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Original Research

Usefulness of laparoscopic restaging surgery for patients diagnosed with apparent early ovarian/fallopian tubal cancer by a prior surgery, a case control observational study in a single institute in Japan

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Summary

This study aimed to demonstrate the feasibility, safety, and short-term oncological outcomes of laparoscopic restaging surgery for patients diagnosed with apparent early ovarian/fallopian tubal cancer by a prior surgery in Japan. A total of 22 patients with apparent early stage ovarian/fallopian tubal cancer underwent laparoscopic restaging surgery. Surgical results and oncological outcomes were retrospectively analyzed. The diagnosis of apparent early stage ovarian/fallopian tubal cancer was determined by prior laparoscopic or laparotomic surgery in 15 cases and 7 cases, respectively. The apparent stages IA, IC, and II were observed in 10, 10, and 2 cases, respectively. The average operation time and estimated blood loss was 266.7 $\pm$ 85.7 minutes and 252 $\pm$ 388.5 mL, respectively. The average total number of harvested lymph nodes was 88.2 $\pm$ 24.4. Up-staging was found in 3 cases (13.6%), 1 case of IIIA1(ii) and 2 cases of IIIB. Lymph node metastasis was detected in 2 cases (9.0%). Intra- and postoperative complications (Clavien-Dindo classification $\geq$ III) occurred in 4 cases (18.1%). Three patients with recurrence were found during the median observation period of 17 months. All of these patients were diagnosed as stage III during restaging surgery. No recurrence was found in cases of stage I or II. Our study demonstrates that laparoscopic restaging surgery for early stage ovarian/fallopian tubal cancer is feasible and safe, and oncological outcomes are comparable to conventional staging surgery. Further large-scale randomized control studies are necessary to confirm the non-inferiority of laparoscopic restaging surgery compared with open surgery.

Key words: Ovarian cancer; Laparoscopic surgery; Staging surgery; Laparoscopic lymphadenectomy.

Introduction

Ovarian cancer has the poorest prognosis among gynecological malignancies in developing countries. Worldwide, in 2018, 295,414 new cases of ovarian cancer were diagnosed and about 184,799 deaths from ovarian cancer occurred in the same year [1]. In Japan the incidence of ovarian cancer is annually increasing and over 10,000 ovarian cancer patients were counted in 2019 (https://ganjoho.jp/reg-stat/statistics/stat/short-pred.html). Ovarian malignancy is sometime unexpectedly found during the surgical removal of an ovarian tumor presumed as benign. The first strategy for ovarian cancer is strongly recommended to be an exploratory laparotomy to diagnose the pathological staging. This includes hysterectomy, bilateral oophorectomy, omentectomy, and para-aortic and pelvic lymphadenectomy leading to the application of adjuvant chemotherapy and a precise prediction of prognosis. However, an exploratory laparotomy requires a large abdominal incision and severe restrictions for post-operative activities. Currently, minimally invasive surgery (MIS) is widely applied for gynecological malignancies, and endometrial cancer especially has been well-examined in large-scale randomized control studies [2]. The studies demonstrated that MIS for early-stage endometrial cancer was associated with reduced surgical blood loss, lower complication rates, shorter hospital stay, and non-inferiority of oncological outcomes compared with open surgery. A similar staging surgery for ovarian cancer is highly recommended, particularly for early endometrial cancer, and due to evidence being produced, surgeons are now shifting to MIS. Therefore, in terms of early ovarian cancer, it may be possible that restaging surgery by MIS would be useful rather than open surgery. However, MIS

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for early stage ovarian malignancy remains controversial. Ovarian/fallopian tubal cancer has some unique biological behaviors, e.g., disseminated peritoneal disease and tumor rupture during surgical removal. Disseminated disease might require careful surgical exploration in the peritoneal cavity to be detected. Some retrospective studies have demonstrated the non-inferiority of MIS in detecting disseminated lesions, compared with laparotomy [3]; however, no randomized prospective study has been performed. In terms of the possibility of an ovarian/fallopian tubal cancer tumor rupturing upon surgical handling, how much it would affect the MIS is still unknown and again would require further investigation such as a randomized prospective study. In the application of MIS for early stage ovarian/fallopian tubal cancer, these two concerns should be separately considered.

This study aimed to demonstrate the feasibility, safety, and short-term oncological outcomes of laparoscopic restaging surgery for patients diagnosed with early ovarian/fallopian tubal cancer during a prior surgery.

