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Original Article

Surgical and survival outcomes of laparoscopic staging surgery for patients with stage I ovarian cancer

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ABSTRACT

Objective: To assess the feasibility and survival outcomes of laparoscopic staging for patients with stage I ovarian cancer.
Materials and methods: Consecutive patients who underwent laparoscopic staging surgery for stage I ovarian cancer from January 2002 to December 2014 were evaluated retrospectively by chart review.
Results: Twenty-four patients with mean age 43.9 ± 9.9 years and mean body mass index 24.0 ± 3.8 kg/m^2 were included, in which 12 (50%) patients were in stage IA and 12 (50%) in stage IC. The histological types included serous in 6 (25%), mucinous in 7 (29.1%), endometrioid in 6 (25%), clear cell in 5 (20.8%) patients. The mean surgical time was 306.4 ± 98.5 min, and the mean blood loss was 204.2 ± 188.6 mL. None of the patients required conversion to laparotomy. The median numbers of resected pelvic and para-aortic lymph nodes were 20 and 4, respectively. One (4.1%) patient encountered bowel injury intraoperatively, and the other 1 (4.1%) patient hydronephrosis postoperatively. The overall survival rate was 95% in the current series in a median follow-up of 31.5 months.
Conclusion: Laparoscopic staging surgery performed for early stage ovarian cancer has better long term survival outcomes than the literature report. Laparoscopic treatment by a trained gynecologic oncologist is an ideal alternative for early stage ovarian cancer with the advantage of minimal invasiveness.
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Introduction

Epithelial ovarian cancer is the fourth most common gynecologic malignancy [1]. One third of patients with ovarian cancer are diagnosed with stage I disease. While advanced-stage ovarian cancer has a poor prognosis, the prognosis of early-stage cancer is good, and early-stage cancer is often cured by surgery alone or surgery plus adjuvant chemotherapy. The five-year survival rate ranges from 80% to 90% [2].

The guidelines for staging surgery for early ovarian carcinoma recommend total hysterectomy, bilateral salpingo-oophorectomy, pelvic/para-aortic lymphadenectomy, omentectomy, and multiple intra-abdominal biopsies by laparotomy via a longitudinal midline incision. Histopathologic evaluation of specimens provided by comprehensive staging surgery provides accurate information on staging and prognosis, including the need for adjuvant therapy [3]. The proper evaluation of patients with ovarian tumors also requires careful preoperative screening using imaging methods.

In the recent years of the rise of minimally invasive surgery, not only has it been used extensively on treatment of benign disease, but it has also applied in the surgery of malignant tumors [4–9]. Consequently, laparoscopic assisted surgical staging (LASS) for endometrial cancer, which has become the golden standard. Sometimes ovarian tumors that are thought to be benign are found to be malignant, or presumed early-stage disease is reclassified as more advanced disease. Querleu et al. first reported in 1994 that laparoscopy could be used for the comprehensive restaging of adnexal tumors by allowing infrarenal para-aortic lymphadenectomy [10].

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Since then, many investigators have reported on the advantages of laparoscopic surgery for the treatment of early-stage ovarian cancer, which include pain reduction, faster recovery, shorter hospitalization, and early initiation of chemotherapy [11,12].

The retrospective and prospective studies on laparoscopic staging surgery for ovarian cancer have enrolled a relatively small number of patients compared with the studies on cervical cancer and endometrial cancer. Concerns about the use of laparoscopic staging surgery for ovarian cancer include tumor implantation after laparoscopy, port site metastasis, and tumor spillage. The accuracy of laparoscopy compared with the accuracy of laparotomy for complete surgical staging is unknown. However, expectations and demands for minimally invasive surgery for early-stage ovarian cancer have increased. The National Comprehensive Cancer Network (NCCN) guidelines have stated that minimally invasive techniques may be used to achieve surgical goals for selected patients with early-stage disease, if they are performed by an experienced gynecologic oncologist [13]. Laparoscopic staging surgery for ovarian cancer has been performed since 1993 in our hospital [14]. Our surgical outcomes have improved with the development of improved techniques. The aim of our study was to report on the recent laparoscopic surgical outcomes of patients with stage I ovarian cancer at our hospital retrospectively.

