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Comparison of surgical outcomes between laparoscopy and laparotomy for early-stage ovarian cancer

Se Hyun Nam, Woo Young Kim

Department of Obstetrics and Gynecology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul (Republic of Korea)

Summary

To investigate the surgical and oncologic outcomes of laparoscopy compared with laparotomy in early-stage ovarian cancer, the authors reviewed medical records of patients with epithelial ovarian cancer at Kangbuk Samsung Hospital, Korea, between January 2001 and December 2014. Forty-nine patients were diagnosed with FIGO Stage I or II epithelial ovarian cancer and 25 and 24 patients underwent surgical staging by laparoscopy and laparotomy, respectively. Most of the clinicopathologic characteristics showed no statistical difference between the two groups. However, incidence of intraoperative tumor rupture was higher in the laparoscopy group (6/25 [24%] *vs.* 1/24 [4.2%]), although the primary tumor size was smaller (7.9 ± 4.2 *vs.* 15.0 ± 5.9, $p = 0.05$). There was no statistical difference between laparotomy and laparoscopy groups according to five-year overall survival (77.2% *vs.* 81.7%, $p = 0.53$) or five-year disease-free survival (76.5% *vs.* 81.3%, $p = 0.77$). Laparoscopic staging surgery showed similar surgical and oncologic outcomes to the laparotomy procedure in early-stage ovarian cancer.

Key words: Laparoscopy; Laparotomy; Early-stage ovarian cancer; Survival.

Introduction

Ovarian cancer accounts for 25% of female genital malignancies but has the highest mortality in the field of gynecologic oncology [1, 2]. The high mortality of ovarian cancer reflects the fact that most patients are diagnosed at an advanced stage [1]. If the ovarian cancer is confined to the ovary, the five-year survival rate is around 90%, but these patients were only 19% in total ovarian cancer patients [3]. Some cases of ovarian cancer are considered to be a benign ovarian mass in imaging studies performed before surgery [4]. If the pathologic results are confirmed to be ovarian malignancy during or after surgery, comprehensive staging surgery should be performed according to recommendations of the International Federation of Gynecology and Obstetrics (FIGO), because it is reported that more than 30% of these patients have micrometastasis [2, 5].

Recently, laparoscopic surgery has been widely used in gynecologic oncology for the treatment of benign or malignant tumors [4, 6]. Laparoscopic surgery shows a similar long-term survival benefit to laparotomy for the treatment of early endometrial cancer and cervix cancer with less surgical morbidity, such as bleeding and infection, as well as a cost benefit [5, 6]. However, there is debate about performing laparoscopy for comprehensive staging in early-stage ovarian cancer.

To date, there are fewer than ten reports comparing surgical outcomes of early ovarian cancer between laparoscopy and laparotomy [1, 2, 4-9]. Most previous reports defined early ovarian cancer from clinically gross findings rather than pathologic findings, and the types of tumors included in the studies are very heterogeneous. Also, laparoscopic surgery was performed in fewer than 20 cases. Therefore, there is limited evidence for the feasibility and safety of staging by laparoscopy in patients with early-stage ovarian cancer.

The authors therefore compared surgical outcomes between laparotomy and laparoscopy in patients with FIGO Stage I or II epithelial ovarian cancer to investigate the staging feasibility and oncologic safety of laparoscopy in early ovarian cancer.

Materials and Methods

The authors retrospectively identified 179 patients who underwent ovarian cancer staging surgery between January 2001 and December 2014, from the tumor registry of Kangbuk Samsung Hospital. Among them, they selected 49 patients with pathologic confirmation of epithelial ovarian cancer and FIGO Stage I or II.

All patients underwent routine laboratory tests and imaging studies such as computed tomography or magnetic resonance imaging before surgery. Peritoneal washing, total abdominal hysterectomy, bilateral salpingo-oophorectomy, multiple random biopsy of peritoneal surface, appendectomy, omentectomy, and pelvic and para-aortic lymphadenectomy were performed for comprehensive staging during surgery.

Surgery was performed by three surgeons with extensive training and experience in gynecologic and laparoscopic procedures. The mode of surgery was either laparoscopy or laparotomy ac-

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cording to the physician's discretion. After surgery, patients received follow-up evaluations with pelvic examination and imaging studies every three months for two years and every six months thereafter. This study was approved by the institutional review board.