Methods

Patients and data collection

Patients diagnosed with apparent early stage ovarian/salpingo-tubal cancer who had undergone laparoscopic staging surgery at Yokohama City Citizen's Hospital between March 2016 and December 2019 were entered into this study. The institutional review board (IRB) approval for this study was obtained (accepted number 15-06-02). The diagnosis of International Federation of Gynecology and Obstetrics (FIGO 2014) stage I and II ovarian/fallopian tubal cancer was obtained by prior surgical removal of an ovarian or fallopian tubal tumor. The prior surgeries the patients underwent were laparoscopic surgery or laparotomy by general gynecologists in our institute or other hospitals.

The pathological diagnosis for all patients, including the patients diagnosed by the prior surgery at other hospitals, were confirmed by pathologists in our institute. The clinical data of patients who underwent prior surgery in other hospitals were carefully collected including the tumor markers, initial size of tumor, surgical procedure, intraoperative rupture, and initial intraperitoneal cytological findings. Enhanced computed tomography (CT) imaging and magnetic resonance imaging (MRI) confirmed neither metastatic lesion nor peritoneal dissemination before the restaging surgery. For patients with obvious retroperitoneal lymph node swelling or suspicion of disseminated peritoneal disease, laparoscopic restaging was not done. Information on the laparoscopic restaging surgery for ovarian/fallopian tubal cancer was provided to the individual patient in accordance with ethics committee guidance in our institute and consensus was obtained.

Surgery

Laparoscopic surgical restaging was carried out within 4 weeks of the prior surgery. Laparoscopic restaging surgery included total simple hysterectomy, salpingo-oophorectomy, and omentectomy, if they remained, and cytological sampling of peritoneal fluid or washing. In all cases, paraaortic and pelvic lymphadenectomies were required. Paraaortic lymphadenectomy, including infrarenal lymph nodes, was performed by the laparoscopic extraperitoneal approach. The procedure for laparoscopic paraaortic lymphadenectomy by the retroperitoneal approach for gynecological malignancy was firstly described by Vasilev and McGonigle (1996) [4] and has subsequently been modified [5]. Briefly, the patients were placed in a supine position, and a 12-mm trocar was inserted into the peritoneal cavity through an incision made in the umbilical site. CO_2 was subsequently insufflated at a pressure of 10 mmHg. A skin incision was made medial to the left anterior iliac spine in the midclavicular line, and Croce forceps were slid between the peritoneum and fascia transversalis and carefully separated from the umbilical port under laparoscopic observation. Subsequently, the 12-mm trocar was placed from the incision, and CO_2 was insufflated into the primary cavity generated between the peritoneum and fascia transversalis under 10 mmHg of pressure. Under endoscopic observation of the retroperitoneal space, the second (5-mm) trocar was inserted under the left costal arch, and the third trocar (5-mm) was inserted between the first and the second trocars. The fourth (12-mm) trocar was placed at a 3-cm inner and 4-cm caudal position. The retroperitoneal cavity was widened to expose the bilateral common iliac arteries, abdominal aorta, vena cava, and left renal vein. Lymphadenectomy was started from the left side of the aorta and removed en bloc. Subsequently, the sacral area, the right side of the vena cava, and the area between the aorta and vena cava were also removed en bloc. The removed tissues were placed in plastic bags and collected after hysterectomy through the vagina. A final view of the entire para-aortic lymphadenectomy is shown in Figure 1. Subsequently, all ports were inserted into the peritoneal cavity, and two additional 5-mm trocars were inserted into the peritoneal cavity in the right and medial part of the lower abdomen at the level of the anterior superior iliac spine. Extra-iliac lymph nodes, obturator lymph nodes, and internal inguinal lymph nodes were resected en bloc. Subsequently, simple partial omentectomy, hysterectomy, and bilateral oophorectomy were additionally performed, when they were remained. In 2 cases of patients who had their uterus and bilateral adnexal organs removed in the prior surgery, both paraaortic and pelvic lymphadenectomy were performed by the extraperitoneal approach. Follow-up was carried out at 2- or 3- months intervals, depending on the patients. The observation period was defined as the period from the staging surgery to the patient follow-up. Data from 22 patients were retrospectively collected from medical records and analyzed.

