Is It the Time for Laparoscopic Management of Early-stage Ovarian Malignancies?

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Abstract

The laparoscopic management of early-stage ovarian cancer remains controversial. Some surgeons hesitate to perform laparoscopic staging due to concern with the adequacy of staging, the possibility of tumor spillage and risk of port-site metastasis. Previous studies and literature reviews have reinforced the argument and supported the use of laparoscopy. However, the results were drawn with limited sample size obtained from case-series and case–control studies which result in difficult to make definite conclusions. Till date, the list of laparoscopic procedures has grown at a pace consistent with improvements in technology and technical skill of the surgeon. The number of studies with larger sample size, more prospective data, and longer duration of follow-up has been increasing. This review serves as an update on safety, feasibility, surgical, and oncological outcomes in cases of early-stage ovarian cancer treated by laparoscopic surgery of the literature published since 2008. We aim to clarify whether laparoscopy is safe and effective enough to be considered as standard management. Rely on nonrandomize studies, the current clinical evidence supports the role of laparoscopy in the management of early-stage ovarian cancer. Laparoscopy appears to offer several perioperative benefits without compromise of surgical morbidity and oncological outcome.

Keywords: Early stage ovarian malignancy, laparoscopic management, minimal invasive surgical procedures, surgical staging, treatment outcome

INTRODUCTION

Key successful treatment for ovarian cancer consists of appropriate surgical staging and optimal surgery. Surgical staging originally necessitated an exploratory laparotomy advised by the Federation of Obstetrics and Gynecology. Since the early 1980s, it has become evident that less-invasive methods of interventional treatment have produced far fewer complications with a reduced risk of morbidities such as decreased blood loss, faster recovery, and shorter hospital stay. Minimally invasive surgery has become increasingly popular and performed extensively. Over the past decade, laparoscopic approach to cancer therapy has been adopted by gynecologic oncologists for the treatment of early-stage endometrial and cervical cancer. This approach offers a means to decrease the morbidity associated with open surgery without compromising oncologic outcome.[1-6] However, the acceptance of laparoscopy for surgical staging women with ovarian cancer remains controversial. Questions remain about the adequacy, feasibility, and standardization of laparoscopic technique, the possible risks of tumor metastases, and impact on survival outcome.

The latest review reported that there was insufficient evidence to evaluate laparoscopy for the management of early-stage ovarian cancer as routine clinical practice. Taking into consideration the lack of high-quality evidence, the laparoscopic approach in the early-stages of ovarian cancer seems safe and effective. In this communication, we reviewed the use of laparoscopy in the management of early-stage ovarian cancer to clarify the outcome and to provide further guidance for optimal management.

METHODS

We included studies those provided the feasibility, adequacy, and outcome of the patient with early-stage ovarian cancer after laparoscopic surgical staging. The articles cited were

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obtained by Medline resource and Cochrane databased in the English language between January 2008 and April 2018. The keywords used were "laparoscopy," "minimally invasive surgery," "laparotomy," "staging surgery," "outcome," and "early-stage ovarian cancer." Additional references were obtained from the initial articles reviewed.

RESULT AND DISCUSSION

In this literature review, we divided the information into four categories which are as follows: the feasibility and adequacy, the additional benefits, the possible risks, and survival outcome. For each category, a further subdivision into case series, comparative studies of laparoscopy versus laparotomy, and systematic reviews/meta-analysis was developed and summarized.

The feasibility and adequacy

It has been argued that laparoscopy imposes limitations in visual and haptic perceptions. Laparoscopy is impossible to evaluate through the pelvis, mesentery, and peritoneum, especially the lesion behind the liver and spleen.[7] This may lead to failure of upstaging and inadequate administration of chemotherapy. However, in early-stage ovarian cancer, the likelihood of metastases in those areas that are difficult to visualize by laparoscopy like the posterior surface of the liver is relatively low.[8] A study by Chi et al. compared laparoscopy and open surgical staging and found no difference in the likelihood of identifying metastasis disease between two groups.[9] Several studies have supported the concept that laparoscopy may offer an advantage by enabling better visualization of an anterior abdominal wall, peritoneal surfaces, sub-diaphragmatic areas, obturator spaces, and cul-de-sacs, as well as magnification and detection of smaller lesions that may be missed at perioperative imaging or during laparotomy.[10]

To determine the adequacy of surgical staging and to evaluate the feasibility of incorporating laparoscopy into general practice, we reviewed the following outcomes: lymph node yield (pelvic and paraaortic node), upstaged cases, conversion rate, and operative time.

Lymph node status is an important predictor of survival outcome. The number of lymph nodes harvested could be a marker of being adequate surgery and considered as a surrogate of radicality. All except one comparative studies have compared retroperitoneal lymph node yields between laparoscopy and laparotomy.[7,11-21] Most of the studies (10 from 12 studies) reported the mean number of total lymph node retrievals was comparable between two groups[7,11-18,22] Two studies found that patients who underwent laparoscopy had more lymph nodes excised than those who underwent laparotomy.[19,20] It could not be concluded that surgical staging by laparoscopy is more radicality than laparotomy, but it is important to underline that the staging quality was not inferior.