Early ovarian cancer was defined as FIGO Stage I or II after a comprehensive staging work up. Intraoperative mass rupture was defined as any rupture that resulted in spillage of cyst contents into the peritoneal cavity in Stage I disease. Fertility saving procedure was defined as preservation of the uterus and at least the opposite ovary. Transfusion was performed in cases of active bleeding with symptomatic anemia and hemoglobin less than 8 g/dL. Postoperative complications were defined as adverse events occurring within 30 days of surgery as a result of the procedure. Patients with high risk factors including high-grade clear cell histologic type, tumor growth through capsule, malignant cells in either ascetic fluid or peritoneal washing, and preoperative rupture were treated with postoperative adjuvant chemotherapy using intravenous paclitaxel and platinum combination.

Overall survival was calculated from the date of surgery to the date of death or last follow-up. Disease-free survival was calculated from the date of surgery to the date of relapse or last follow-up among patients with no recurrence.

All statistical analyses were performed using SPSS version 21.0. Continuous parametric and non-parametric variables were compared between groups using Student *t*-test and Mann-Whitney U-test, respectively. Frequency distribution was analyzed using Chi-square or Fisher's exact test. Survival curves and rates were calculated using the Kaplan-Meier method, and differences in survival were calculated using the log-rank test. All statistical tests were two-sided. The level of significance was set at $p < 0.05$.

Results

Among 179 patients with epithelial ovarian carcinoma, 49 were diagnosed with FIGO Stage I or II ovarian cancer. Among these, 25 patients underwent laparoscopic surgery, and 24 underwent laparotomy. Baseline characteristics of the patients are presented in Table 1. Mean age of patients was 51 ± 12 years in the laparoscopy group and 60 ± 17 years in the laparotomy group, with no significant difference between the groups, although there was a trend toward younger age in the laparoscopy group ($p = 0.07$). Other baseline characteristics such as body mass index, menopausal status, and previous history of abdominal surgery were not different between the groups. The number of patients referred from an outside hospital after ovarian surgery was 11 (44%) in the laparoscopic group compared with three (12.5%) in the laparotomy group and was statistically higher in the laparoscopic group ($p = 0.02$).

In the laparoscopic group, 21 patients were FIGO Stage I, and four were FIGO Stage II. In the laparotomy group, 18 patients were FIGO Stage I, and six were FIGO Stage II. Histologic cell type, tumor grade, peritoneal washing cytology, and final FIGO Stage were not statistically different between groups (Table 2). Serous carcinoma was dominant in both groups, and high-grade carcinoma was also more prevalent in both groups.

The number of patients with positive washing cytology was two in the laparoscopy group and one in the laparotomy group.

The mean tumor size was larger in the laparotomy group compared with the laparoscopy group. Operation time was longer in the laparoscopy group compared with laparotomy (302 ± 99 *vs.* 252 ± 81 minutes, $p = 0.06$). The number of harvested lymph nodes during surgery was 27 ± 10 in laparotomy and 34 ± 12 in laparoscopy ($p = 0.08$), and the proportion of fertility-saving surgeries was 12.5% (n=3) in laparotomy and 16% (n=4) in laparoscopy ($p = 0.73$), with no significant difference between the two groups. Among the 39 patients with Stage I disease, six in the laparoscopic group and one in the laparotomy group experienced iatrogenic rupture during surgery. The rate of tumor rupture was

Table 1. — *Baseline patient demographics.*

	LPS group ($n = 25$)	LPT group ($n = 24$)	*p*-value
Age (years)	51±12	60±17	0.07
BMI	24.4±4.0	23.5±4.7	0.48
Previous abdominal surgery	17 (68.0)	16 (66.7)	0.92
Menopause	13 (52.0)	14 (58.3)	0.66
Referred for restaging	11 (44.0)	3 (12.5)	0.02
Previous surgery			
UOC	3 (27.3)	0 (0)	
USO	5 (45.5)	1 (33.3)	
BSO	1 (9.1)	0 (0)	
Hysterectomy and BSO	2 (18.2)	2 (66.7)	

BSO: bilateral salpingo-oophorectomy; LPS: laparoscopic surgery; LPT: laparotomy; UOC: unilateral ovarian cystectomy; USO: unilateral salpingo-oophorectomy. Data are expressed as mean ± standard deviation or number (%).

