Original Article

Improvement of Prognostic Outcome in Minimally Invasive Surgery for Stage I Epithelial Ovarian Cancer

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Abstract

Objectives: Minimally invasive surgery (MIS) is a limited treatment option for early-stage ovarian cancer. The National Comprehensive Cancer Network® guidelines that salpingo-oophorectomy should be performed with every effort to keep an encapsulated mass intact during removal. We aimed to investigate whether, if tumor rupture was controlled, patients' oncological outcomes for Stage I ovarian cancer would not be worse in MIS. An endobag was prepared and used to prevent the ovarian cancer cells from spilling into the peritoneal cavity. We report a recent 10-year clinical outcome of MIS for ovarian cancer by oncological endoscopists in gynecology.

Materials and Methods: We retrospectively collected clinical data from an electric chart. Collective clinical data included age, body mass index (BMI), operative time (OT), estimated blood loss (EBL), intraoperative rupture (IR), duration of hospital stay (HS), time from the operation date to the first infusion of chemotherapy (TOFC), disease-free survival (DFS), and overall survival (OS) at 5 years. The data were statistically analyzed using EZR.

Results: The median age, BMI, OT, EBL, IR, HS, TOFC, and DFS were 50 years, 23.9 kg/m^2, 363 min, 100 mL, 65 (98%) patients, 7 days, 15 days, and 43.4 months, respectively. The OS was 98%. The data were consistent with those from the past 10 years, except for a tendency toward an increasing trend in the proportion of ruptured tumors during surgery.

Conclusion: Tumor rupture within the prepared endobag during MIS did not affect the oncological outcomes of early-stage ovarian cancer.

Keywords: Frozen section, minimally invasive surgery, prognosis, Stage I epithelial ovarian cancer

Introduction

In 2022, ovarian cancer was the seventh and sixth highest cause of morbidity and mortality, respectively, globally.[1] The standard of care for early-stage epithelial ovarian cancer consists of comprehensive staging surgery and systemic chemotherapy for patients with recurrent risk factors.[2] Open surgery is the standard of care for the surgical treatment of ovarian cancer.[2,3] According to the National Comprehensive Cancer Network® guidelines, minimally invasive surgery (MIS) for ovarian cancer is recommended for selected patients whose tumor is at an early stage and can be performed by a well-trained oncological endoscopist in gynecology.[2]

Chi *et al*. reported that patients with early-stage ovarian cancer can undergo MIS safely and feasibly.[4] The diagnosis of early-stage ovarian cancer may change from an early stage to an advanced stage depending on the postoperative pathological diagnosis.[5] Stage IA disease can also progress to IC1 in cases of intraoperative tumor rupture. Surgical outcomes may influence oncological outcomes in early-stage ovarian cancer.[6] Lee *et al*. reported that a minimally invasive procedure for apparent Stage I ovarian cancer should be performed by a well-trained oncological endoscopist in gynecology.[7-11] The prognosis is determined by pathological

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staging.[12] The prognosis of ovarian cancer is based on surgeons' decisions and institutional factors.[13] This affects not only MIS but also open laparotomy. Adjuvant therapy after primary debulking surgery in advanced epithelial ovarian cancer should be administered within 28 days of the first chemotherapy infusion, and the dose intensity should be maintained.[14,15] In this study, we report improvements in surgical and oncological outcomes in patients with apparent Stage I ovarian cancer who underwent MIS performed by an oncological endoscopist in gynecology between 2014 and 2023. We also provide a clinical review of MIS for ovarian cancer.

Materials and Methods

This was a single-institutional retrospective study. We were provided with patient identification numbers by the medical records, performed an electronic medical record review, and collected clinical data.

Study population

Patients included in the study underwent MIS for Stage I ovarian cancer between January 2014 and February 2023 at our institution. The patients were preoperatively diagnosed with Stage I ovarian cancer. Written informed consent was obtained from all patients who underwent surgery. Patients who met the following criteria were excluded: Stage II or advanced ovarian cancer preoperatively, multiple abdominal surgical procedures at the time of ovarian cancer diagnosis, or suspected dense or deep adhesions to the ovarian tumor before or during surgery. The total number of participants included in the study was 67.