The upstaging rate on the final pathological can be considered as another index of staging accuracy. The overall upstaging rates after laparoscopic surgery from case series were 16%–41% [Table 1]. Most of the patients were upstaged to stage III due to metastatic disease spreading to lymph nodes, diaphragm, and omentum. In comparison to laparotomy, eight of nine studies evaluated the overall upstaging rate found no difference between two approaches [Table 2].[7,11,12,15,16,18,19,22] Melamed et al. in their study reported women who underwent laparoscopy were less likely to be upstaged (LPS 12.2% vs. LPT 19.2% P < 0.001). In this study, the proportion of women with lymph node metastasis in laparotomy group was higher (LPS 4% vs. LPT 7. 08% P = 0.05).[19]

Laparoscopic staging was completed in 91%–100% of patients. One of 20 patients in Colomer's study, a conversion to laparotomy was necessary as the para-aortic lymphadenectomy was completed because of a vessel lesion that was repaired without difficulty.[22] In similar, Lee et al. found 1 of 26 patients in laparoscopic group converted to laparotomy due to severe pelvic adhesion from endometriosis.[11] In the large-scale studies, Gallotta et al. and Melamed et al.[19,24] reported the conversion rates reported were 9% (27 of 300 cases) and 17% (190 in 1112 cases), respectively. The former study found the conversion to laparotomy occurred more in immediate-staging than delayed-staging group (16% vs. 2% P = 0.0001). In this study, the patients undergoing immediate-staging were characterized by a higher frequency of adverse pathological features, such as poor grade of differentiation. The higher conversion rate might be likely dictated by concerns about the risk of leaving sites of peritoneal and/or lymph node disease as unidentified. Indeed, the patients in delayed-staging group were younger and presumed to benign adnexal lesions on the basis of preoperative imaging finding. Most were referred from the centers lacking using frozen section analysis. It is conceivable that patients accurately studies at preoperative workup, who are shown to bear Grade 1–2 tumor, might be very safety managed through laparoscopy staging.[24]

The results of the median operative time were similar among cases series studies, 210–306 min. Nevertheless, the results were inconclusive when compared to laparotomy.

Eleven comparative studies reported the operative time, which ranges from 193 to 337 min in the laparoscopic group [Table 2]. Five studies found no significant difference of operative time between two approaches.[12-14,16,17] Two studies reported operative time was higher in laparotomic versus laparoscopic staging,[7,15] while significant increase in operative time in laparoscopic group was reported in four studies.[11,18,20,21] The longest added time in laparoscopic surgery was 105 min (377 vs. 272 and 335 vs. 230 min).[20,21] There was no report of increasing postoperative complication in the studies with longer operative time in patients with undergoing laparoscopy.

The results from four systematic reviews and meta-analysis have suggested the feasibility and accuracy of a laparoscopic approach [Table 3]. There were no significant differences in harvested lymph node number, upstaging cases, and conversion rate. Park et al. did not sum up and reported the operative time due to considerable heterogeneity.[30] Two studies reported

Author/ study design	Study period	n	FSS (%)	Overall upstaging, n (%)	Intra-operating spillage, n (%)	OP time (min), mean	EBL (ml), mean	Conversion rate, n (%)	Complication		FU time (months) mean	Survival outcome, n (%)
									Intra-operative, n (%)	Postoperative, n (%)		
Colomer et al., 2008[23]/PS	2003-2017	20 7 BOTs 11 EOC 2 GCT	8 (40)	4 (20)	1 (5)	223 (180-230)	NA[a]	1 (5) vein lesion	1 (5)	24.7	24.7	RR 1 (5) DFS: 95% OS: 100%
Nezhat et al., 2009[25]/RS	1995-2007	20 11 BOT 5 non-EOC	NA	7 (35)	NA	222 (59-386)	195 (25-500)	0 (0)	0	55.9	55.9	RR 3 (15) OS: 100%
Jung et al., 2009[26]/PS	2004-2007	24	NA	10 (4.1)	NA	253±65.7	567±170	0 (0)	None	10 (2-39)[b]	10 (2-39)	RR 1 (4) Patient with serous CA Stage III Lost to FU
Schreuder et al., 2012[27]/RS	2001-2009	25	4 (16)	8 (32)	NA	235 (100-285)	100 (10-1500)	0 (0)	2 (8) arterial bleeding	43	43	RR: 5 (20) DOD: 2 (8)
Ghezzi et al., 2012[22]/PM	NR	82	14 (17)	21 (25)	18 (21.9)	263±81	100 (20-3000)	0%	1 (1.2) IVC injury	28.5 (3-86)	28.5 (3-86)	RR: 6 (7.3) DFS: 95.1% OS: 98.8%
Brockbank et al., 2013[28]/PM	2008-2012	35	16 (45)	8 (24)	NA	210 (90-210)	75 (10-1000)	2 (6%) IVC, colon injury	4 (11.4) injury to bowel, IVC Chest wall emphysema	18 (3-59)	18 (3-59)	RR: 2 (5.7) DFS: 94%, OS: 100%
Gallotta et al., 2014[24]/RM	2000-2014	300	48 (16)	48 (16)	4 (1.3)	320 (48525)	150 (10-3000)	28 (9%)	8 (2.6)	24 (3-145)	24 (3-145)	RR: 25 (8.3) OS: 25 (95.2) Death rate: 10 (3.3)
Lee et al., 2018[29]/RS	2002-2014	24	0	0	9 (37.5)	306±98	204±188	0%	1 (4.1) sigmoid perforated	1 (4.1) hydro-nephrosis	31.5	RR: 2 (8.3) DFS: 83% OS: 95%