Patients and methods

From January 2002 to December 2014, records of consecutively 24 patients undergoing laparoscopic staging surgery for stage I epithelial ovarian cancer at Chang Gung Memorial Hospital were retrieved. Preoperatively, all patients were evaluated by sonography and tumor markers. CT scan was performed if clinically suspicious of ovarian malignancy and patients were excluded if suspicious of beyond stage I ovarian malignancy in this study. Patients were excluded postoperatively if pathological examination confirmed beyond stage I ovarian malignancy. This study was reviewed and approved by the human investigational review board of Chang Gung Memorial Hospital (IRB: 201601209B0). All patients who underwent surgery gave their written informed consent.

Surgical techniques

For most patients, five trocars were used, including one 10-mm and four 5-mm trocars (Covidein, Boulder, CO, USA, or LAGIS, Taichung, Taiwan). A 10-mm laparoscope (KARL STORZ GmbH &Co. KG, Tuttlingen Germany) was introduced at the midpoint between the umbilicus and xiphoid process (Lee-Huang point) [15–17]. All other ancillary ports were inserted laterally, as described previously [15–17].

Two experienced surgeons (C.L.L.: Trained endoscopist, K.G.H.: Trained gynecologic oncologist) performed all the surgeries. Routinely the affected side of ovary was retrieved via an endobag (Tyco Healthcare, Taipei, Taiwan) to avoid contact with the port sites and spillage into abdominal cavity, and were submitted for frozen sections. Any necessary manipulation with tumor puncture or drainage, was performed within the containment of endobag. For patients with a tumor initially too large to fit into the endobag, a mini-laparotomy with 5-cm pfannenstiel or 3-cm longitudinal umbilical incision would first be made, and aspiration of cyst fluid would be performed through a tiny incision before employing the endobag by using 2 or 3 suspending sutures fixed on the cystic wall and the well protection of gauze packing around to avoid leakage. Intraoperative mass rupture was defined as any rupture of cystic contents into the abdominal cavity. Aspiration of cystic fluid without spillage, as mentioned above, was not considered to be the intraoperative mass rupture.

Patients with diagnosis of epithelial ovarian cancer by frozen sections and without the desire to preserve fertility underwent a comprehensive staging procedure, which consisted of laparoscopic hysterectomy with contralateral salpingo-oophorectomy, infracolic omentectomy, pelvic and infrarenal para-aortic lymphadenectomy, a thorough inspection of entire abdomen and biopsy of any suspicious peritoneal lesions, and careful vaginal extraction of the uterus. Patients with mucinous cystadenocarcinoma also underwent appendectomy.

Treatment protocol

Patients with stage IA, grade 1 disease were observed after surgery unless there was incomplete staging or fertility preservation surgery was performed. Adjuvant chemotherapy was administered to patients with risk factors such as grade 2 or 3 ovarian cancer, or substage IB/C disease, or clear cell/undifferentiated carcinoma, or at the discretion of the treating physician. Platinum-based regimens of 3–6 courses were used for adjuvant chemotherapy.

Data collection and statistical analysis

Patient demographics included age, parity, and body mass index (BMI), as well as the perioperative data, including the operation time, number of retrieved lymph nodes, estimated blood loss (EBL), length of hospitalization stay; and the complications including major organ injuries, laparoconversion, blood transfusion, and/or febrile status were recorded. All patients were staged per FIGO 1988 standard based on the surgical and histopathological findings. The pathological data including the histological type, cytological findings, and the number of lymph nodes in the pelvic and para-aortic areas were recorded. At the end of the study, the patterns of recurrence, disease-free survival, and overall survival were analyzed. Overall survival was defined from the time from admission in hospital for surgery to death or the last follow-up.

All the data were analyzed using SPSS for Windows release 19.0.0/2010 (IBM-SPSS Inc., Chicago, IL). Continuous variables such as age, and body mass index (BMI) values were presented as Mean ± SD, whereas parity was presented as median value and range. The cumulative event rates (recurrence and death) were calculated by the Kaplan–Meier method, with the time to the first event as the variable.

Results

Patient characteristics are shown in Table 1. The mean age was 43.9 ± 9.9. The mean body mass index was 24.0 ± 3.8 kg/m^2. There were 12 (50%) cases with stage IA and 12 (50%) with stage IC ovarian cancer. The histological types were as follows: serous in 6 (25%), mucinous in 7 (29.1%), endometrioid in 6 (25%), and clear cell adenocarcinoma in 5 (20.8%).

