receive postoperative adjuvant treatment, and 6 cycles of adjuvant chemotherapy with a combination of carboplatin and paclitaxel was recommended for other patients.[14,15] Recurrence was classified by the site of the first recurrence. Overall survival was calculated from the date of diagnosis of ovarian carcinoma to death of any causes. Disease-free survival was calculated from the date of diagnosis of ovarian carcinoma to disease recurrence. We confirmed the accuracy of the patients' information and status by direct interviews and clinical examinations. Follow-up evaluations were scheduled 1 month postoperatively then every 3 months for the first 2 years, every 4 months for the next 2 years, and every 6 months thereafter.

Statistical Analysis

Data were analyzed using SPSS statistic software version 22.0 (SPSS version 22.0; SPSS, Inc., Chicago, IL). The independent sample t test was used for comparison of median, and the χ^2 test for comparison of proportions. A P value of <0.05 was considered significant for all tests. Survival data were estimated using Kaplan−Meier curves.

RESULTS

Forty-two patients underwent comprehensive laparoscopic surgical staging, and 50 underwent traditional abdominal surgical staging. Age was similar between the 2 groups; likewise, no significant differences were found in histological type, grade, or tumor stage. Various patient characteristics are shown in Table 1. The operative data are summarized in Table 2.

TABLE 1. Patients' Characteristics According to Treatment Approach

Characteristic	Laparoscopic (n = 42)	Laparotomy (n = 50)	P Value
Age (y), median (range)	54 (14–69)	58 (25–76)	0.11
BMI (kg/m²)	23.5 ± 4.0	24.8 ± 3.2	0.17
Surgical FIGO stage			0.15
Ia	30 (71.4%)	35 (70%)	
Ic	3 (7.14%)	5 (10%)	
IIa	2 (4.76%)	1 (2%)	
IIIa	4 (9.52%)	5 (10%)	
IIIc	3 (7.14%)	4 (8.0%)	
Grade			0.75
1	9 (21.4%)	12 (24%)	
2	15 (35.7%)	18 (36%)	
3	18 (42.9%)	20 (40%)	
Histology			0.65
Serous	22	30	
Mucinous	9	12	
Endometrioid	9	4	
Clear cell	2	4	

BMI = body mass index, FIGO = International Federation of Gynecology and Obstetrics.

TABLE 2. Comparison of Operative Outcome

Variables	Laparoscopy (n = 42)	Laparotomy (n = 50)	P Value
Operative time (min), median (range)	200 (150–460)	240 (180–570)	0.18
Estimated blood loss (mL), median (range)	110 (50–450)	370(20–1000)	0.01
Blood transfusion (case)	1	2	0.00
Pelvic lymph nodes, median (range)	20 (10–35)	22 (12–33)	0.87
Para-aortic lymph nodes, median (range)	8 (4–17)	7 (3–20)	0.95
Intraoperative complications			0.34
Hemorrhage	0	1	
Postoperative complications			0.75
Fever	0	2	
Lymphocele	3	1	
Upstaging (%)	21.4%	20%	0.86
Hospital stay (d), median (range)	3 (2–14)	7 (3–10)	0.00

FIGO = International Federation of Gynecology and Obstetrics.

The supposed stage I ovarian cancer was upstaged in 9 patients in the laparoscopy group and 10 in the laparotomy group ($P > 0.05$). Among patients restaged to IIA occult extra-ovarian microscopic metastasis to the fallopian tube occurred in 2 patients in the laparoscopy group and in 1 in the laparotomy group. Among patients with stage IIIA cancer established by the surgical staging procedure, sites of occult spread included the omentum (n = 2) and peritoneum (n = 2) in the laparoscopy group and bowel mesentery (n = 2), omentum (n = 1), and peritoneum (n = 2) in the laparotomy group. Among patients restaged to IIIC, sites of microscopic metastasis included the para-aortic lymph nodes (n = 1) and pelvic lymph nodes (n = 2) in the laparoscopy group and para-aortic lymph nodes (n = 2), and pelvic lymph nodes (n = 2) in the laparotomy group. All upstaged patients in these groups underwent 6 cycles of platinum-based chemotherapy with paclitaxel or platinum, adriamycin, and cyclophosphamide. No conversion to laparotomy or intraoperative complications occurred in the laparoscopic group.

