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.

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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How to cite this article: Tantitamit T, Lee CL. Is it the time for laparoscopic management of early-stage ovarian malignancies? Gynecol Minim Invasive Ther 2018;7:93-103.

Quick Response Code:

Website: www.e-gmit.com

DOI: 10.4103/GMIT.GMIT_59_18
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 para-aortic 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.[7,11-23] 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].[17,11,12,15,16,18,19,22] 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,[15,18] 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.[20] Two studies reported
operative times were similar between the two approaches,\textsuperscript{[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], 2.59–59.2).\textsuperscript{[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.\textsuperscript{[11,22-29]}

Colomer et al. did not report EBL, but no cases received a blood transfusion in this study.\textsuperscript{[25]} In comparison with laparotomy, EBL was lower in the laparoscopic group in all studies but not significantly different in three studies.\textsuperscript{[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 1: Case series of laparoscopic staging of early ovarian cancer (study period 1995-2017)

| Author/study design | Study period | n | FSS (%) | Overall upstaging, n (%) | Intra-operative spillage, n (%) | OP time (min), mean | EBL (ml), mean | Conversion rate, n (%) | Complication | FU time (months) mean | Survival outcome, n (%) |
|---------------------|--------------|---|---------|--------------------------|-------------------------------|---------------------|-------------------|------------------|--------------|----------------------|----------------------------|
| Colomer et al., 2008\textsuperscript{[23]/PS} | 2003-2017 | 20 | 8 (40) | 4 (20) | 1 (5) | 223 (180-230) | NA* | 1 (5) | vein lesion | 1 (5) | 24.7 | 24.7 | RR 1 (5) | DFS: 95% | OS: 100% |
| Nezhat et al., 2009\textsuperscript{[25]/RS} | 1995-2007 | 20 | NA | 7 (35) | NA | 222 (59-386) | 195 (25-500) | 0 (0) | None | 0 | 55.9 | 55.9 | RR 3 (15) | OS: 100% |
| Jung et al., 2009\textsuperscript{[26]/PS} | 2004-2007 | 24 | NA | 10 (4.1) | NA | 253±65.7 | 567±170 | 0 (0) | None | 10 (2-39)\textsuperscript{[2]} | 10 (2-39) | RR 1 (4) | Patient with serous CA Stage III | Lost to FU |
| Schreuder et al., 2012\textsuperscript{[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) | DFS: 95.1%, OS: 98.8% |
| Ghezzi et al., 2012\textsuperscript{[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: 94%, OS: 100% |
| Brockbank et al., 2013\textsuperscript{[28]/PM} | 2008-2012 | 35 | 16 (45) | 8 (24) | NA | 210 (90-210) | 75 (10-1000) | 2 (6%) | 4 (11.4) | IVC, colon injury | 18 (3-59) | 18 (3-59) | RR: 2 (5.7) | DFS: 95% | OS: 100% |
| Gallotta et al., 2014\textsuperscript{[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\textsuperscript{[29]/RS} | 2002-2014 | 24 | 0 | 306±98 | 204±188 | 0% | 1 (4.1) | sigmoid perforated | 1 (4.1) | hydro-nephrosis | 31.5 | 31.5 | RR: 2 (8.3) | DFS: 83% | OS: 95% |

\textsuperscript{a}No transfusion, \textsuperscript{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.
### Table 2: Ree cohort studies of laparoscopic surgical staging versus open surgery for early ovarian cancer (13 studies)