The surgical outcomes are shown in Table 2. The mean operative time was 306.4 ± 98.5 min. The estimated volume of blood loss was 204.2 ± 188.6 mL, and none of the patients required intraoperative blood transfusion. The median numbers of resected pelvic and para-aortic lymph nodes were 20 (range 5–42) and 4 (range 3–8), respectively.

The procedure was successfully completed in all patients without conversion to laparotomy. Intraoperative rupture occurred in 9 patients (37.5%) There were 2 perioperative complications (8.3%) (Table 3). One patient (4.1%) sustained an intraoperative complication, and one patient (4.1%) developed a postoperative complication.

The average duration of hospital stay was 8 days. Of 24 patients, 20 patients (83.3%) were administered platinum-based adjuvant-

Table 1
Characteristics of patients with early-stage ovarian cancer who underwent laparoscopic staging surgery.

Characteristics	Value
BMI (kg/m2), median (range)	24.0 ± 3.8
Age (year), median (range)	43.9 ± 9.9
Stage	
1A	12 (50)
1C	12 (50)
Histologic type	
Serous adenocarcinoma	6 (25)
Mucinous adenocarcinoma	7 (29.1)
Endometrioid adenocarcinoma	6 (25)
Clear cell adenocarcinoma	5 (20.8)
Grade	
1	8 (33.3)
2	1 (4.1)
3	8 (33.3)
Unknown	7 (29.1)

BMI, body mass index; Data are expressed as Mean ± SD or number (%).

Table 2
Surgical outcomes.

Characteristics	Value
Operative time (min)	306.4 ± 98.5
Blood loss (mL)	204.2 ± 188.6
Size of tumor (cm)	12.1 ± 5.6
Intraoperative rupture	
No	15 (62.5)
Yes	9 (37.5)
Washing/ascites cytology	
Negative	20 (83.3)
Positive	4 (16.6)
Lymph nodes retrieved	
Pelvic lymph node	20 (5–42)
Para-aortic lymph node	4 (3–8)
Fertility-preserving surgery	4 (16.6)

Data are expressed as median (range) or number (%).

therapy. The median duration of follow up was 31.5 months. There were no metastases to the trocar site. Two patients (8.3%) developed tumor recurrence. Recurrence-free survival was 83%. There was 1 patient death. OS was estimated to be 95% except a patient who died of other disease (Fig. 1).

Discussion

About 5%–25% of patients with presumed stage I ovarian cancer are upstaged during comprehensive surgical staging to advanced-stage disease by the findings of metastatic lymph nodes, and 30%

Table 3
Postoperative outcomes.

Characteristics	Value
Intraoperative complication	
Bowel perforation	1
Postoperative complication	
Hydronephrosis	1
Postoperative treatment	
None	4 (16.6)
Chemotherapy	20 (83.3)
Days in hospital	8 (3–35)
Deaths	
Died of ovarian cancer	1
Died of other disease	1
Recurrence	2 (8.3)
Median follow-up (month)	31.5 (5–118)

Data are expressed as median (range) or number (%).

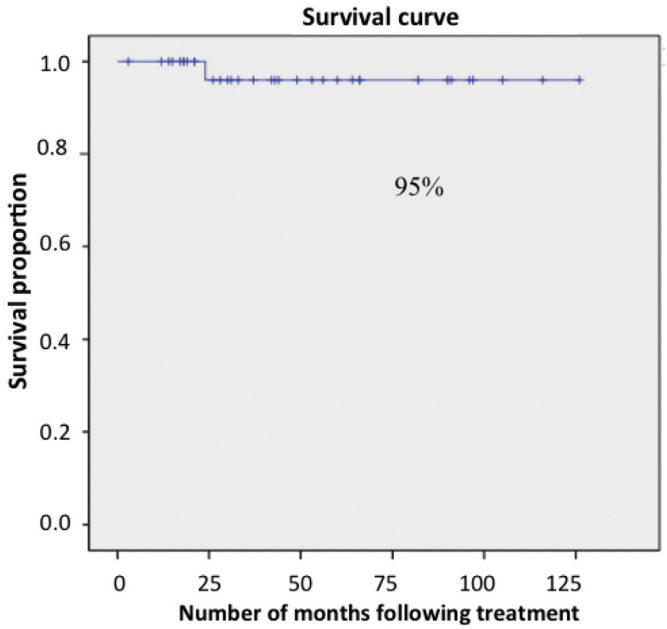

Fig. 1. Overall survival of patients with early-stage ovarian cancer who underwent laparoscopic staging surgery. Kaplan–Meier plot shows that overall survival was 95%.