Table 2. — *Histopathologic characteristics.*

	LPS group ($n = 25$)	LPT group ($n = 24$)	*p*-value
Histologic type			0.63
Serous	9 (36.0)	11 (45.8)	
Mucinous	4 (16.0)	5 (20.8)	
Endometrioid	4 (16.0)	3 (12.5)	
Clear cell	5 (20.0)	5 (20.8)	
Squamous cell	1 (4.0)	0 (0)	
Histologic grade			0.37
1	6 (24.0)	10 (41.7)	
2	15 (60.0)	12 (50.0)	
Unknown	4 (16.0)	2 (8.3)	
Cytology			0.61
Negative	20 (91.3)	20 (95.2)	
Positive	2 (8.7)	1 (4.8)	
Final stage			0.79
Ia	8 (32.0)	7 (29.2)	
Ib	2 (8.0)	3 (12.5)	
Ic	11 (44.0)	8 (33.3)	
IIa	1 (4.0)	3 (12.5)	
IIb	3 (12.0)	3 (12.5)	

LPS: laparoscopic surgery; LPT: laparotomy. Data are expressed as number (%).

Table 3. — *Surgical outcomes.*

	LPS group (n = 25)	LPT group (n = 24)	p-value
Operation time (minutes)*	302±99	252±81	0.06
Transfusion required, n (%)	6(24.0)	9(37.5)	0.31
Pelvic lymph nodes (n)*	20±6	16±8	0.09
Para-aortic lymph nodes (n)*	13±10	12±6	0.70
Fertility saving, n (%)	4(16)	3(12.5)	0.73
Intraoperative tumor rupture, n (%)	6(24.0)	1(4.2)	0.05
Tumor size (cm)*	7.9±4.2	15.0±5.9	0.01
Adjuvant chemotherapy, n (%)	23(92.0)	19(79.2)	0.20

*LPS: laparoscopic surgery; LPT: laparotomy. *Mean ± standard deviation.*

Table 4. — *Intraoperative and postoperative complications.*

	LPS group (n = 25)	LPT group (n = 24)
Ileus (n)	1	4
Lymphocele (n)	4	3
Rectal perforation (n)	1	0
Ureter injury (n)	1	0
Subcutaneous emphysema (n)	1	0
Wound dehiscence (n)	1	0

LPS: laparoscopic surgery; LPT: laparotomy.

Table 5. — *Recurrence according to type of surgery.*

	LPS group (n = 25)	LPT group (n = 24)	p-value
Recurrence, n (%)	5 (20%)	7 (29%)	
Time to recurrence (months)*	19±12	16±12	0.78
Recurrence site, (n)			0.12
Peritoneal seeding	2	6	
Lymph node	2	0	
Colon	1	0	
Liver	0	1	

*LPS: laparoscopic surgery; LPT: laparotomy. * Mean ± standard deviation*

statistically higher in the laparoscopic group compared with laparotomy (p = 0.05, Table 3). There was one case of intraoperative ureter injury during laparoscopy that was converted to open surgery for repair.

There were no differences in perioperative complications between the two groups (Table 4). Ileus occurred in four patients who underwent laparotomy and one patient who underwent laparoscopy. Lymphocele greater than 3 cm was observed in three patients in the laparoscopy group and four in the laparotomy group. One patient in the laparoscopy group underwent Hartman operation due to rectal perforation three days after staging surgery, in which a shaving procedure was performed for removal of cancer implant on rectal serosa.

Post-operative follow-up period was 66 ± 47 months and

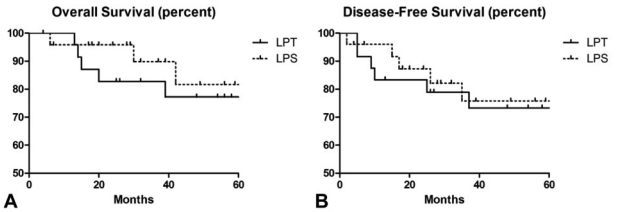

Figure 1. — Comparison of overall survival between laparoscopy and laparotomy groups. Five-year overall survival: laparotomy 77.2% *vs.* laparoscopy 81.7% (p = 0.53). Five-year disease-free survival: laparotomy 76.5% *vs.* laparoscopy 81.3% (p = 0.77). LPT: laparotomy; LPS: laparoscopic surgery.