The operating time was 200 minutes (range 150–460 min) in the laparoscopic group and 240 minutes (range 180–570 min) in the laparotomy group ($P > 0.05$). The median blood loss was 110 mL (range 50–450 mL) in the laparoscopy group and 370 mL (range 20–1000 mL) in the laparotomy group. One patient in the laparoscopy group needed blood transfusion, whereas 2 patients in the laparotomy group underwent an intraoperative or postoperative transfusion. The median length of hospital stay was 3 days in the laparoscopy group and 7 days in the laparotomy group ($P < 0.01$). A similar mean number of pelvic and para-aortic lymph nodes were obtained in both groups. No intraoperative complications occurred in the laparoscopy group. One patient developed a post-cava injury during the laparotomy staging procedure. Three patients in the laparoscopy group and 1 patient in the laparotomy group were diagnosed with an asymptomatic lymphocele postoperatively by routine abdominal ultrasound. None required percutaneous drainage or surgical intervention; the lymphoceles were instead treated by external application of the traditional Chinese medicines *Rheum palmatum* and mirabilite. One patient in the laparotomy group developed a bowel obstruction 2 days postoperatively.

The median follow-up time was 82 (range, 16–152) months in the laparoscopy and laparotomy groups, respectively.

No long-term complications were observed. No port site metastasis occurred. Among the 19 patients upstaged after comprehensive surgical staging, 5 (13%) in the laparoscopy group developed recurrence versus 6 (13%) in the laparotomy group. One patient with recurrence in the laparoscopy group had hydrothorax. Two patients in the laparoscopy group relapsed at pelvis. Two patients in laparoscopic group had no obvious sites of recurrence, but only an elevated CA125 level. No recurrences developed at the laparoscopy port sites. Two patients in the laparotomy group developed ascites. Two patients in the laparotomy group developed a relapse at the vaginal stump and pelvis, and 2 recurrences developed in the peritoneum and liver. The time to recurrence was >20 months postoperatively. All of the patients with recurrence underwent at least 6 cycles of platinum-based chemotherapy with paclitaxel or platinum, adriamycin, and cyclophosphamide. However, 8 patients with recurrence died after the chemotherapy treatment (3 in the laparoscopy group and 5 in the laparotomy group). There was no recurrence among the remaining patients with FIGO stage I disease. There were no differences in the recurrence or survival rate between the laparoscopy and laparotomy groups. The 5-year survival rate was 91.3% in the laparoscopy group and 88.4% in the laparotomy group. The overall survival rate in the laparoscopy group was 92.9%, and that in the laparotomy group it was 90.0% ($P = 0.35$) (see Table 3 and Figure 1). Excluding the upstaged patients, the overall, 5-year and disease-free survival rates of patients with

TABLE 3. Comparison of Clinical Course

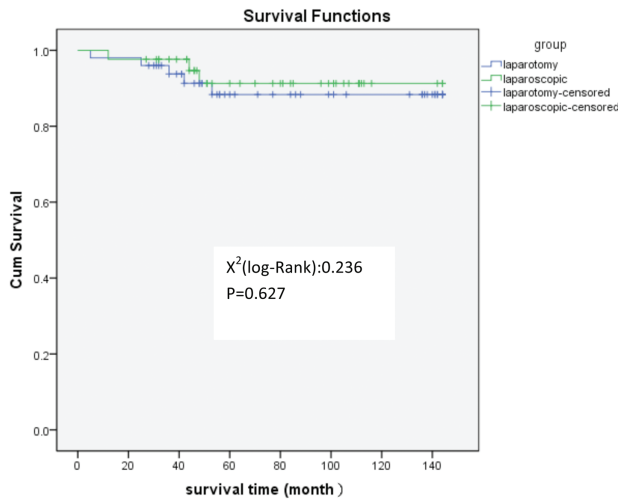|	Laparoscopic (n = 42)	Laparotomy (n = 50)	P Value
Follow-up time (mo)	82 (16–152)	82 (16–152)	NS
Recurrence (n)	5 (13%)	6 (13%)	NS
5-year survival	91.3%	88.4%	NS
Overall survival	92.9%	90%	NS
Death (n)	3	5	NS

NS = nonsignificant.

FIGURE 1. Overall survival of the laparoscopy and laparotomy groups.

stage I disease were all 100% in both the laparoscopy and laparotomy groups.

DISCUSSION

In 1973, Bagley et al were the first to publish a report on the use of laparoscopy in patients with ovarian cancer.[16] In 1983, the Ovarian Cancer Study Group described the results of a prospective, multicenter, restaging study of 100 patients with a diagnosis of early ovarian cancer.[17] In 1994, Querleu and Leblanc reported the feasibility of complete laparoscopic surgical staging procedures for ovarian cancer.[9] Since then several investigators from pioneering centers have reported small case series of comprehensive laparoscopic surgical staging of early stage ovarian cancer with limited follow-up periods. Thus far, however, only 5 studies have included a control group between the laparoscopic and laparotomy procedures[10–13] (see Table 4). The use of laparoscopic staging procedures in patients with early ovarian cancer remains controversial.