[a]No transfusion, [b]Only 1 case from total 8 studies had port-site metastasis: The lesion occurred at the suprapubic port, during the 3rd cycle of CMT. The mass resection was performed. There is no metastasis finding in the intraabdominal cavity. DFS: Disease-free survival, DOD: Dead of disease, EBL: Estimated blood loss, FSS: Fertility-sparing surgery, n: Number of patients, NA: Not assessed, OS: Overall survival, PM: Prospective multicenter study, PS: Prospective single study, RFS: Recurrence-free survival, RM: Retrospective multicenter study, RS: Retrospective single study, RR: Recurrence rate, OP: Operative

operative times were similar between the two approaches,[31,32] while Bogani et al. observed that patients undergoing laparoscopy experienced a longer operative time without statistically significant (weighted mean difference 28.3 min; 95% confidence interval [CI], 2 2.59–59.2).[33]

The additional benefits
The additional benefits focus on the estimated blood loss (EBL), perioperative complication, hospital stay, and the interval from the surgery to chemotherapy.

The mean EBL reported from six studies of patients performed laparoscopic staging for early-stage ovarian cancer ranged from 75 to 567 ml.[11,22-29] Colomer et al. did not report EBL, but no cases received a blood transfusion in this study.[25] In comparison with laparotomy, EBL was lower in the laparoscopic group in all studies but not significantly different in three studies.[16,20,21] Almost all of the studies reported that the EBL of patients in laparotomy groups were approximately twofold higher than LPS group [Table 2].

Table 2: Ree cohort studies of laparoscopic surgical staging versus open surgery for early ovarian cancer (13 studies)

				A. Study and patient characteristics		Patient characteristics	
Author	Surgery	Study period	n	EOC, n (%)	FSS, n (%)	Referred for restaging, n (%)	Time interval from initial surgery to restaging (days)
Ghezzi et al., 2007[21]	LPS	2003-2006	15	13 (86)	Total: 2 (13.3)	5 (33.3)	Total: 8 (5-14)
	LPT	1997-2003	19	18 (94.7)	-	2 (10.5)	-
	P					0.2	
Park et al., 2008a[12]	LPS	2001-2006	17	100 (100)	4 (23.5)	6 (31.6)	35.8
	LPT		19	100 (100)	17 (89)	15 (88.2)	32
	P			-	-	0.001	0.825
Park et al., 2008b[7]	LPS	2004-2007	19	18 (94.7)	3 (15.8)	7 (36.8)	19 (7-34)
	LPT		33	31 (93)	5 (15.2)	5 (15.2)	13 (9-16)
	P			0.5	-	0.074	0.19
Wu et al., 2010[34]	LPS	1984-2006	34	100 (100)	NR	NR	Total: 21 (8-60)
	LPT		174	100 (100)	NR	NR	-
	P			-	-	-	-
Lee et al., 2011[11]	LPS	2005-2010	26	22 (84)	0	NA	NA
	LPT		87	71 (81)	0	NA	NA
	P			0.4	-	-	-
Bogani et al., 2014[20]	LPS	2003-2010	35	48 (89)	NA	NA	NA
	LPT	2003-2010	32	48 (75)	NA	NA	NA
	P			0.14	-	-	-
Koo et al., 2014[16]	LPS	2006-2012	24	83.3	NA	14 (58.3)	NA
	LPT		53	88.7	NA	9 (17)	NA
	P			-	-	<0001	-
Liu et al., 2014[17]	LPS	2002-2010	35	100 (100)	NA	NA	NA
	LPT		40	100 (100)	NA	NA	NA
	P			-	-	-	-
Lu et al., 2016[13]	LPS	2002-2014	42	100 (100)	Exclude	0	NA
	LPT		50	100 (100)	Exclude	0	NA
	P			-	-	-	-
Ming et al., 2016[14]	LPS	2008-2014	50	100 (100)	NA	20 (40)	NA
	LPT	2006-2014	58	100 (100)	NA	12 (22)	NA
	P			-	-	0.048	-
Gallotta et al., 2016[15]	LPS	2007-2013	60	100 (100)	Excluded	0	NA
	LPT	2000-2011	120	100 (100)	Excluded	0	NA
	P			-	-	-	-
Melamed et al., 2017[19]	LPS	2010-2012	1096	100 (100)	Excluded	NA	NA
	LPT		1096	100 (100)	Excluded	NA	NA
	P			-	-	-	-
Ditto et al., 2017[18]	LPS	2005-2015	50	100 (100)	12 (24)	20 (40)	NA
	LPT		50	100 (100)	11 (22)	18 (36)	NA
	P		-	-	1.0	0.83	-

EOC: Epithelial ovarian cancer, FSS: Fertility sparing surgery, LPS: Laparoscopy, LPT: Laparotomy, NA: Not assessed, NR: Not reported

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Table 2: Contd...