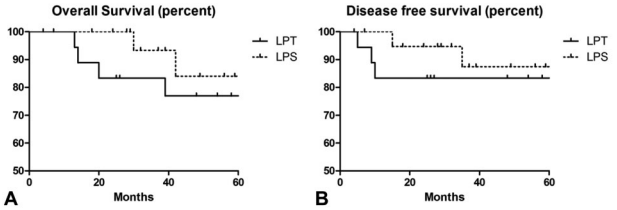

Figure 2. — Comparison of overall survival and disease-free survival between laparoscopy and laparotomy groups with FIGO Stage I. (A) Overall survival. (B) Disease-free survival. LPT: laparotomy; LPS: laparoscopic surgery.

45 ± 30 months for laparotomy and laparoscopy groups, respectively. During the follow-up period, five patients in the laparotomy group and three patients in the laparoscopy group died (p = 0.40). The number of patients with recurrence was seven for laparotomy and five for laparoscopy (p = 0.68). Among these, eight patients had peritoneal seeding and two showed multiple lymph node recurrence. The other two patients had sigmoid colon and liver parenchymal recurrence, respectively (Tables 5 and 6). The median time from staging surgery to recurrence was 27 months in laparotomy and 35 months in laparoscopy (p = 0.56). There were no statistical differences in five-year overall survival and five-year disease-free survival between the two groups (Figure 1).

Five-year overall survival rate of Stage I patients was 77% in the laparotomy group and 84% in the laparoscopy group (p = 0.39), and the five-year disease-free survival rate was 77% in the laparotomy group and 87% in the laparoscopy group (p = 0.32), with no statistical differences (Figure 2). The authors did not compare the survival of Stage II patients by surgical type because of the small number of patients, but the five-year overall survival rate of total Stage II patients was 79%.

Table 6. — *Characteristics of patients with recurrence.*

	Mode	Stage	Age	Histologic type	Grade	Fertility saving	Rupture	Recurrence site	Status*	DFS (months)	OS (months)
1	LPS	Ia	28	Mucinous	High	Done	-	Lymph node	D	15	30
2	LPS	Ib	54	Endometrioid	Low	-	-	Peritoneal seeding	D	35	42
3	LPS	IIa	53	Serous	Unknown	-	-	Colon	NED	26	97
4	LPS	IIb	68	Serous	High	-	-	Peritoneal seeding	D	2	6
5	LPS	IIb	52	Endometrioid	High	-	-	Lymph node	AW	17	17
6	LPT	Ic	41	Clear cell	High	Done	+	Peritoneal seeding	D	9	13
7	LPT	Ia	85	Endometrioid	Low	-	-	Peritoneal seeding	D	10	20
8	LPT	Ib	72	Endometrioid	Low	-	-	Peritoneal seeding	D	27	39
9	LPT	Ic	19	Mucionous	Low	Done	-	Peritoneal seeding	D	5	14
10	LPT	IIa	52	Serous	Low	-	-	Peritoneal seeding	D	5	15
11	LPT	IIb	50	Serous	Unknown	-	-	Peritoneal seeding	NED	25	32
12	LPT	IIb	72	Serous	High	-	-	Liver	NED	37	56

AW: alive with disease; D: death; DFS: disease-free survival; LPS: laparoscopic surgery; LPT: laparotomy; NED: no evidence of disease; OS: overall survival.
**Current disease status.*

Discussion

With improvements in laparoscopic techniques and instruments, it is now possible to perform laparoscopic staging surgery for early ovarian cancer. However, the role and safety of laparoscopic staging in early ovarian cancer are not yet established.

To date, there are limited studies about laparoscopic staging surgery in early ovarian cancer. Among studies where laparoscopic staging included lymphadenectomy, only 16 included more than ten patients [1, 2, 4-17], eight of which compared laparotomy and laparoscopy in early ovarian cancer [1, 2, 4-9]. However, in six of these eight studies, early ovarian cancer was defined clinically by preoperative imaging. After surgery, 19-43% of patients had up-staging, and 4-32% of patients in the laparoscopic groups were determined to have advanced ovarian cancer such as FIGO Stage III [1, 5-9].

Seven of the eight studies included not only epithelial ovarian tumor, but also borderline, stromal, or germ cell tumors or sarcomas (5-29% of cases) [1, 2, 4-8]. Borderline and germ cell tumors are more prevalent in young patients and have a more favorable prognosis than epithelial ovarian carcinoma [18, 19]. In contrast, ovarian sarcoma has a rare incidence and poor prognosis regardless of FIGO Stage [20, 21]. Therefore, if non-epithelial tumors are included in comparative studies, the surgical outcomes might be over- or underestimated.