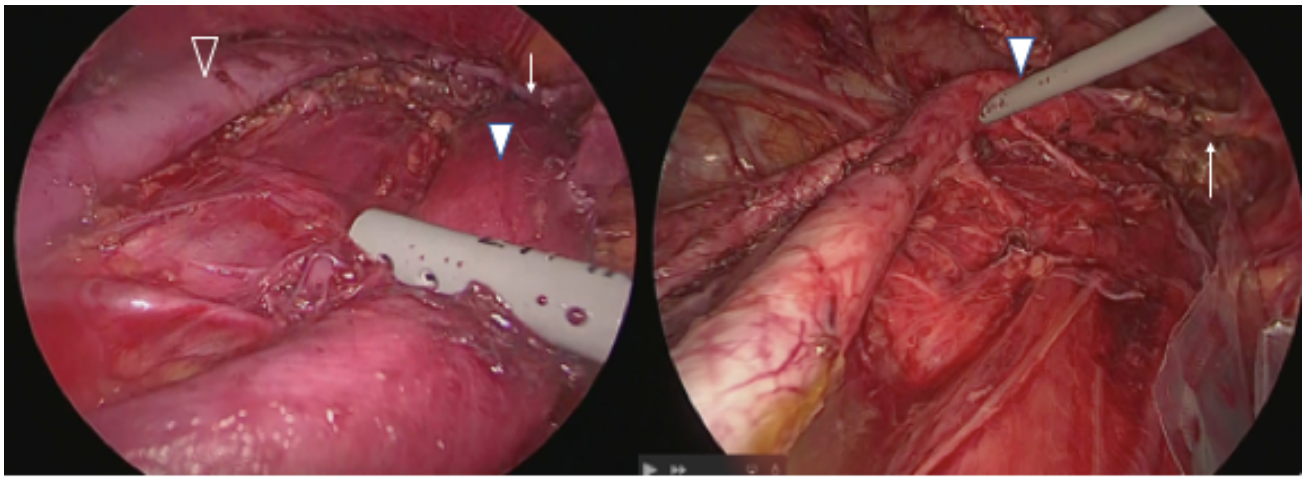

Figure 1. — A final view of a laparoscopic extraperitoneal paraaortic lymphadenectomy. Closed arrowhead: aortic artery, opened arrowhead: vena cava, arrow: left renal vein.

Results

A total of 22 patients, including a single fallopian tubal cancer and 21 ovarian cancer patients, were enrolled in this study. Individual patient characteristics are described in Table 1. The mean age and body mass index of patients was 52.0 years old and 20.9 kg/m^2, respectively. A total of 15 cases were diagnosed as apparent early stage ovarian/fallopian tubal cancer by prior laparoscopic salpingo-oophorectomy, and 7 cases were diagnosed by prior laparotomic surgery. Four patients underwent hysterectomy and bilateral salpingo-oophorectomy and 3 of these individuals had been diagnosed as border line malignant ovarian tumor or benign ovarian tumor by frozen section during the prior surgery. The apparent stages IA, IB, IC, and II were diagnosed in 10, 0, 10, and 2 cases, respectively. Endometrioid carcinoma, high grade serous carcinoma, clear cell carcinoma, and other pathological types were diagnosed in 7, 5, 6, and 4 patients, respectively. The average adnexal tumor size was 113.8 mm.

Surgical results are shown in Table 2. The average operation time and estimated blood loss was 266.7 minutes and 252 mL, respectively. The average number of harvested lymph nodes was 38.8 in the pelvic area and 47.4 in paraaortic area. Up-staging was found in 3 cases, whose diagnosed stages were IIIA1 (ii) (n = 1) and IIIB (n = 2). Intraoperative complications, classified over Clavien-Dindo III, occurred in one case where there was small intestine injury and a shift to open surgery was required. Post-operative complications were seen in 3 cases, a case with infectious lymphocele that required trans-abdominal drainage, a case with stenosis of the right external iliac artery that required permanent intra-arterial stenting, and a case with hydronephrosis that required a temporal double-J ureteral stent.

Adjuvant chemotherapy, which configurated with paclitaxel (180 mg/m^2) and carboplatin (AUC6.0), was performed through 4-6 cycles in 16 cases and bevacizumab was not administrated in any cases. Chemotherapies in any cases were applied within 3 and 4 weeks after the surgery. only in a case, chemotherapy was delayed to 6 weeks, who was shifted to open surgery due to intestinal injury. Adjuvant chemotherapy was omitted in 6 patients with stage IA low grade carcinoma. Three patients with recurrence were found during the median observation period of 17 months. All of these patients were diagnosed as stage III by the restaging surgery. No recurrence was found in patients with stage I or II ovarian/fallopian tubal cancer during the observation period. Individual cases of recurrence are summarized in Table 3.