We conducted chart reviews and collected clinical data such as age, body weight, height, stage, tumor histological type, tumor grade, operative time (OT), estimated blood loss (EBL), tumor size, intraoperative rupture (IR) (yes or no), positive or negative washing/ascites cytology, and number of lymph nodes retrieved. Collected data on patient outcomes included intraoperative complications, postoperative complications, postoperative treatment, days of hospital stay (HS), date of first chemotherapy infusion, date of death, date of first recurrence, and the median follow-up period. The study was conducted in accordance with the Declaration of Helsinki and was approved by Chang Gung Medical Foundation Institutional Review Board (approval number: 202400185B0). The surgical procedures and devices used have been described previously.[8-11] Briefly, five trocars were used, including one 10-mm and four 5-mm trocars (Covidien, Boulder, CO, USA, or LAGIS, Taichung, Taipei). A 10-mm laparoscope (KARL STORZ GmbH and Co., KG, Tuttlingen, Germany) was introduced at the midpoint between the umbilicus and the xiphoid process (Lee-Huang point). All the other ancillary ports were inserted laterally. Two experienced surgeons performed all the surgical procedures. The suspected site of the ovarian cancer was retrieved via an endobag (Tyco Healthcare, Taipei, Taiwan) to avoid spillage into the abdominal cavity and contact with port sites. Frozen sections were obtained from all specimens. The most necessary manipulations, such as tumor puncture or drainage, were performed within the endobag. In cases of a large tumor exceeding the size of an endobag, mini-laparotomy was first performed through a 5-cm Pfannenstiel or 3-cm longitudinal umbilical incision. Fluid aspiration from the ovarian tumor was performed carefully to avoid the spillage of tumor cells into the abdominal cavity, as described previously.[7-11] Patients who were diagnosed with malignant ovarian tumors by intraoperative frozen section underwent comprehensive staging surgery, including hysterectomy, contralateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymphadenectomy. In cases of mucinous carcinoma, appendectomy was performed. Patients diagnosed pathologically with risk factors, including high-grade tumor, aggressive histology subtype, substaging not Stage IA, or undergoing fertility-preserving surgery, would be offered adjuvant chemotherapy.

Statistical analysis

All data were analyzed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is available on the website (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html) (R-4.3.3-arm64.pkg) Mac OS X, Apple, USA.[16] The cumulative event rates (recurrence and death) were calculated using the Kaplan–Meier method, with the time to the first event

Table 1: Characteristics

Median age (year)		50	19-85
Median BMI (kg/m^2)		23.9	18.2-42.5
Stage	IA	2	
	IC	65	
	IC1	49	
	IC2	6	
	IC3	10	
Histology	Serous high grade	6	
	Serous low grade	1	
	Endometrioid	15	
	Clear cell	22	
	Mucinous	14	
	Others	9	
Grade	1	16	
	2	4	
	3	33	
	unknown	14	
Total		67	

Characteristics of patients who underwent laparoscopic staging surgery for stage I ovarian cancer. BMI, body mass index

as the variable. Sequencing data were stored on a laboratory computer with electronic encryption, which was accessed only by the clinical doctors and investigators of the study.

Results

The patient characteristics are described in Table 1. The median patient age was 50 years. The median body mass index was 23.9 kg/m^2. There were 2, 49, 6, and 10 cases of Stage IA, IC1, IC2, and IC3 diseases, respectively. The histologic subtypes were high-grade serous, endometrioid, clear cell, and mucinous in 6 (8.9% 6/67), 15 (22.3% 15/67), 22 (32.8% 22/67), and 14 (20.8% 14/67) cases, respectively. Stage IC disease was more than 90% because any intraoperative tumor rupture was diagnosed as Stage IC1, even during specimen retrieval.

Table 2 describes surgical outcomes. The median OT was 363 min. The estimated volume of blood loss was 100 mL, and no blood transfusion was required. The median number of retrieved pelvic and para-aortic lymph nodes was 15.5 (range, 3–34) and 4 (range, 1–12), respectively. This procedure was successfully performed in all the patients. None of the patients converted from MIS to laparotomy. IRs occurred in 65 patients. All patients, except one, were preoperatively prepared for tumor rupture. One patient (1.4%) had an intraoperative ureter injury, which was repaired intraoperatively. Four patients were readmitted after discharge because of urinary retention, ureteral infection, fever, or deep venous thrombosis. The median duration of HS was 7 days. The median duration from the date of MIS to the date of the first chemotherapy infusion was 15 days. The median follow-up duration was 43.4 months. No trocar site metastases were observed. Seven patients experienced recurrence, and one patient died of the disease. The median disease-free survival (DFS) and overall survival (OS) were both 43.4 months [Figure 1]. The differences between