The first controversial issue regarding laparoscopic surgery for the treatment of ovarian cancer is the accuracy of laparoscopic surgical staging. Among patients with surgical stage I ovarian cancer, those who have undergone comprehensive surgical staging have a lower risk of recurrence than do those who have not.[18] It has been argued that laparoscopy does not allow for a thorough inspection of the pelvis, mesentery, and peritoneum leading to failure of upstaging and in adequate administration of chemotherapy.[12] Alternative evaluations of the accuracy of comprehensive surgical staging can be inferred by comparing the rate of upstaging and lymph node yield between laparoscopic and laparotomic cases. A case-control series of 34 patients showed no difference in the lymph node yield between laparoscopy and laparotomy. Additionally, a meta-analysis of 3 comparative studies revealed no significant difference between the upstaging rates of laparoscopy and laparotomy.[19] Likewise, in the present study, there were no significant differences in the upstaging rate or lymph node yield between the 2 groups.

The second controversial issue is the rate of tumor rupture between the laparoscopic and laparotomic approaches and the prognostic value of tumor rupture during surgery. In general, reported tumor rupture rates range from 11.4% to 30.3%.[13,20–23]

However, the risk of tumor rupture is not only limited to laparoscopic surgery, and some studies have reported that the risk of tumor rupture is similar between laparoscopic and laparotomic surgery. One previous study reported that the incidence of tumor rupture in patients with ovarian cancer was similar between the laparoscopy and laparotomy groups (10.5% versus 12.1%, respectively; $P = 1.000$).[13] Other studies demonstrated that the rate of tumor rupture was 8% in both procedures.[22,24] The clinical significance of tumor rupture during surgery remains uncertain. The largest study of cyst rupture was a retrospective, multicenter study involving >1500 patients. The study demonstrated that tumor rupture was an independent predictor of disease-free survival. In contrast, no difference in survival was noted in a retrospective review of 394 patients.[25] However, these findings have not been confirmed in prospective studies. The prognostic value of intraoperative tumor rupture must be more clearly examined based on large-scale randomized controlled trials (RCTs) in patients with early ovarian cancer.[19] All efforts should be made to reduce the incidence of tumor contamination of the abdominal cavity, including liberal use of a laparoscopic bag, controlled aspiration, and minimization of the risk of rupture.[26] In the present study, thorough irrigation of the intraperitoneal cavity was performed using distilled water and cisplatin at the end of the surgical procedure, which may have reduced the negative impact of potential tumor rupture on recurrence and survival. Intraperitoneal administration of anticancer drugs has many pharmacokinetic advantages and induces high response rates in the abdomen because the ''peritoneal plasma barrier'' provides dose-intensive therapy.[27,28]

The third point of controversy is port-site metastasis. Large series of patients with malignant disease undergoing transperitoneal laparoscopy suggested that the incidence of port site implantation was <1%.[29,30] Zivanovic et al reported that the port site recurrence rate of 1.96% following laparoscopy for ovarian, fallopian tube, or primary peritoneal cancer among 796 patients was comparable with the wound recurrence rate following laparotomy.[31,32] Nezhat et al found that the rate of port-site metastasis in laparoscopic management of ovarian cancer was not higher than that in laparotomic management.[33] The precise origin of port-site metastasis remains unclear. Several mechanisms of the development of port-site metastasis have been proposed. Among the most common are hematogenous spread, direct wound contamination and implantation, multiple effects of pneumoperitoneum, the effects of the gases used for insufflation, the ''chimney effect,'' aerosolization of tumor cells, local immune reactions, and the surgical technique used.[30] We observed no port-site metastasis in the present study. We placed a pipe in the vaginal canal and removed the specimen from the pipe through the vaginal canal to avoid contact with the vaginal wall; the vaginal was then thoroughly irrigated before suturing.

The fourth point of controversy is the efficiency of laparoscopic staging compared with that of traditional laparotomic procedures. Standard survival outcomes must not be compromised for a procedure to be accepted as the standard treatment for early ovarian carcinoma. In agreement with this, we found no significant differences in survival analyses based on surgical management approaches. The overall and 5-year survival rates were 92.9% and 91.3% in the laparoscopy group and 90.0% and 88.4% in the laparotomy group. Ghezzi et al[34] reported the largest study to date of laparoscopically managed early ovarian cancer. In their prospective study of 82 patients with a median follow-up time of 28.5 (range, 3–86) months, the overall and disease-free survival rates were 98.8% and 95.1%, respectively.