of these patients are further upstaged by the findings of dissemination to the diaphragm or omentum [18,19]. Traditionally, laparotomy is the standard approach for the surgical staging of patients with ovarian cancer. In 2005, Chi and 2013 Chen et al. reported a study that compared laparoscopy to laparotomy for staging patients with apparent early-stage ovarian and fallopian tube cancer [4,12,20]. They reported lower estimated blood loss, shorter hospital stay, and longer operating time for laparoscopy compared with laparotomy, which confirm the feasibility of laparoscopic surgical staging for ovarian cancer.

Table 4 summarizes the studies published since 2002 on laparoscopic staging surgery for ovarian cancer patients [14,21–32]. Several investigators concluded that laparoscopic staging surgery for selected patients with early-stage adnexal malignancies is safe and feasible when performed by an experienced gynecologic oncologist [21,23,33,34].

In 2010, we reported a retrospective study of stage I epithelial ovarian cancer comparing patients between 1984 and 2006 who underwent either initial laparoscopy followed by subsequent laparotomy (laparoconversion, n = 34) or with straight forward conventional laparotomy (n = 174) [14]. The 5-year OS and recurrence-free survival rates of the laparoscopy patients were 67.4% and 69.5%, and of the laparotomy patients 88.7% and 78.7%, respectively. Since recent decade has seen many progress of laparoscopic treatment of ovarian malignancies in both conceptual and technical evolvement; however, many treatment pitfalls were noted from the viewpoints of today for those included for laparoscopy then, and that made the surgical outcomes in the article relatively worse than reported by other studies [21–32]. Many patients of the ovarian malignancies in that study were not initially operated by the trained gynecologic oncologic endoscopists, and even approximately half the patients did not receive intraoperative frozen-section examination. The phenomenon highly suggested that many encounters of ovarian malignancies could be inadvertent. Subsequently, the malignant lesion could not be handled and excised as precisely an experienced endoscopists, and after laparoconversion surgery, patients might be over-treated which could potentially result in multiple iatrogenic stress and complications,

Table 4
Laparoscopic staging surgical outcomes of patients with early-stage ovarian cancer.

Author, year	Number	Operative time (min)	EBL (mL)	PLN	PALN	Complication (%)		Median follow up (Month)	Recurrence rate (%)	Overall survival (%)
						Intraoperative	Postoperative			
Ditto, 2017	50	207 ± 72	150 ± 53	16.6 ± 7.9	16.7 ± 6.6	0	2	Mean 49.5	14	NR
Gallotta, 2016	60	NR	NR	NR	NR	NR	NR	Mean 38	8.3	89
Lu, 2016	42	200 (150–460)	110 (50–450)	20 (10–35)	8 (4–17)	0	7.1	82 (16–152)	11.9	92.9
Minig, 2016	50	225 (180–240)	200 (200–225)	15 (10–21)	10 (4–15)	6	28	26 (11–39)	12	98
Bogani, 2014	35	335.9 ± 74.7	415 ± 512	22 ± 5.9	10 ± 7	0	2.8	64 (37–106)	11.4	NR
Gallotta, 2014	300	NR				0.3	11	24 (3–145)	8.3	95.2
Koo, 2014	24	192.9 ± 73.5	697.9 ± 396.9	26.8 ± 8.5	17.7 ± 10.1	0	NR	Mean 31	8.3	86.1 (3 year)
Liu, 2014	35	210 ± 18	197 ± 98	NR	NR	0	11.4	NR	5.7	94
Brockbank, 2013	35	210 (90–210)	75 (10–1000)	6 (1–32)	5.6 (1–19)	11.4	2.8	18 (3–59)	5.7	100
Ghezzi, 2012	82	263 ± 81	100 (20–3000)	23 (3–39)	13 (3–43)	1.2	15.8	28.5 (3–86)	7.3	98.8
Schreuder, 2012	25	235 (100–285)	100 (10–1500)	8 (3–31)	6 (2–12)	8	8	Mean 43	20	92
Lee, 2011	26	227.6 ± 105.8	230.4 ± 183.6	23.5 ± 9.3	9.9 ± 7.4	0	7.7	12 (1–42)	0	100
Jung, 2009	24	253.7 ± 65.7	567 ± 170.9	22.5 ± 8.9	11.0 ± 5.8	0	4.1	10 (2–39)	NR	NR
Colomner, 2008	20	NR	NR	18 (14–21)	11.3 (7–23)	0	5	24.7 (1–61)	5	100
Nezhat, 2008	36	229 (59–386)	195 (25–500)	14.84 (0–45)	12.23 (0–53)	0	11.1	Mean 55.9	8.3	100
Park, 2008	19	220.7 ± 82.7	240 ± 228.3	27.2 ± 9.7	6.6 ± 6.2	5.3	5.3	17 (2–40)	0	100
Chi, 2005	20	321 ± 64	235 ± 138	Right Left 6.5 ± 3.9 5.8 ± 2.9	Right Left 3.8 ± 1.8 2.9 ± 1.7	0	0	NR	NR	NR
Leblanc, 2004	42	238 (120–370)	NR	14 (4–27)	20 (7–40)	7.5		54 (8–116)	7.1	97.6
Tozzi, 2004	24	176 (102–306)	NR	19.8 (14–29)	19.6 (5–35)	0	0	46.4 (2–72)	8.3	100
Previous study, 2010	34	NR	NR	NR	NR	NR	NR	NR	29.4	67.4
Current study	24	306.4 ± 98.5	204.2 ± 188.6	20 (5–42)	4 (3–8)	4.1	4.1	31.5 (5–118)	8.3	95