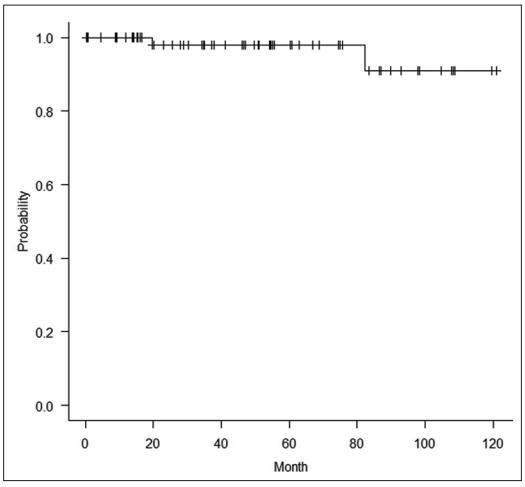

Figure 1: Overall survival. The survival rate at 5 years was 0.98

Table 2: Clinical outcome

Median operation time (min)	363	102-762
Median estimated blood loss (mL)	100	10-1300
Tumor size (cm)	10	3.4-33
Tumor ruptured *		
No	2	
Yes	65	
Lymph node retrieved		
Pelvic lymph node	15.5	3-34 (N 60)
Paraaortic lymph node	4	1-12 (N 19)
Fertility-preserving surgery	8	
Complication		
Conversion	0	
Intraoperative	1	Ureteral injury
Post operative†	4	
Hospital stay (day)	7	1-24
Median time to first date of Chemotherapy (day)‡	15	
Median CTx cycles	6	4-6 cycles
Recurrent case	7	IC1 4, IC2 1, IC3 2
Disease specific death§	1	IC1 1
Median PFS (month)	43.4	0.2-120
Median OS (month)	43.4	0.2-120
Follow up periods (month)	43.4	0.2-120

*The definition of tumor rupture is when it is detected or judged to have occurred at any point during the surgery. †Complications postoperatively occurred in four patients, and the causes were fever, infection, urinary retention, and deep venous thrombosis in one patient each. ‡47 received adjuvant therapy. The treatment starts date ranges from 3 to 184 days. Thirty-five patients were able to begin treatment within 30 days. §One of the stages IC1 patients died due to disease progression.

the past 10 years and the recent 10 years are that the OT, EBL, length of HS, and number of intraoperative complications changed from 306 to 363 min, from 204 mL to 100 mL, and from 8 to 7 days, respectively. Oncological outcomes were consistent between 2006–2014 and 2014–2023, although an increased intraoperative tumor rupture rate and fewer retrieved pelvic lymph nodes were recorded [Table 3].

Discussion

In this study, we included 67 patients who underwent staging surgery for early-stage ovarian cancer. With respect to surgical outcomes, operation time and EBL did not significantly differ from those in previous reports over 10 years; however, the IR rate increased from 37.5% (9/24) to 97.0% (65/67), and the number of retrieved pelvic lymph nodes decreased from 20 to 15 [Table 3].[8] With respect to oncological outcomes, recurrent patients are two patients (8.2%) to seven (10.4%), and death patients were one in both the previous and recent decades. Avoiding inadvertent tumor rupture could slightly affect or improve OS. Early-stage ovarian cancer, especially Stage IA, may change to Stage IC if the tumor ruptures during surgery. In MIS, large ovarian tumors must be operated on in a narrow space, and securing the surgical field is important for

Table 3: Comparison of the Clinical Outcomes

	2002-2014	2014-2023
Case number	24	67
Operative time (min)	306	363
Blood loss (mL)	204	100
Size of tumor (cm)	12.1	10
Intraoperative rupture		
No	15	2
Yes	9	65
Washing/ascites cytology		
Negative	20	42
Positive	4	9
Atypia	0	9
Lymph node retrieved		
Pelvic lymph node	20	15.5
Paraaortic lymph node	4	4
Fertility-preserving surgery	4	8
Conversion	0	0
Intraoperative complication	1	1
Bowel perforation	1	0
ureter injury	0	1
Post operative complication	1	4
Hydronephrosis (UTI)	1	1
Febrile	0	1
Deep venous thrombosis	0	1
Urinary retension	0	1
Postoperative treatment		
None	4	17
Chemotherapy	20	47
Days in hospital (day)	8	7
Disease specific death	1	1
Recurrence	2	7
Median follow up (month)	31.5	43.4