B. Operative outcome

Author	Surgery	Intraoperative spillage, n (%)	Up staging, n (%)	OP time (min)	EBL (ml)	Conversion (%)	Tumorsize (cm), mean	Pelvic node, n	PAN, n	Complication, n (%) Intra-operative	Complication, n (%) Postoperative	Hospital stay (day)	Interval to CMT (day), mean
Ghezzi et al., 2007[21]	LPS	3 (20)	4 (26.7)	377	250	0 (0)	NA	25±9.3	6.5	0 (0)	2 (13.5)	3 (2-12)	NA
	LPT	2 (10.5)	6 (31.6)	272	400		NA	25.1±5.8	7±4.5	0 (0)	8 (42)	7 (4-14)	NA
	P	0.63	1.0	0.002	0.28		-	0.96	0.78	-	0.13	0.001	-
Park et al., 2008a[12]	LPS	0 (0)	1 (5.8)	303.8	231.2	0 (0)	4.0±1.0	13.7±5.6	8.9±7.1	2 (11.8)	0 (0)	9.4±4.1	11.1±2.9
	LPT	0 (0)	6 (31.5)	290	505.5		4.5±1.0	19.3±10	6.4±3.9	1 (5.3)	4 (21.1)	14.1±4.2	14.3±6.2
	P	-	0.92	0.706	0.001		0.6	0.52	0.187	-	-	0.02	-
Park et al., 2008b[7]	LPS	2 (10.5)	5 (21.1)	221±83	240±228	0 (0)	8.9±6.3	27.2±9.7	6.6±6.2	1 (5.2)	1 (5.2)	8.9±6.1	12.8±4.9
	LPT	4 (12.1)	7 (21.2)	275±63	568±451		11±6	33.9±14.5	8.8±8.1	0	10 (3.03)	14.5±5.6	17.6±8.3
	P	1.0	0.98	0.012	0.005		0.2	0.07	0.32	-	-	0.02	0.049
Wu et al., 2010[34]	LPS	NA	0 (0)	NA	NA	7 (20)	NA	NA	NA	NA	4 (11)[a]	NA	NA
	LPT	NA	0 (0)	NA	NA		NA	NA	NA	NA	NA	NA	NA
	P	-	-	-	-		-	-	-	-	-	-	-
Lee et al., 2011[11]	LPS	0 (0)	1 (4)	227±105	230±183	1 (3.8)	9.1±5	23.5±0.3	9.9±7.4	0	2 (8)	6.4±2.6	8.5
	LPT	13 (14.9)	5 (6)	184±61	184±61		14±8.3	22.8±10.2	4.8±4.1	1 (1.14)	19 (21)	12.4±5.5	10.3
	P	0.037	-	0.016	0.016		0.01	0.867	0.003	-	-	<0.001	0.007
Bogani et al., 2014[20]	LPS	6 (17)	15 (42)	335	300	0 (0)	NA	22	10	0	1 (3)	4 (2-30)	22
	LPT	4 (12)	15 (46)	230	400		NA	15	6	0	9 (28)	6 (3-14)	30
	P	0.59	>0.05	<0.001	0.28		-	0.002	0.08	-	0.005	0.03	<0.001
Koo et al., 2014[16]	LPS	13 (54.3)	NA	193	698	0 (0)	7.3±4.3	26.8±8.5	17.7±10	0	13 (54)	13.7±5.4	NA
	LPT	21 (39.6)	NA	224	973		11.2±4.5	27.8±11.2	21.2±11.2	3 (5.7)	30 (56)	13.1±4.1	NA
	P	0.46	-	0.127	0.127		0.001	0.2	0.12	0.54	-	0.054	-
Liu et al., 2014[17]	LPS	3 (8.5)	6 (17)	209.7	197	NA	6.7±1.5	Total LN: 18.23±3.2		NA	4 (11.4)	16.3±6.2	NA
	LPT	5 (12)	9 (22)	200.5	345		11.5±3.4	Total LN: 19.3±3.15		NA	5 (12.5)	21.8±4.8	NA
	P	-	>0.05	>0.05	<0.05		<0.05	>0.05		-	>0.05	<0.05	-
Lu et al., 2016[13]	LPS	0 (0)	9 (21.4)	200	110 (50-450)	0 (0)	NA	20 (10-35)	8 (4-17)	0	3 (7.1)	3 (2-14)	NA
	LPT		10 (20)	240	370 (20-1000)		NA	22 (12-33)	7 (3-20)	1 (1.14)	3 (6)	7 (3-10)	NA
	P		0.86	>0.05	0.01		-	0.87	0.95	-	-	0.00	-
Minig et al., 2016[14]	LPS	0 (0)	12 (24)	225 (180-240)	200 (200-225)	0 (0)	6.75 (5-10)	15	10	3	14 (28)	2 (1.5-3)	31 (23-46)
	LPT	0 (0)	8 (14)	220 (120-240)	500 (300-1000)		10 (7.7-15.2)	13	10	5	22 (38)	5 (4-6.3)	38.5 (32.8-49)
	P	-	0.173	0.48	0.0001		0.001	-	-	-	0.275	<0.001	0.318
Gallotta et al., 2016[15]	LPS	NA	NA	NR	NR	0 (0)	NA	Total LN: 16 (2-50)		NA	NA	3 (2-7)	NA
	LPT	NA	NA	Longer	Higher		NA	Total LN: 18 (3-65)		NA	NA	7 (2-31)	NA
	P	-	-	0.01	0.032		-	0.46		-	-	0.001	-
Melamed et al., 2017[19]	LPS	NA	133 (12)	NA	NA	190 (17)	NR	Total LN 14 (7-22)		NA	31 (2.8)[b]	3 (1-4)	NA
	LPT	NA	210 (19)	NA	NA		NR	Total LN 12 (6-20)		NA	42 (3.9)	4 (3-5)	NA
	P	-	0.173	-	-		0.83[c]	0.05		-	0.37	<0.001	-
Ditto et al., 2017[18]	LPS	NA	10 (20)	207.6	150	0 (0)	NA	16.6±7.9	16.7±6.6	0	1 (2)	4±2.6	NA
	LPT	NA	13 (26)	180.7	339		NA	19.5±9.3	18.4±9.2	1 (2%)	2 (4)	6.1±1.6	NA
	P	-	-	0.04	<0.001		-	0.13	0.45	-	-	<0.01	-