EBL, estimated blood loss; PLN, retrieved pelvic lymph nodes; PALN, retrieved para-aortic lymph nodes; NR, not reported. Data are expressed as median (range) or number (%).

which were not the positive effects to the surgical outcomes. Besides, during that period of time, as endobag has not been emphasized as a must of routine usage, upstaging of the disease and port-site metastasis could occur once unexpected malignancy was encountered. Furthermore, neglection of the intraoperative frozen-section examination would no wander result in inadequate staging, second surgery, and delayed comprehensive treatments. However, all these flaws have been noted in the last decade and overcome greatly nowadays.

In the current series, endobag was used for all patients, and 83% of patients (20/24) received intraoperative evaluation of specimens submitted for frozen section. The operative time, EBL, and the number of retrieved lymph nodes found in this study were similar to those of other reports [21–32]. Comparison with previous study, this series surgery were performed by experienced endoscopic oncologists and all patients received complete surgical staging, which may be the reason of better survival outcomes.

There are concerns about the serious risks involved in using laparoscopic surgery for ovarian cancer, which include immediate upstaging caused by intraoperative rupture of the tumor and the occurrence of port-site metastasis. The size of an ovarian tumor is a primary concern for laparoscopic removal. Specialized devices are needed to remove the tumor while avoiding tumor spillage. However, removal of an ovarian tumor without rupture sometimes cannot be avoided. Intraperitoneal spillage and upstaging from IA to IC had been considered to reflect prognosis [35,36]. Vergote et al. reported on the prognostic factors of 1545 patients with stage I epithelial ovarian cancer. Rupture during surgery had unfavorable impact on disease-free survival [37]. However, Suh et al. reported that surgical rupture has no effect on survival by reassigning stage IC into surgical spillage (IC1), capsule rupture before surgery or tumor on the surface (IC2), and positive cytology results (IC3) [38]. The 5-year OS of patients with IC1, IC2, and IC3 after sub-staging were 92.0%, 85.0%, and 71.0%. These data were reflected new FIGO ovarian cancer staging in 2014. Although the relationship between intraoperative rupture and outcome is unclear, we must try to minimize spillage by various techniques. In our study, rupture and drainage of ovarian cysts were performed within the endobag, and the specimen was removed without spillage of tumor cells.

The rate of occurrence of port-site metastasis is 1%–2% for patients undergoing laparoscopic surgery for malignancies; and most of the reported cases had ascites, advanced-stage ovarian cancer, or primary peritoneal cancer [39–41]. Oliver et al. reported that port-site metastasis occurred in 20 of 1694 patients (1.18%) and 15 of 767 (1.96%) patients who underwent laparoscopic procedures for a malignant intra-abdominal condition or for ovarian cancer, respectively. Of the 20 patients, 19 (95%) had carcinomatosis or metastases to other sites at the time of the port-site metastasis [40]. They suggested that port-site metastasis can be regarded as a surrogate for advanced disease rather than an isolated event or a complication of the laparoscopic procedure.