TABLE 4. Survival Outcomes of Patients With Early Stage Ovarian Cancer in Published Studies

	Dennis et al[10]		Lecure et al[11]		Ghezzi et al[34]		Jeong-Yeol (2008)		Maria Lee (2011)[36]		Present study	
	LPS	LPT	LPS	LPT	LPS	LPT	LPS	LPT	LPS	LPT	LPS	LPT
Number of patient	20	30	34	114	15	19	19	33	26	87	42	50
FIGO stage	NR	NR	NR	NR								
Ia					5	8	8	14	11	45	30	35
Ib					0	0	0	1	0	3	0	0
Ic					6	5	7	11	14	34	3	5
IIa					0	0	0	0	0	0	2	1
IIb					0	0	0	0	0	2		
IIc					0	0	1	1	0	3	0	0
IIIa					2	3	0	0	0	3	4	5
IIIc					2	3	3	6	1	0	3	4
Operative time (min)	321±64	276±68	NR	NR	377±47	272±81	NR	NR	227.6±105.8	184.6±61.4	200 (150–460)	240 (180–570)
Blood loss (mL)	235±138	367±208	NR	NR	250 (50–1000)	400 (150–1000)	NR	NR	230.4±183.6	474.8±329.2	110 (50–450)	370 (20–1000)
Average no. of pelvic nodes	12.3	14.7	NR	NR	25.2±9.3	25.1±5.8	27.2	33.9	23.5±9.3	22.8±10.2	20 (10–35)	22 (12–33)
Average number of para-aortic nodes	6.7	9.2	NR	NR	6.5±3.9	7±4.5	6.6	8.8	9.9±7.4	4.8±4.1	8 (4–17)	7 (3–20)
Sites of metastasis (%)	2 (10%)	3 (10%)	NR	NR	4 (27%)	7 (37%)	4 (21%)	7 (21%)	1 (3.8%)	NR	7 (17%)	9 (18%)
Uterus	1	1			0	0	0	0	0		0	0
Nodes	1	2			2	4	3	6	1		3	4
Omentum	0	0			2	1	0	0	0		2	2
Bowel mesentery	0	0			0	2	0	0	0		0	1
Pelvic peritoneum	0	0			0	0	1	1	0		2	2
Mean follow-up (mo)	NR	NR	34±28	41±26	16 (4–34)	60 (32–108)	17 (2–40)	23 (1–44)	12 (1–42)	25 (1–74)	82 (16–152)	82 (16–152)
Recurrences	NR	NR	2	17	0	4	0	0	0	8	5	6
Overall survival	NR	NR	100%	97%	100%	100%	100%	100%	13.1±10.2	27.7±15.4	92.9%	90%

FIGO = International Federation of Gynecology and Obstetrics, LPS = laparoscopic group, LPT = laparotomy group, NR = no report.

These findings of similar survival outcomes between laparoscopic and laparotomic approaches could be the first step in accepting laparoscopy as the standard surgical approach for patients with early ovarian cancer. In the present study, the median follow-up period was 82 months in the laparoscopy and laparotomy group, respectively. To the best of our knowledge, our follow-up time is the longest among all published studies. Our survival rate is not as satisfactory as that in other studies, however, because all cases of recurrence and death occurred in the upstaging group. Excluding the upstaged patients, the overall and 5-year survival rates of patients with stage I disease were 100% in both the laparoscopy and laparotomy groups.

The fifth controversial issue is whether laparoscopic staging is actually minimally invasive. Our data indicate that both laparoscopic and laparotomic approaches are feasible in patients with early ovarian cancer but that laparoscopy may have more advantages than laparotomy with respect to operative blood loss and length of hospitalization. The optical magnification of laparoscopy provides an excellent view of the peritoneal surface, even better than direct visualization during laparotomy. However, a shortcoming of laparoscopic staging is the lack of tactile sensation. Therefore, some surgeons propose the use of hand-assisted laparoscopic surgery. Hand-assisted laparoscopic surgery is a unique surgical approach that combines traditional laparoscopy with the ability to place a hand intraperitoneally, thus retaining tactile sensation for the surgeon.[35]

Limitation of the Study

The risk of bias in our series should not be overlooked. Only 19% of patients with a diagnosis of ovarian cancer are classified as having FIGO stage I disease. Stage I disease is usually diagnosed incidentally during laparoscopic or laparotomic surgery for benign-looking ovarian tumors. Therefore, prospective randomized studies have been difficult to conduct.

CONCLUSION

Our findings suggests that laparoscopic staging surgery of early ovarian cancer has an adequacy and accuracy similar to those of laparotomic staging surgery, with a similar long-term survival rate and significantly reduced hospital stay. A prospective multicenter randomized trial is required to more fully evaluate the overall oncologic outcomes.

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