UTI, Urinary tract infection

safe surgery. In addition, in order to remove a large ovarian tumor through a small incision, the tumor must be cut into smaller pieces. Ovarian tumors usually need to be removed without rupturing. However, in staging surgery for Stage I ovarian cancer, the organs are normal, except for the ovarian tumor, and if intraoperative tumor rupture or destruction can be controlled, there are many advantages to performing MIS. Lee *et al*. showed that by performing intraoperative ovarian tumor rupture in a well-prepared state, tumor dispersion can be controlled, and life prognosis further improves.[7] Lee *et al*. reported that the 10-year outcome was improved based on their 20-year experience.[7] It was not a randomized trial; most patients who were not suspected of having malignant tumors preoperatively were in the MIS group, and most did not undergo MIS procedures completely. Most cases were converted to open surgery without MIS, or surgery was rescheduled for another day. Then, Lee *et al*. changed the flow of preoperative diagnosis and surgical operation systems for ovarian tumor patients who would undergo the MIS approach. There are three preparations: first, preparing for an endobag in case of a sudden tumor rupture; second, sending specimens to a frozen section and changing the procedures to staging surgery immediately; and third, performing by a well-trained oncological endoscopist in gynecology.[7] The increased OT may be related to the fact that a frozen section, an intraoperative rapid pathological diagnosis, was performed, and suctioning intratumoral fluid through a small pore in an endobag usually takes time in almost all cases. It is necessary to make a large tumor large enough to remove it from the endobag, but careful manipulation is required to avoid damaging the endobag. Ten years prior to this study, 37.5% of cases had intraoperative spillage, but the oncological prognosis was comparable to that of nonruptured cases, and the overall prognosis was good. Lee *et al*. considered that the suppression of tumor leakage by intra-endobag manipulation affects the prognosis. When removing the tumor from the small incision, great care was taken to place it in an endobag and perform the procedure in a way that prevents the tumor from scattering at this stage. According to conventional wisdom in ovarian cancer surgery, techniques that do not rupture the tumor should be pursued; however, unintentional rupture of ovarian tumors is quite common. A characteristic of laparoscopic surgery is that to remove a large tumor through a small incision, it is necessary to reduce the tumor volume. A hole is made in the tumor at a position that makes it easy to aspirate the internal fluid, and the procedure is performed inside an endobag to prevent scattering of the tumor contents. This reduces tumor volume, expands the surgical field, and facilitates surgical procedures, allowing surgery to be performed safely. Ronsini *et al*. reported that the 3-year and 5-year DFS rates of laparoscopic surgery for early-stage ovarian malignant tumors were 86.1%–100% and 69.5%–91.3%, respectively. They also reported 3-year and 5-year OS rates of 92%–100% and 67.4%–98%, respectively.[17] Tantitamit and Lee reviewed the laparoscopic management of early-stage ovarian malignancy, which mentioned the risk of laparoscopic procedures, port-site metastasis, intraoperative tumor rupture or spillage, and the effect of pneumoperitoneum on tumor spreading. Improper tissue retrieval techniques, such as directly contacting the tumor with the incision or squeezing the tumor, may lead to metastasis, although port-site metastasis is usually seen in advanced-stage patients. Tumor rupture remains an important issue during laparoscopic surgery, as it may lead to the spread of tumor cells and predict worse outcomes in terms of recurrence and survival. Currently, no conclusions regarding prognosis can be established from intraoperative shedding of tumor cells in prospective studies; therefore, every effort should be made to reduce the incidence of contamination.[18] Garcia *et al*. reported single-institutional data comparing laparoscopic and open laparotomies. The surgical outcomes were consistent for both procedures, except for OS. The data

included patients with Stage II disease, and more than half of the patients had high-grade disease. In their study, the laparoscopic approach was shown to be feasible for early-stage ovarian cancer.[19] Wu *et al*. reported a 5-year OS rate of 95%.[8] In this study, the OS rate at 5 years was 98%. Our surgical strategy is feasible for early-stage ovarian cancer in accordance with our oncological outcomes.

Tumor rupture is, to some extent, inevitable in most ovarian cystic tumors with dense adhesions or large sizes.[20] This occurs not only with laparoscopic approaches but also in laparotomies.[6] Ghirardi *et al*. reported a preoperative risk of tumor rupture, and most patients in our study cohort were at risk of rupture.[20] Tumor rupture itself is associated with a poor prognosis; therefore, preoperative preparation and appropriate procedures are crucial to avoid tumor spillage into the abdominal cavity. Based on 10 years of experience, inevitable tumor rupture should be controlled to minimize spillage prior to rupture.[7] Lee *et al*. reported that preparation for rupture and a careful procedure for port-site metastasis may prevent tumor cell spillage or tumors from contacting the port site using an endobag. If the tumor size exceeds that of the endobag, a mini-laparotomy is considered for safer aspiration and tumor size reduction. In a recent study of 67 cases who underwent MIS for ovarian cancer from 2014 to 2023, one patient was not initially suspected of ovarian cancer. However, abnormal tissue was noted leaking from the cystic tumor, and an intraoperative frozen section revealed malignancy.