Advanced disease, the presence of ascites, contamination of the wound from instruments or due to pneumoperitoneum, surgical trauma, and even ischemia of the port site have been reported to increase the risk of implantation [42,43]. Topical application of povidone-iodine to trocar wounds and peritoneal closure have been reported to be effective for preventing metastasis to the port site [44,45].

Though concern about the incidence of port-site metastasis is still controversial, laparoscopic staging surgery of ovarian cancer should be reserved for selected patients with early-stage disease and without peritoneal carcinomatosis. In our previous study, four of 34 laparoscopy patients (11.6%) developed port-site metastasis. The results of that study indicated that age, substage, the type of initial surgical intervention, port-site metastasis, and recurrence had significant impact on OS [14,46]. For all these cases of port-site metastasis, the tumors were removed directly through the cannula, with subsequent recurrence at the port. This latest study evaluated cases where an endobag was used for all ovarian tumors, along with controlled drainage of the cysts and retrieval of tumor under direct vision, which prevented fluid leakage; during follow up, there were no occurrences of port-site metastasis.

The complication rate in our latest study was 8.3% (2/24). One patient sustained an intraoperative perforation of the sigmoid

colon, which was managed by laparoscopy. The hydronephrosis of the patient was caused by a ureteral stricture due to laceration, which was treated by ureterotomy and placement of a D-J stent.

The complication rate of laparoscopic staging surgery for ovarian cancer has ranged from 0% to 17% [21–32]. A Gynecologic Oncology Group study found that laparoscopic surgery for 20% of their patients was converted to laparotomy [47]. There were no conversions to laparotomy in our study, and the complication rate was relatively low. We believe that complications are mostly a result of the inadequate skills and lack of experience of physicians who perform laparoscopic surgery. Although laparoscopic surgery [24, 48] requires specific training for all procedures, there have been few reports on the learning curve of laparoscopic surgery for ovarian cancer. In addition, as mentioned previously, the safety of laparoscopic surgery for ovarian cancer requires not only excellent surgical technique but also careful patient selection.

The OS in our study was 95%, and our data demonstrated that laparoscopic surgery for early stage ovarian cancer is effective and safe. The median follow up was 31.5 months, and 2 patients (8.3%) developed recurrence. Their histological types were clear cell carcinoma and serous adenocarcinoma. Both of them underwent fertility-preserving surgery. A patient who died of the disease had undergone bilateral salpingo-oophorectomy and omentectomy following neoadjuvant chemotherapy. The histological type of the patient's tumor was serous adenocarcinoma. Twenty-four months after treatment, the patient was found to have ascites with peritoneal carinomatosis and metastases to the liver.

In 2009, Nezhat et al. reported the longest mean follow-up, 55.9 months with 36 patients having presumed early-stage adnexal cancers. Three patients (8.3%) developed recurrence, and the OS was 100% [26]. Gallotta et al. reported on the largest study of laparoscopy for early-stage ovarian cancer in 2014, a multi-institutional, retrospective study for early-stage ovarian malignancies [21]. Recurrence and death from disease were documented in 8.3% of the 150 patients who underwent immediate laparoscopic staging and 3.3% of the 150 who underwent delayed laparoscopic staging. The 3-year disease-free survival and OS were 85.1%, and 93.6%, respectively.

Our study was limited because it was a small, retrospective, single-institutional study. A short and small study cannot easily validate the benefits of laparoscopic staging surgery for ovarian cancer. Additional studies are needed to provide information on surgical outcomes and the long-term efficacy and safety of laparoscopic surgery.

In conclusion, laparoscopy provides good visualization of the operative field and enhanced magnification, which allows detection of implants on the surfaces of the peritoneum, liver, and diaphragm. Furthermore, it contributes to earlier recovery, decrease in operative blood loss, and shorter hospital stay, compared with laparotomy. Because of these advantages, laparoscopic staging of early-stage ovarian cancer may be adequate. Surgical treatment by laparoscopy performed by trained gynecologic oncologic endoscopists for selected patients with ovarian cancer is feasible, safe, and effective. Laparoscopic staging surgery for ovarian cancer can be an alternative to laparotomy. More well designed, randomized multicenter trials are required to evaluate long-term survival outcomes.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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