#### A. Study and 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)   |                             |                                                       |
| Park et al., 2008a[22] | LPS     | 2001-2006    | 17  | 100 (100)  | 4 (23.5)   | 6 (31.6) | 35.8             |
|                 | LPT     | 1997-2003    | 19  | 100 (100)  | 17 (89)    | 15 (88.2) | 32               |
| Park et al., 2008b[23] | LPS     | 2004-2007    | 19  | 18 (94.7)  | 3 (15.8)   | 7 (36.8) | 19 (7-34)       |
|                 | LPT     | 1997-2003    | 33  | 31 (93)    | 5 (15.2)   | 5 (15.2) | 13 (9-16)       |
| Wu et al., 2010  | LPS     | 1984-2006    | 34  | 100 (100)  | NR         | NR         | Total: 21 (8-60) |
|                 | LPT     | 1984-2006    | 174 | 100 (100)  | NR         | NR         |                                                       |
| Lee et al., 2011[24] | LPS     | 2005-2010    | 26  | 22 (84)    | 0          | NA | NA               |
|                 | LPT     | 2005-2010    | 87  | 71 (81)    | 0          | NA | NA               |
| Bogani et al., 2014[25] | LPS     | 2003-2010    | 35  | 48 (89)    | NA         | NA | NA               |
|                 | LPT     | 2003-2010    | 32  | 48 (75)    | NA         | NA | NA               |
| Koo et al., 2014[26] | LPS     | 2006-2012    | 24  | 83.3       | NA         | 14 (58.3) | NA               |
|                 | LPT     | 2006-2012    | 53  | 88.7       | NA         | 9 (17)    | NA               |
| Liu et al., 2014[27] | LPS     | 2002-2010    | 35  | 100 (100)  | NA         | NA | NA               |
|                 | LPT     | 2002-2010    | 40  | 100 (100)  | NA         | NA | NA               |
| Liu et al., 2016[28] | LPS     | 2002-2014    | 42  | 100 (100)  | Exclude    | 0          | NA               |
|                 | LPT     | 2002-2014    | 50  | 100 (100)  | Exclude    | 0          | NA               |
| Minig et al., 2016[29] | LPS     | 2008-2014    | 50  | 100 (100)  | NA         | 20 (40)   | NA               |
|                 | LPT     | 2006-2014    | 58  | 100 (100)  | NA         | 12 (22)   | NA               |
| Melamed et al., 2017[30] | LPS     | 2010-2012    | 1096| 100 (100)  | Excluded   | 0          | NA               |
|                 | LPT     | 2000-2011    | 120 | 100 (100)  | Excluded   | 0          | NA               |
| Gallotta et al., 2016[31] | LPS     | 2007-2013    | 60  | 100 (100)  | Excluded   | 0          | NA               |
|                 | LPT     | 2000-2011    | 120 | 100 (100)  | Excluded   | 0          | NA               |
| Ditto et al., 2017[31] | LPS     | 2005-2015    | 50  | 100 (100)  | 12 (24)    | 20 (40)   | NA               |
|                 | LPT     | 2005-2015    | 50  | 100 (100)  | 11 (22)    | 18 (36)   | NA               |

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...