aPort site metastases, bRemission within 30 days, cThe number of patient with tumor >10 cm in both groups were not difference. CMT: Chemotherapy, EBL: Estimated blood loss, LN: Lymph node, LNM: Lymph node metastases, LPS: Laparoscopy, LPT: Laparotomy, NA: Not assessed, NR: Not reported, PAN: Paraaortic lymph node

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Table 2: Contd...

C. Survival outcome

Author	Surgery	Mean time Follow up (mo)	Recurrence Rate, n (%)	Recurrence Time/site (n)	Survival outcome
Ghezzi et al., 2007[21]	LPS	16	0	-	OS 100%
	LPT	60	4 (7.1)	-	OS 100%
	P	-	-		-
Park et al., 2008a[12]	LPS	19 (5-56)	2 (11.7)	7,14 months	OS 88%
	LPT	14 (5-61)	0	-	OS 100%
	P	-	-		0.28
Park et al., 2008b[7]	LPS	17 (2-40)	0	-	OS 100%
	LPT	23 (1-44)	0	-	OS 100%
	P	-	-		-
Wu et al., 2010[34]	LPS	48.4	44 (21.1)	-	DFS 69.5%, 5 years OS 67.4%
	LPT	67		-	DFS 78.7%, 5 years OS 88.7% (OS h 3.52)
	P	-			<0.05
Lee et al., 2011[11]	LPS	12	0	-	PFS 100% OS 100% (FU 1 years)
	LPT	25	8 (9.2)	-	PFS 91% OS 96.6% (FU 25 months)
	P	-	0.1		-
Bogani et al., 2014[20]	LPS	64	4 (11)	-	NR
	LPT	100	9 (28)	-	NR
	P	0.001	0.12		0.12 (5 years DFS) 0.26 (OS)
Koo et al., 2014[16]	LPS	31.7	2 (8.3)	-	NED 22 (91.7%) DFS 59 months
	LPT	31.1	2 (3.8)	-	NED 51 (96.2%) DFS 66 months
	P	0.9	0.5		-
Liu et al., 2014[17]	LPS	36-48 months	2 (5.7)	-	PFS 54.3 months, 5 years OS 94.1%
	LPT		2 (5)	-	PFS 57.2 months, 5 years OS 96.3%
	P		>0.05		>0.05
Lu et al., 2016[13]	LPS	82 (16-152)	5 (13)a	-	92%
	LPT	82 (16-152)	6 (13)a	-	90%
	P	-			0.35
Ming et al., 2016[14]	LPS	25.9 (11.2-38.5)	6 (12)	Peritoneum5, LN1	PFS 73.6 months OS 85.4 months
	LPT	34.3 (28.4-47.8)	7 (12)	Peritoneum6, LN1	PFS 64.8 months OS 67 months
	P	0.004	0.785		0.63 (PFS) 0.42 (OS)
Gallotta et al., 2016[15]	LPS	38 (24-48)	5 (8.3)	Peritoneum 4, parenchymal 1	4 years PFS 89%, OS 92%
	LPT	38 (24-48)	16 (13.3)	Peritoneum 8, LN2, parenchymal6	4 years PFS 81%, OS 91%
	P	-	0.651		0.651 (DFS) 0.719 (OS)
Melamed et al., 2017[19]	LPS	28.7 (20.4-38.9)	NA	-	DOD 55 (5.01) 4 years OS 91.5%
	LPT	29.3 (20.6-39.3)	NA	-	DOD 71 (6.4%) 4 years OS 88.5%
	P	0.77			0.17 (OS)
Ditto et al., 2017[18]	LPS	49.5	NA	-	DFS h: 0.79, OS h: 0.87
	LPT	52.6	NA	-	
	P	0.01	-		0.63 (DFS) 0.91(OS)

aThe number of recurrence case per total upstaged case. DFS: Disease-free survival, DOD: Dead of disease, HR: Hazard ratio, LN: Lymph node, LPS: Laparoscopy, LPT: Laparotomy, n: Number of patients, NA: Not assessed, OS: Overall survival, PFS: Progressive-free survival, OP: Operative

Table 3: Systematic review and meta-analysis (4 studies)