Ovarian cancer is not definitively diagnosed until specific tumor tissues are histopathologically proven to be malignant. Frozen sections are critical for the diagnosis of early-stage ovarian cancer. Palakkan *et al*. reported the accuracy and usefulness of this modality, with the malignant tumor showing 90% sensitivity, 97% specificity, 90% positive predictive value, and 97% negative predictive value with frozen sections.[21] A case in which metastatic ovarian tumors from colorectal cancer were diagnosed through intraoperative rapid diagnosis of a ruptured ovarian tumor and laparoscopic sigmoidectomy was performed, followed by appropriate chemotherapy.[22] Preoperative imaging evaluation and surgical planning are important for early-stage ovarian cancer, especially in patients undergoing MIS. However, surgeons should consider dissecting tumors without rupture first because Stage IA has a better prognosis than Stage IC1, although both Stages IA and IC1 are the preferred diagnoses.[12] The number of retrieved pelvic lymph nodes decreased, but oncological outcomes, DFS, and OS did not deteriorate. With respect to lymphadenectomy in advanced ovarian cancer, Harter *et al*. reported that prognostic outcomes for patients with advanced ovarian cancer were not influenced by whether the patients had normal-sized regional lymph nodes or had undergone systematic lymphadenectomy.[23] Patients in Stage I were upstaged from Stage I to Stage IIIA when metastatic lymph nodes were pathologically noted even with normal-sized lymph nodes. In this study, none of the patients were suspected of having lymph node metastasis preoperatively. In addition, a decrease in the number of harvested lymph nodes did not appear to affect the oncological outcomes. This study was conducted before the introduction of poly (ADP-ribose) polymerase inhibitors (PARPi) to the adjuvant setting and the benefit of adding PARPi as maintenance therapy after first-line chemotherapy should be considered in advance-stage patients with germline or somatic BRCA mutations or those with homologous recombination deficiency.[24,25] Patients diagnosed with apparent early-stage ovarian cancer can undergo MIS by well-trained oncological endoscopists in gynecology. Preoperative evaluation, preparation for endobags, and frozen sections for diagnosis are mandatory procedures. The oncological outcomes of Stage IC1 ovarian cancer rupture during surgery are not inferior to those of Stage IA ovarian cancer.

Strengths and weaknesses

The limitations of this study include its retrospective and single-institutional design, with MIS performed by well-trained surgeons. While Lee *et al*. reported favorable outcomes of MIS, the study emphasizes its use by a well-trained oncological endoscopist in gynecology.[7] Although this was a retrospective study conducted at a single institution with a limited number of cases, it is believed that a favorable oncological prognosis was achieved due to a thorough understanding of ovarian cancer and advanced surgical techniques based on in-depth knowledge of gynecological tumors and more than 30 years of experience. In the future, we believe that if we can compare the oncological prognosis of MIS and open surgery in cases where early-stage ovarian cancer is strongly suspected and there is no strong adhesion to surrounding organs and prove noninferiority, it will be possible to generalize this method. This study demonstrates that patients diagnosed with suspected early-stage ovarian cancer can safely undergo MIS by oncological endoscopists in gynecology. Preoperative evaluation of patients with early-stage ovarian cancer, preparation inside the endobag, and rapid intraoperative diagnosis are the key steps for performing MIS. The oncological outcomes of Stage IC1 ovarian cancer, in which tumor scattering was avoided by intentional rupture in the endobag during surgery, did not differ from those of Stage IA ovarian cancer.

Conclusion

Although an ovarian tumor will inevitably rupture during surgery, poor prognosis can be prevented if preparations are made. Laparoscopic comprehensive staging surgery is

feasible and safe for selected Stage I ovarian cancers and can be performed by a well-trained oncological endoscopist in gynecology.

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Author contributions

Conceptualization, K.O. and CL.L.; Methodology, K.O.; Software, K.O.; Validation, K.O., CL.L., and KG.H.; Formal Analysis, K.O.; Investigation, K.O.; Resources, K.O.; Data Curation, K.O.; Writing—Original Draft Preparation, K.O.; Writing - Review & Editing, K.O.; Visualization, K.O.; Supervision, K.O.; Project Administration, K.O.; Funding Acquisition, CL.L. All authors have read and agreed to the final version of the manuscript.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Conflicts of interest

Prof. Chyi-Long Lee and Dr. Kuan-Gen Huang, an editorial board member at *Gynecology and Minimally Invasive Therapy*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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