Discussion

Ovarian cancer behaves differently than other cancers. For example, disseminative growth in the peritoneal cavity is common, compared to endometrial cancer and cervical carcinoma, and capsule rupture tends to occur during ovarian tumor surgery. Therefore, several issues remain in staging using minimally invasive procedures for early stage ovarian cancer. These include: (1) the possibility of insufficient intraperitoneal observation and detection rate for upper stage disease, (2) the possibility of worse oncological outcomes compared with laparotomic procedures, and (3) the possible rupture of tumor capsules during laparoscopic handling. Our study demonstrated that laparoscopic restaging surgery for early stage ovarian and fallopian tubal cancers was feasible and safe. Furthermore, the up-stage detection rate and oncological outcomes seemed to be comparable to conventional staging surgery.

To date, there have been a handful of retrospective studies regarding surgical and oncological outcomes in laparoscopic staging for early stage ovarian cancer. These studies, including over 20 patients with early stage ovarian cancer, are summarized in Table 4. The surgical time, estimated blood loss, conversion rate to open surgery, and complication rate in our study were shown to be similar to those of previous reports. Furthermore, there have been several

Table 1. —*Patient characteristics.*

No.	Age (year)	BMI (kg/m^2)	Gravida	Parity	Prior surgery	origin of tumor	tumor size (mm)	CA125	apparent FIGO stage	Histological type
1	66	20.6	2	2	LpSO	f	38	20.8	IA	HGSC
2	34	23.9	0	0	LpSO	o	50	659.8	IC 3	LGSC
3	53	20.9	0	0	LpSO	o	70	160.6	IA	HGSC
4	64	22.1	2	2	ASH/LSO	o	109	836.3	IIA	HGSC
5	46	20.9	2	1	LpSO	o	41	505.8	IC1	HGSC
6	70	19.6	2	2	LSO	o	60	365.7	IIB	MC
7	59	23.1	3	2	LpSO	o	54	67.2	IA	EC grade1
8	55	21.3	2	2	LSO	o	128	364.8	IC1	EC grade1
9	65	22.9	0	0	ASH/LSO/OMT	o	240	18.9	IA	MC
10	43	17.8	0	0	LpSO	o	193	21.7	IC1	SCC
11	52	20.3	0	0	ASH/LSO/OMT	o	64	9.1	IA	CCC
12	44	18.9	2	2	LpSO	o	78	120.1	IA	EC grade1
13	25	18.5	0	0	LpSO	o	85	91.2	IC1	EC grade3
14	50	25.5	2	2	LpSO	o	61	94.4	IC 3	CCC
15	65	17.7	2	2	LSO	o	150	38	IA	CCC
16	48	19.8	2	2	LpSO	o	73	24.4	IA	CCC
17	50	18.9	2	2	LpSO	o	79	13.5	IC1	HGSC
18	50	20.8	1	1	LpSO	o	42	14.8	IC 3	CCC
19	55	18.2	0	0	LpSO	o	81	24.2	IC 2	EC grade1
20	43	23.0	2	2	LpSO	o	47	120.1	IA	EC grae2
21	52	25.5	0	0	LpSO	o	33	16.7	IA	EC grade1
22	37	19.7	0	0	ASH/LSO/OMT	o	260	35.2	IC3	CCC
Mean (± SD)	52.0 (± 11.0)	20.9 (± 2.3)	1.25 (±1.03)	1.17 (± 0.91)			113.8 (± 34.6)			

LpSO; laparoscopic salpingo-oophorectomy, LSO; laparotomic salpingo-oophorectomy, ASH; abdominal simple hysterectomy, OMT; omentectomy, HGSC; high grade serous carcinoma, LGSC; low grade serous carcinoma, MC; mucinous carcinoma, EC; endometrioid carcinoma, CCC; clear cell carcinoma, SCC; squamous cell carcinoma. SD; standard deviation.

retrospective studies comparing surgical results between a laparoscopic procedure and open surgery for the staging surgery in early stage ovarian cancer [6-11]. The average surgical time in these studies was reported to be 200-275 min for open surgery and 209-337 min for laparoscopic surgery. The estimated blood loss was reported to be 345-568 mL in open surgery and 197-250 mL in laparoscopic surgery. In all of these retrospective comparative studies, blood loss tended to be lower in laparoscopic surgery than in open surgery. Again, in our study, the operation time and the estimated blood loss were similar to or lower than those of previous reports.