Author	n	Study period	Intra-operating spillage	Up-staging	OP time (min)	EBL (ml)	Trans-fusion rate	Complication		Time to CMT (day)	Hospital stay (day)	Recurrent rate	Death rate
								Intra-operating	Postoperating				
Zhang et al., 2015[31]	8	2005-2013	NA	NA	NA	NA	NA	NA	Lower OR 0.433, (95% CI: 0.21-0.87) P=0.019		Shorter MD-0.974	OR 0.707 (95% CI: 0.24-2.04) P=0.521	NA
Park et al., 2013[30]	11	2004-2012	25.4% (17.7%-35.1%)	22.6% (95% CI: 18.1-27.9)	NA	Lower MD-233 (95% CI: −195.7-−321) P<0.001					P<0.001	9.9% (95% CI: 6.7%-14.4%)	NA
Lu et al., 2015[32]	11	2005-2012	NA	NA	MD 15.33 95% CI (3.8-34.5) P=0.12	Lower MD-1.73 (95% CI: 2.41-1.04) P=0.00001		OR 1.34 (95% CI: 0.37-4.93) P=0.66	OR 0.26 (95% CI: 0.13-0.52) P=0.000		Shorter MD-4.87 (95% CI: −7.26-−2.47) P<0.0001	Lower OR 0.32; (95% CI: 0.13-0.82) P=0.02	OR 0.47; (95% CI: 0.09-2.59) P=0.83
Bogani et al., 2017[33]	11	2005-2016	OR 1.32; (95% CI: 0.52-3.38) P=0.84	OR 0.81; (95% CI: 0.55-1.20) P=0.18	Longer MD-28.3 (95% CI: −2.59-59.2) P<0.0001	Lower MD -56.47 (95% CI: −216-−96.5) P<0.0001	Lower OR 0.21 (95% CI: 0.10-0.43) P<0.0001	OR 0.93 (95% CI: 0.34-2.5) P=0.9	Lower OR 0.48; (95% CI: 0.29-0.81) P=0.006	Shorter MD -5.16 (95% CI: 28.7-21.6) P<0.0001	Shorter MD - 3.7 (95% CI: −5.2-−2.1) P<0.0001	OR, 0.75: (95% CI: 0.47-1.2) P=0.23	OR,076; (95% CI, 0.55-1.05) P=0.1

CMT: Chemotherapy, MD: Mean difference, n: Number of studies, NA: Not assessed, OR: Odds ratio, CI: Confidence interval, OP: Operative

With regard to perioperative complication, the intraoperative and postoperative complication rates ranged from 0%–11% to 0%–15.8%, respectively. Compared to laparotomy, all of the studies revealed the laparoscopy reduced the perioperative complication rates, but no significant differences were detected. Only one study showed significantly lower risk of postoperative complication in laparoscopic group [Table 2].[20] The following complications have been reported in laparoscopy; vascular injury,[7,12,14,22,24,27,28] large bowel injury,[14,24,28] thermal ureteric injury[12] abdominal and chest wall emphysema,[28] lymphatic complication,[13,16,17] partial gut obstruction,[17] fever,[7,16] umbilical hernia,[11] and port-site metastases (PSMs).[34] The reported complications in laparotomy group included vascular injury,[13,14,18] bladder and ureteric injury,[11,14] small bowel injury,[7] lymphatic complication,[7,11,16-18,35] partial gut obstruction,[13] fever[11-13] bacteremia[17] wound dehiscence,[11-13,35] bowel ileus, and renal failure.[7]

Twelve comparative studies have reported the lengths of hospital stay, which were significantly shorter with laparoscopy in eleven studies[7,11-15,17,18,20,21] and not statistically significant difference in one study [Table 2].[16]

The early initiation of adjuvant chemotherapy after surgery will improve the overall survival (OS) rates of ovarian cancer patients.[17] Till date, five out of thirteen comparative studies have evaluated the interval from the surgery to the initiation of adjuvant chemotherapy administration [Table 2]. Three of these reported a statistically significantly shorter interval in the laparoscopic group[7,11,20] and two studies reported no significant difference.[7,14]

The systematic reviews and meta-analysis studies supported that laparoscopic technique offers more benefits regarding perioperative morbidity compared with laparotomy [Table 3]. The patients undergoing laparoscopy experienced a significantly lower EBL[30,32,33] and transfusion requirement.[32] No statistically significant difference regarding the intraoperative complication.[32,33] The most impressive benefit of laparoscopic surgery appears to be in postoperative period. All of meta-analysis studies revealed that laparoscopic staging is associated with lower postoperative complication and lower hospital stay as well as shorter interval time to chemotherapy administration.

Although the additional benefits were not the primary outcome of all studies and the definitions of evaluated outcomes, such as complications, blood loss, and hospital stay, were different among these studies. Most of them reported the same results which preferred laparoscopy regarding decreasing perioperative morbidity, decreasing the length of recovery, and reducing the time interval from surgery to the initiation of chemotherapy.

Possible benefits of laparoscopic staging
Lee *et al*. reported the higher average cost for staging completed via a laparoscopic procedure. A mean difference of 761USD in surgical procedure costs reflects the extra costs of disposable instrumentation cost and longer operative time.[11] To date, there has been no study comparing the cost-effectiveness of laparoscopy and laparotomy in early-stage ovarian cancer. Even more costly in laparoscopic technique, it tends to decrease hospital stay, complication rates, and improve postoperative performance status. Laparoscopic-staging should be encouraged to consider recommendation if it could improve clinical result at an acceptable level of increased cost. Further studies are needed.