The authors compared surgical outcomes between laparoscopy and laparotomy for pathologically confirmed FIGO Stage I or II epithelial ovarian cancers. In this study, laparoscopic staging surgery showed operative feasibility with similar surgical outcomes, including number of harvested lymph nodes, to those of laparotomy for early-stage epithelial ovarian cancer. Our results also showed no statistical difference in survival or recurrence rate between the two groups. In the present study, the five-year survival of Stages I and II was 81% and 79%, respectively. In previous studies, the five-year survival of Stage I was reported to be 66.6-91% for patients over the age of 65 years and 88.3-96% for those younger than 65 years, and corresponding five-year survival rates of Stage II were 53.9-76% and 79.7-88% [22, 23]. In addition, Siegel *et al.* reported survival rates as high as 94% in Stage I and 73% in Stage II [24]. Although the present study did not analyze age factors because of the small number of patients, the results showed a similar range to those of previous studies.

Laparoscopy is known to have advantages of reduced surgical morbidity, a shorter hospital stay, and improved cosmetic outcome compared to laparotomy [8, 25-27]. Laparoscopy showed a similar long-term survival benefit in cervix cancer and endometrial cancer [25, 26], but there is no explicit evidence of the feasibility or safety of laparoscopic staging surgery in early-stage ovarian cancer.

One of the concerns of laparoscopic staging surgery in early-stage ovarian cancer is the accuracy of staging. Prognosis of ovary cancer is directly associated with FIGO Stage and postoperative residual tumor volume; therefore, the accuracy of staging is very important [28]. Laparoscopic surgery has weaknesses of lack of tactile sensation and difficult observation of the liver dome and posterior aspect of liver and spleen [4], but isolated metastasis in this area is very rare in early ovarian cancer. In contrast, laparoscopy has the merits of showing a more detailed tumor resection margin and peritoneal surface and a decrease in small vessel injury as a result of optical magnification [14, 29]. Laparoscopy and laparotomy showed similar surgical outcomes in recent published studies, and the present study also showed no difference in LN acquisition between the two surgical methods [4, 9].

The second point to consider is an increased risk of intraoperative rupture during laparoscopy. Ovarian cancer has a higher proportion of cystic component than other malignancies [11]. According to previous studies, the rate of intraoperative tumor rupture in early ovarian cancer was 10.5-54.2% in laparoscopic surgery and 8-39.6% in laparotomy [1, 2, 4-9]. The present study showed that laparoscopy had a higher incidence of intraoperative rupture

than laparotomy (6/25 [24%] *vs.* 1/24 [4.2%], $p = 0.05$); however, intraoperative ovarian tumor rupture was not associated with tumor recurrence or survival rate in this study. Among 12 patients who had recurrence, only one experienced intraoperative rupture. Many studies have shown that intraoperative tumor rupture is not significantly associated with poor prognosis of ovarian cancer [30, 31], although some studies found that intraoperative tumor rupture predicts a higher risk of disease recurrence [31, 32]. The relationship between the recurrence of disease and intraoperative tumor rupture is still controversial; therefore, intraoperative tumor rupture should not be used as a reason to avoid laparoscopic surgery in early-stage ovarian cancer.

The third point to be considered is the risk of port site metastasis as a result of using CO_2 gas. Pneumoperitoneum by CO_2 induces a lower blood pH, disturbance of microcirculation, and weakened local immune defense [33, 34]. In particular, ovarian cancer is reported to be a risk factor of port site metastasis in laparoscopic surgery [35]. However, port site metastasis generally occurs in cases of advanced ovarian cancer [36]. In the present study, only one patient had multiple peritoneal seeding including port site metastasis after laparoscopic staging surgery for early ovarian cancer.

This study has limitations due to the small number of patients enrolled and the retrospective study design. However, early-stage ovarian cancer is rare, and there are only six previous studies with more than 50 patients for comparison of the two surgical methods.

In conclusion, laparoscopic staging surgery showed surgical feasibility and similar outcomes to laparotomy staging surgery for early-stage (FIGO Stages I or II) epithelial ovarian cancer. A large randomized controlled trial is necessary to confirm the present results and those of other previous studies.

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Corresponding Author:
WOO YOUNG KIM, M.D., PHD
Department of Obstetrics and Gynecology
Kangbuk Samsung Hospital
Sungkyunkwan University School of Medicine
29 Saemunan-ro, Jongno-gu
Seoul 03181 (Republic of Korea)
e-mail: obgykim@gmail.com