The total harvested lymph nodes in our study, including paraaortic lymph nodes, was 88 on average, which is higher than in previous reports, even though the surgical time and estimated blood loss in our study were comparable. It should be noted that the count of harvested paraaortic lymph nodes included lymph nodes in the common iliac and sacral areas. One study reported that the number of resected lymph nodes may be a marker measuring the quality of the surgical staging for ovarian cancer [22]. Because of this, it is important to resect enough lymph nodes during staging, even with laparoscopic surgical staging.

The intra- and postsurgical complication rate in our case series was 18.1% (4 cases), which is slightly higher than other reports. One reason for the difference might be that there are various definitions of surgical complications in each report. Another reason could be that the surgical complications in our study were due to restaging surgery after previous surgery. In three of these cases, salpingo-oophorectomy was carried out under laparoscopy or laparotomy, and in another case, salpingo-oophorectomy and simple hysterectomy were carried out under laparotomy. In two of these cases, severe intraperitoneal adhesion was present due to the previous open surgeries. The transition to open surgery was required in one of these patients due to intestinal injury during the laparoscopic procedure, and an extraperitoneal approach for laparoscopic pelvic lymphadenectomy was required in the remaining case. In the other two cases of complications, severe fibrotic change and adhesion between the ureter and iliac artery was observed, which required adhesiolysis of the ureter and common iliac

Table 2. — *Surgical results.*

No.	Operation time (min)	Estimated blood loss (ml)	Hospital stay (day)	Total number of lymph nodes removed	Pelvic nodes/para aortic nodes	Positive lymph node	Cytology of peritoneal cavity	FIGO stage	Complication (Clavien-Dindo ≥ III)
1	380	220	6	62	41/21	no	negative	IA	
2	372	100	5	109	69/40	yes	positive	IIIB	
3	371	150	5	116	50/66	no	negative	IA	
4	341	150	7	95	56/39	no	positive	IIA	infectious lymphocele
5	348	50	6	84	39/45	yes	negative	IIIA1(ii)	
6	326	200	7	58	19/39	no	negative	IIB	external iliac artery stenosis
7	260	250	8	95	42/53	no	negative	IA	
8	449	570	18	60	19/41	no	negative	IC1	bowel injury, transition to open surgery
9	255	0	6	116	42/74	no	negative	IA	
10	222	150	6	65	33/32	no	negative	IC1	
11	83	0	6	95	40/55	no	negative	IA	
12	239	400	6	84	38/46	no	negative	IA	
13	223	650	11	86	41/45	no	negative	IIIB	
14	284	100	5	51	33/18	no	positive	IC3	
15	195	50	8	92	36/56	no	negative	IA	
16	265	275	8	69	34/35	no	negative	IA	
17	257	150	6	103	40/63	no	negative	IC1	
18	197	50	5	125	46/79	no	positive	IC3	hydroureter
19	209	50	7	87	46/57	no	negative	IC2	
20	243	200	6	134	46/77	no	negative	IA	
21	194	0	5	106	46/70	no	negative	IA	
22	155	100	5	74	46/28	no	negative	IC3	

Table 3. — *Individual case with recurrence.*

Individual case No.	Age	FIGO stage (2014)	TNM	Pathological type	Disease free period (month)	Site of recurrence	Follow up time (month)	Current status
2	34	IIIB	pT3bN1M0	HGSC	19	peritoneum	45	NED
5	46	IIIA1 (ii)	pT1c1N1M0	HGSC	16	Lymph node (326a1)	36	NED
13	25	IIIB	pT3bN0M0	EM G3	12	peritoneum	16	NED

HGSC: high grade serous carcinoma, EM G3: endometrioid carcinoma grade 3, NED: no evidence of disease.

vessels for pelvic lymphadenectomy. This may have been caused by hydroureter and stenosis of the iliac artery. The rate of intra-and postoperative complications was higher than in our previous report on laparoscopic staging surgery for endometrial cancer, which reported a 9.1% complication rate [23]. Surgeons should be careful when carrying out laparoscopic restaging after laparotomic surgery, even for a simple salpingo-oophorectomy. The impact of perioperative complications on starting adjuvant chemotherapy was trivial; in one patient who needed shifting to open surgery, chemotherapy was delayed by two weeks. Even considering the above situations, however, laparoscopic restaging surgery for early stage ovarian/tubal cancer patients was both feasible and safe.