The fertility-saving laparoscopic surgical staging can be offered to selected women with EOC as a viable-sparing alternative to traditional laparotomy. Ghezzi *et al*. reported the largest series of 65 patients undergoing laparoscopic fertility-sparing surgery for the treatment of EOC. The recurrent and survival rates were comparable with open surgery 84.6% and 95.4%, respectively. The conception rate was 60% for those women that wished to conceive after a procedure.[36]

In addition, anecdotal evidence suggests that the increased visibility and precision afforded by laparoscopic approach as well as shorter patient recovery time, provide more satisfactory outcomes for surgeons trained in the technique.[37]

The possible risks
The possible risks focus on PSMs, intraoperative tumor rupture/spillage, and effect of CO_2 pneumoperitoneum.

Port-site metastases
Reports of recurrent disease at the laparoscopic port sites have created concern in many surgical specialties. The incidence of PSMs in gynecological cancers reported <2% of patients. A tangible role is attributed to ovarian cancer, primary peritoneal cancer, presence of ascites, biologically aggressive disease, surgery-related factors including tumor manipulation and wound contamination.[38] An analysis of a large prospective database of all patient undergoing laparoscopic procedures for malignant condition by the gynecological oncologist reported the incidence of PSMs was only 1.18% (20 of 1694 patients). Of these, 15 patients had a diagnosis of EOC or fallopian tube carcinoma. Nineteen of 20 patients (95%) had simultaneous carcinomatosis or metastases to other sites at the time of port-site metastasis.[39]

From our review, there was one case of PSMs from eight case series (0.18%, 1/530 patients).[25] In this patient, the specimen was safety removal in endobag via 12-mm trocar site superior to the symphysis pubis. During the third cycle of chemotherapy, the port-site metastasis of approximately 1 cm was identified at the trocar site for tumor extraction. There were no metastatic findings in the intra-abdominal cavity during second-look laparoscopy, which was performed simultaneously with mass excision, and no evidence of disease occurred. One comparative study of Wu *et al*. reported four cases of PSMs in 34 cases of laparoscopy group. This study did not provide the surgical technique in this study and the data were collected over 30 years ago (operations during 1984–2006).[34] The improper technique of specimen retrieval

in the past may explain the high incidence of PSMs in this paper. The recent Cochrane database review concluded that PSMs may be technique-related and limited mostly to patients with advanced stage.[40] The use of endoscopic bag, avoidance tumor rupture, and a layered closure are important steps to prevent this problem. An endoscopic bag must be used safely. After placing the unruptured tumor in the bag, suction should be used to reduce a volume of the tumor during extraction. Some authors emphasized the importance of using unused clean suction equipment to irrigate the abdominal cavity. If a previously used laparoscopic suction system is reused, tumor cells are able to spread directly to the port site.[26] In summary, laparoscopy-related PSMs almost always occur in the setting of advanced disease. The concern for PSMs should not preclude the use of laparoscopy in properly selected oncologic patients with proper surgical techniques.

Intraoperative tumor rupture/spillage

Intraoperative tumor rupture remains an important issue when performing laparoscopic approach. It may cause the spread of tumor cell, predicting a worse outcome regarding recurrence rate and survival.[10,37] Our review found that the rate of intraperitoneal spillage varies from 1.3% to 37.5%. Lee *et al.* reported the highest rate (37.5%) of intraoperative rupture compared with others studies. Although the rate of tumor spillage was higher, the recurrent rate (RR) was similar, and survival was better than other studies. The mean tumor size in this study was 12.1 cm (6.5–17.1 cm) while others did not report.[33] Almost all of the comparative studies found the rates of tumor spillage were similar between the two approaches except one study found the higher rate in laparotomy group (LPT 14.9% vs LPS 0% *P* 0.037). In this study, the mean tumor diameter of LPT group (14 cm) was higher than LPS group (9 cm) significantly (*P* 0.01).[11] The higher incidence of tumor ruptured was related to the higher mean tumor diameter.[11,41] The definitions of tumor spillage/rupture and tumor size were different among these studies and were not detailed in some studies [Table 2]. One systematic review reported a similar rate of cyst ruptured between laparoscopy and laparotomy.[33] Regarding the prognosis of the patient with tumor rupture, one meta-analysis found that intraoperative rupture may not decrease progressive free survival (PFS) when compared with no rupture in patients with early-stage EOC who underwent optimal complete surgical staging and adjuvant chemotherapy [Table 3].[42] Even in clear-cell carcinoma, surgical spillage of tumor cells does not appear to have a negative impact on survival outcomes in patients with stage I who received at least three courses of chemotherapy.[43] However, no conclusion about the prognosis has been proved from the prospective study and intraoperative spillage of tumor cells necessitating adjuvant chemotherapy; therefore, all efforts should be made to reduce the incidence of contamination. Once cyst is securely in the bag, it can be decompressed by controlled aspiration. If there is some solid or semi-solid-part, it can be "piece-mealed" in a bag with the scissor or harmonic scalpel. Caution should be taken when using any instrument within the specimen

bag. The operator should continuously view the device tip completely, to avoid damage to intraabdominal organs as well as risking spillage.[44]

Effect of pneumoperitoneum on tumor spreading

Several studies have compared tumor growth after laparotomy and after pneumoperitoneum in animal models, and most of them found a greater tumor growth after laparotomy.[9,45] Abu-Rustum *et al.* evaluated the effect of laparoscopic approach with CO_2 pneumoperitoneum on survival outcome in 289 patients with persistent disease of ovarian cancer or primary peritoneal cancer by comparing between the second-look laparotomy versus laparoscopy. The result showed the OS appears to be independent of the surgical approach.[35]