The most complex part of the laparoscopic surgical procedure for restaging in early stage ovarian/fallopian tubal cancer is the paraaortic lymphadenectomy, which has previously been performed using extra-peritoneal or trans-peritoneal approaches. Laparoscopic para-aortic lymphadenectomy by the retroperitoneal approach, first described by Dargent *et al*. (2000) [5], was modified and applied in our extra-peritoneal procedure. The retroperitoneal approach has several benefits over the transperitoneal approach; for example, the bowels need not be disturbed, and the patient need not be in the Trendelenburg position. A recent systematic review and meta-analysis indicated that the retroperitoneal approach was associated with a shorter operating time and fewer complications and could harvest more lymph nodes compared to the transperitoneal approach in laparoscopic para-aortic lymphadenectomy [24]. Furthermore, when disseminated peritoneal disease or positive peritoneal cytology exists. non-opening of the peritoneum

Table 4. — *Published studies on laparoscopic staging of early stage ovarian cancer.*

Author (reported year)	n	Mean OP time (min)	Mean EBL (mL)	Lymph node count PLN/PAN	Hospital stay (days)	Conversion rate n (%)	Complication rate n (%)
[12]	24	176	N/A	19.4/19.6	7	0 (0%)	4 (16.7%)
[13]	42	238	N/A	14/20	3.1	0 (0%)	3 (7.1%)
[14]	20	321	235	12.3/6.7	3.1	0	0
[15]	20	223	N/A	18/11.3	3	1 (5%)	1 (5%)
[16]	36	222	195	14.8/12.2	2.4	0 (0%)	4 (11%)
[17]	24	253	567	22.5/11.0	N/A	0 (0%)	0
[18]	26	228	230	23.5/9.9	6.4	1 (3.8%)	2 (7.7%)
[19]	25	235	100	8/6	4	0	4 (16%)
[7]	82	263	150	23/13	3	0 (0%)	14 (17%)
[20]	35	210	75	6/5.6	2	2 (6%)	5 (14%)
[11]	300	320	150	20/10	N/A	27 (9%)	41 (13.7%)
[21]	24	306	204	20/4	8	0 (0%)	2 (8.3%)
Current study	**22**	**266 ± 85.7**	**252 ± 388.5**	**38.8 ± 12.6/ 47.4 ± 18.2**	**6.8 ± 2.8**	**1 (4.5%)**	**4 (18.1%)**

Author (reported year)	Upstaging rate n (%)	Recurrent rate n (%)	Mean follow up time (month)	Overall survival (%)
[12]	5 (20.8%)	2 (8.3%)	46.4	100%
[13]	8 (19%)	4 (9.5%)	54	97.6%
[14]	2 (10%)	N/A	N/A	N/A
[15] †	4 (20%)	1 (5%)	24.7	100%
[16]‡	7 (35%)	6 (16.7%)	55.9	100%
[17]	10 (4.1%)	1 (4%)	10	N/A
[18]	10 (3.8%)	0	12	100%
[19]	8 (32%)	2 (8%)	43	92%
[7]	21 (25%)	6 (7.3%)	28.5	98.8%
[20]	8 (24%)	2 (5.7%)	18	100%
[11]	48 (16%)	25 (8.3%)	24	96.7%
[21]	0	2 (8.3%)	31.5	95%
Current study	**3 (13.6%)**	**3 (13.6%)**	**17 (3-42)***	**100%**

*Mean ± SD, *median (range), OP; operation time, EBL; estimated blood loss, N/A; not available, †Including 7 low-malignant-potential tumors, ‡Including 11 low-malignant-potential tumors,[c]Including 4 low-malignant-potential tumors.*

in the upper abdomen could prevent the scattering of cancer cells into the retroperitoneal space. It would be easier to apply the extra-peritoneal approach for ovarian/fallopian tubal cancer patients than for endometrial cancer patients, because ovarian/fallopian tubal cancer patients have lower rates of obesity than endometrial cancer patients.

In our study, out of the 22 patients who were diagnosed with apparent stage I or II ovarian/fallopian tubal cancer, three patients (13.6%) had upstaged to FIGO stage III by laparoscopic restaging surgery. The results of our study were almost consistent with previous publications (Table 4). On the other hand, it was reported that the ratio of detection for higher stages by laparoscopic staging surgery in apparent early stage ovarian cancer was 21.1-24.0% in the comparative studies with open surgery [6, 25, 10], which was higher than in our study. In these previous reports, patients with laparoscopic restaging surgery made up 33.3-40% of the total patients who underwent laparoscopic staging surgery. Bae *et al*. (2015) [26] reported on 14 patients who underwent laparoscopic restaging surgery for unexpected ovarian malignancy. In their report, they detected four cases (28.6%) of upstaging, including one case of > 2 cm peritoneal metastasis and one case of contralateral ovarian metastasis, which may have been detected under a carefully performed prior surgery. Reports addressing restaging by open surgery for apparent early ovarian cancer patients demonstrated that the up-stage rate was 16-30% [27, 28], which is higher than the up-stage rate in our study. A reason for this may be careful exploration of the peritoneal cavity during the prior surgery. In our study, patients with macroscopic peritoneal dissemination primarily underwent laparotomic staging surgery, rather than laparoscopic restaging surgery. This means that diseases newly detected by restaging surgery could be microscopic omental and peritoneal metastasis and lymph node metastasis, unless there was oversight during the prior surgery. Unexpected ovarian malignancy was detected in less than 1% of premenopausal and in 3% of menopausal females during laparoscopic surgery [29]. Despite the low frequency of unexpected ovarian malignancy, careful exploration of