Survival outcome

According to the National Cancer Institute, Surveillance Epidemiology, and End Results database, based on patients diagnosed from 2004 to 2010, 5-year OS rates of early-stage ovarian cancer are approximately 95% and 85% for stage Ia and Ic, respectively.[46] Of the eight studies (4 prospective and 4 retrospective studies) reported survival data with the mean follow-up time varies from 18 to 55.9 months [Table 1]. Most of the studies reported the good survival outcome; OS of 95%–100%, disease-free survival of 83%–95%. Two small studies have reported recurrence rate of 15%–20%,[25,27] while the recurrence rates form other studies have been reported to be <10%. From Nezhat's study, three patients had recurrences: 2 with low malignant potential tumors in the remaining ovary and 1 with clear-cell carcinoma in the pelvis. These three patients were among the patients who had fertility-preserving operations.[25] Schreuder reported five recurrence cases: 1 mucinous low malignant potential tumors with incomplete staging and 4 with clear-cell carcinoma.[27] The high recurrence rates may be related to small sample size, high-grade histology, and inadequate staging. Follow-up lengths might influence the evaluation of recurrence and death rates.

There were thirteen comparative studies of laparoscopy versus laparotomy for early-stage ovarian cancer published during the past 12 years [Table 2]. Most of the studies, except one,[34] reported high OS rate in LPS group with no significant difference from LPT group. Ten studies reported the RRs and five studies reported PFS, all of these studies showed both RR and PFS were not influenced by surgical approach. However, the length of follow-up time in six studies varied widely[7,11,14,20,21] and was not reported in one study.[17] Only one study reported unfavorable survival outcome with laparoscopy significantly. The 5-year OS and recurrence-free survival rates were 67.4% and 69.5% in LPS group, and 88.7% and 78.7% in the LPT group, respectively.[34] The result of this study should be interpreted with much caution. First, data analyzed included the patients who diagnosed apparent stage 1 ovarian cancer by clinical staging. Not all patients underwent comprehensive staging and distribution of these population were significant difference between two groups. The landmark paper in 1983 showed that 31% of patients in clinical stage I were restaged

and 25% (16%–42%) of patients were restaged to stage III. They all lead to the notion that non-staged or inadequately staged clinical early-stage ovarian carcinoma is a mixture of real early-stage disease on the one hand and stage IIB or III disease on the other hand. This may explain the why this study results in poorer survival outcomes compared with others. Second, the two groups studied were not comparable in all respected. The distribution of tumor grading, frozen section performed and treatment after diagnosis were different significantly. The improperly staged patients and inappropriate method of this study cause false conclusion and potentially misleading.

Four systematic reviews and meta-analysis reemphasized that the laparoscopy did not worsen survival outcome [Table 3]. Lu 2015 and Bogani 2017 indicated that the mortality rate was not influenced by the route of surgery.[32,33] The recurrence rates were similar in three studies.[30,31,33] One systematic review[32] indicated significantly lower recurrence rates in laparoscopy group (odds ratio 0.32; 95% CI [0.13, 0.82]; $P = 0.02$). The pooled data included the nonepithelial histology type; sex cord-stromal, germ cell tumor, and carcinosarcoma. The survival data used to define the survival outcome might be insufficient.

The survival outcome is of utmost importance when considering laparoscopic surgical staging for early-stage ovarian cancer. Current evidence suggests that the laparoscopic approach is equivalent to laparotomy regarding survival outcome. However, till date, there have been no reports of randomized control trial (RCT) of laparoscopic surgery for ovarian cancer. The recruiting a sufficient number of participants and standardizing the quality of the surgery and the skill of surgeon are the major barrier to conducting RCTs[40] ClinicalTrials.gov reports a registered trial comparing LPS with LPT (NCT02686463). The primary outcome measures PFS within time frame 5 years. The status of the trial is ''not yet recruiting,'' and the estimated study completion date is in June 2023.

CONCLUSION

Laparoscopic surgical staging is feasible, safe, and as effective as laparotomy in the treatment of early-stage EOC. It may be associated longer operative time, but there is no impact on perioperative complication. Moreover, the patients benefit from a less traumatic technique, reduced morbidity with quicker recovery, shorter hospitalization, and the opportunity to start the chemotherapy earlier. The major concerns with the laparoscopic approach are port-site metastasis and intraoperative cyst rupture. Standardized oncological technique and preventive measures could decrease tumor seeding and spillage. The strongest independent prognostic factor is the completeness of surgical staging. The route of surgical approaches did not influence the survival outcome.

We believed that laparoscopic management of early-stage ovarian malignancies could be considered the standard treatment and recommended in accord with the following principles; complete preoperative evaluation, available frozen section, accessible gynecological oncologist, prevention of tumor spillage/port-site contamination and complete surgical staging. Particular attention should be paid to a possible occult malignancy of the ovarian tumor, especially in patients who underwent emergency surgery in which the most reliable modality cannot be used for evaluation. The gynecologists should have basic knowledge and perform surgery based on oncologic principles.

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Conflicts of interest
There are no conflicts of interest.

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