the peritoneal cavity, including the upper abdomen, is essential to prevent overlooking metastasis while performing laparoscopic surgery, even in a patient with suspected benign gynecological disease. Retroperitoneal lymph node metastasis was detected in two cases (9.1%) in our study. The frequency of regional lymph node metastasis was 7.2% and 11.4% in patients with stage I and stage II ovarian cancer, respectively [30]. Considering this consistency, the sensitivity of detection for metastatic retroperitoneal lymph nodes is comparable to open surgery.

In our study, three cases (13.6%) of recurrent disease were found, with no deaths from those diseases. The previous case series reported the almost similar rate of recurrence rate and overall survival (Table 4). To date, in several retrospective comparative studies, it has been demonstrated that there is no significant difference in the recurrence rate in laparotomy and laparoscopic staging surgery for early ovarian cancer. Gallotta *et al*. (2016) [31] investigated the oncological outcomes in early stage epithelial ovarian cancer patients, comparing 60 cases treated by laparoscopic staging and 120 cases treated by open surgery. They reported that both the progression-free survival and overall survival were not significantly different between groups. In their report, recurrence was found in five cases (8.3%) of the laparoscopic staging group, four cases with peritoneal dissemination, and a single case with parenchymal organ recurrence. No port site metastasis was found.

Furthermore, three meta-analyses for laparoscopic surgery in early stage ovarian cancer have been conducted. Park *et al*. (2013) [32] analyzed 11 observational studies addressing oncological outcomes in laparoscopic surgery for early ovarian cancer. The overall recurrence rate was 9.9%, with a median follow-up period of over 19 months. Bogani *et al*. (2014) [8] reviewed six prospective comparison studies addressing oncological outcomes in laparoscopic surgery and open surgery for early ovarian cancer. They demonstrated that there were no differences in disease-free survival and overall survival between laparoscopic surgery and open surgery. Bogani *et al*. (2017) [33] also recently published a systemic review and meta-analysis for laparoscopic surgery in early stage ovarian cancer that included 3065 patients: 1450 undergoing laparoscopy and 1615 undergoing open surgery. They demonstrated that survival outcomes were not influenced by the route of surgery in early stage ovarian cancer (however, they suggested that further randomized study would be warranted, because their meta-analysis included one study with a low level of evidence). Furthermore, Melamed *et al*. (2017) [34] analyzed a national population database and reported that the four-year survival rates of early ovarian/fallopian tubal cancer patients were 91.5% and 88.5%, with no significant difference, when patients underwent laparoscopic staging and open surgery, respectively. They suggested that in apparent stage I ovarian/fallopian tubal cancer, laparoscopic staging surgery was comparable to conventional staging surgery. They adjusted for each patient's demographic characteristics, socioeconomic status, comorbidities, and adjuvant treatment. However, the observation period was relatively short and the power to detect small differences in survival was not sufficient. Early stage ovarian cancer is relatively rare; therefore, careful judgement must be used in the application of laparoscopic resection of ovarian/fallopian tubal tumors. Radosa *et al*. (2018) [35] reported on the survey of the German Society of Gynecologic Endoscopy (AGE) members with regard to the laparoscopic treatment of ovarian malignancies [35]. The report demonstrated that a majority of AGE members believed that early stage ovarian cancer and ovarian borderline tumor should be treated laparoscopically with currently available data for such a treatment being insufficient, and that 66% of participants would take part in a clinical trial, such as a randomized trial addressing laparoscopic surgery for early ovarian cancer. Considering all of the above, a randomized control study addressing laparoscopic surgery for early stage ovarian cancer is warranted.

Ovarian cysts over 6-10 cm are more frequently ruptured, compared to smaller ovarian cysts, during laparoscopic adenectomy [36, 37]. In the report, cysts associated with endometriosis were excluded, as these are easily ruptured. The surgical removal of endometrial cysts should be carefully considered, as an endometrial cyst is associated with the occurrence of clear cell carcinoma and endometrioid carcinoma of the ovary. It also remains controversial whether an intraoperative rupture of an ovarian tumor capsule affects prognosis [38, 39, 40, 41]. Recently, the association between intraoperative capsule rupture and prognosis was analyzed using population-based data in patients with stage I epithelial ovarian cancer who underwent primary surgical treatment. In that report, intraoperative capsule rupture cases resulted in poorer prognosis than unruptured cases. In particular, an intraoperative rupture in patients with clear cell carcinoma resulted in an almost twofold increase in the mortality ratio compared with unruptured patients [42].

In our study, 15 patients who underwent laparoscopic restaging surgery had been pathologically diagnosed by prior laparoscopic salpingo-oophorectomy. In some of these cases, levels of serum CA125 were elevated before the prior surgery. In those cases, the thickness of the cyst wall or nodule on the cyst wall was not detected by transvaginal ultrasonography or diagnostic MRI, and an advanced stage of ovarian cancer was not strongly suspected before the prior surgery. The average tumor size was 68.3 ± 38.6 mm in those cases. Up-staging due to intraoperative capsule rupture was found in four cases (26.7%) in the prior laparoscopic surgery. The ratio of intraoperative capsule rupture was seen in 20-48% of patients with ovarian cancer [43, 38, 44]. Technical aspects may affect the rate of intraoperative capsule rupture in both laparotomy and laparoscopy. In addition, for endometriosis-related tumors, most are ruptured at the time of resection, so there is a possibility that laparotomy may be less advantageous. Our study did not

propose to examine whether a laparoscopic approach is appropriate for the pathological diagnosis of ovarian tumors, especially when they would be suspected as a malignancy. Further precise examination is expected regarding the utility of laparoscopy to obtain a pathological diagnosis in a patient who has a suspected malignant tumor.

We carried out laparoscopic restaging surgery in seven patients who had been diagnosed by a prior open surgery. Three of these seven cases were diagnosed as a borderline malignant tumor or benign tumor by frozen pathological examination in the prior operation. They ended without lymph node dissection but were diagnosed as ovarian cancer by permanent pathological examination and required restaging surgery. The average tumor size was 144.4 $\pm$ 79.2 mm in these seven cases, which is larger than in cases diagnosed by laparoscopic salpingo-oophorectomy. Up-staging due to intraoperative capsule rupture was found in a single case (16.7%). A patient who had been diagnosed with a borderline malignant ovarian tumor by pathological examination of intraoperative frozen sections was re-diagnosed as ovarian cancer by permanent pathological examination at a rate of 4.1-8.6% [45]. A Cochrane database review reported that 21% of patients who were diagnosed with a borderline malignancy by frozen sections turned out to have invasive ovarian cancer by examination of permanent sections [46]. Laparoscopic restaging would provide great benefit to a patient diagnosed with a borderline malignant ovarian tumor through this diagnostic process by laparotomy. However, two of the seven patients who underwent a prior laparotomy had severe post-operative adhesion with the peritoneum and bowels, which made it difficult to perform laparoscopic surgery and required a retroperitoneal approach for pelvic lymphadenectomy. It should be noted that laparoscopic restaging required a careful technique in a patient who underwent the prior laparotomy.

Conclusions

Laparoscopic restaging surgery for early stage ovarian and fallopian tubal cancer was both feasible and safe. In addition, laparoscopic restaging was comparable to conventional staging surgery in terms of oncological outcomes such as up staging rate and recurrence rate.

However, our study has some limitations: (1) it is a prospective case control study in a single institute, (2) it had a short observation period, and (3) there is a higher incidence of clear cell carcinoma in Asian females. Further large-scale randomized control studies confirming the comparable outcomes of laparoscopic restaging surgery in early ovarian/fallopian cancer compared with open surgery are required.

Ethics approval and consent to participate

The IRB in Yokohama Municipal Citizen's Hospital approved this study; the trial registration number is 15-06-02. Written informed consents were obtained from all patients for publication of this study and accompanying an image.

Authors' contributions

HY, MY, MM, and HS designed the research study. HY, MY, and MM performed the research and analyzed the data. MY, HM, MI, MS, and TH assisted in data analysis. HY, MY, and MM wrote the manuscript. All authors contributed to editorial changes to the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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