| Author                  | Surgery | Intraoperative spillage, n (%) | Up staging, n (%) | OP time (min) | EBL (ml) | Tumorsize (cm), mean | Pelvicnode, n | PAN, n | Complication, n (%) | Intra-operative Postoperative | Hospital stay (day) | Interval to CMT (day), mean |
|-------------------------|---------|--------------------------------|-------------------|---------------|----------|----------------------|---------------|--------|---------------------|--------------------------|------------------|----------------------------|
| Ghezzi et al., 2008a    | 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                         |
| Park et al., 2008a      | LPT     | 2 (10.5)                       | 6 (31.6)          | 272           | 400      | 0.002                | 0.28          | 0.96   | 0.78 (0 (0))        | 8 (42)                  | 7 (4-14)         | NA                         |
| Bogani et al., 2016     | LPS     | 0.63                           | 1.0               | 0.002         | 0.28     | 0.52                 | 0.17          | 0.05   | 0.01                | 0.01                     | -                | -                          |
| Minig et al., 2016      | LPS     | 0 (0)                          | 1 (5.8)           | 303.8         | 213.2    | 4.0±1.0              | 19.3±10       | 6.4±9.3| 1 (5.3)             | 4 (21.1)                | 14.1±4.2         | 14±4.6±6.2                 |
| Koo et al., 2014        | LPS     | 2 (10.5)                       | 5 (21.1)          | 221±83        | 240±228  | 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                   |
| Lee et al., 2017        | LPS     | 4 (12.1)                       | 7 (21.2)          | 275±63        | 568±451  | 11±6                 | 33.9±14.5     | 8.8±8.1| 0                   | 0 (0)                   | 14.5±5.6         | 17.6±8.3                   |
| Lui et al., 2014        | LPS     | 0 (0)                          | 1 (4)             | 227±105       | 230±183  | 1 (3.8)              | 9.1±5         | 23.5±0.3| 9.9±7.4             | 0 (0)                   | 2 (8)            | 6.4±2.6                     |
| Liu et al., 2017        | LPS     | 13 (149.6)                     | 12 (14)           | 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                        |
| Lu et al., 2015         | LPS     | 0.59                           | 0.001             | 0.98          | 0.012    | 0.28                 | 0.02          | 0.005  | 0.03                | 0.03                     | -                | <0.001                     |
| Minig et al., 2016      | LPS     | 13 (54.3)                      | 193               | 698           | 0 (0)    | 7.3±4.3              | 26±8.5±4      | 17.7±10| 0                   | 13 (54)                  | 13.7±5.4         | NA                         |
| Lui et al., 2014        | LPS     | 13 (39.6)                      | 224               | 973           | 112±4.5  | 27.8±11.2            | 21.2±12.2     | 3 (5.7) | 30 (56)             | 13.1±4.1                 | NA               | NA                         |
| Liu et al., 2015        | LPS     | 3 (8.5)                        | 6 (17)            | 209.7         | 197      | 6.7±1.5              | Total LN: 18.2±3.2| NA     | 4 (11.4)            | 16±3.6±2                 | NA               | 0.054                      |
| Lui et al., 2017        | LPS     | 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               | NA                         |
| Lu et al., 2016         | LPS     | 0 (0)                          | 9 (21.4)          | 200           | 110 (50-450)| 0 (0)           | 20 (10-35)   | 8 (4-17) | 0                   | 3 (7.1)                  | 3 (2-14)         | NA                         |
| Minig et al., 2016      | LPS     | 12 (24)                        | 225 (180-240)     | 500 (300-1000)| 10 (7.7-15.2)| 13 (10)      | 5 (22) (38)  | 5 (4-6.3) | 31 (23-46) | 2 (15-3)                  | 8 (4-17)         | 31 (23-46)                 |
| Gallotta et al., 2016   | LPS     | 0.173                          | 0.48              | 0.0001        | 0.001    | 0.46                 | 0.46          | 0.46   | 0.01                | 0.01                     | -                | 0.318                      |
| Melamed et al., 2017    | LPS     | 133 (12)                       | 190 (17)          | NR            | NA       | 190 (17)             | Total LN: 14 (7-22)| NA     | 3 (2.8)             | 3 (1-4)                  | NA               | NA                         |
| Dito et al., 2017       | LPS     | 10 (20)                        | 150               | 0 (0)         | 16±7.9   | 16±7.6               | 0 (0)         | 1 (2)  | 2 (4)               | 6.1±1.6                  | NA               | NA                         |
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*Port site metastases, †Remission within 30 days, ‡The 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: Paraortic lymph node.*

Contd...
### Table 2: Contd...

| Author          | Surgery | Mean time Follow up (mo) | C. Survival outcome | Recurrence | Survival outcome |
|-----------------|---------|--------------------------|---------------------|------------|------------------|
|                  |         |                          |                     | Rate, n (%) | Time/site (n)    |                |
|                  |         |                          |                     |            | Survival outcome |
|                  |         |                          |                     |            | OS 100%          |
|                  |         |                          |                     |            | OS 100%          |
|                  |         |                          |                     |            | OS 100%          |
|                  |         |                          |                     |            | 0.28             |
|                  |         |                          |                     |            | OS 100%          |
|                  |         |                          |                     |            | OS 100%          |
|                  |         |                          |                     |            | DFS 69.5%, 5 years OS 67.4% |
|                  |         |                          |                     |            | DFS 78.7%, 5 years OS 88.7% (OS h 3.52) |
|                  |         |                          |                     |            | <0.05            |
|                  |         |                          |                     |            | PFS 100% OS 100% (FU 1 years) |
|                  |         |                          |                     |            | PFS 91% OS 96.6% (FU 25 months) |
|                  |         |                          |                     |            | NR               |
|                  |         |                          |                     |            | NR               |
|                  |         |                          |                     |            | 0.12             |
|                  |         |                          |                     |            | NED 22 (91.7%) DFS 59 months |
|                  |         |                          |                     |            | NED 51 (96.2%) DFS 66 months |
|                  |         |                          |                     |            | 0.12 (5 years DFS) 0.26 (OS) |
|                  |         |                          |                     |            | DFS 54.3 months, 5 years OS 94.1% |
|                  |         |                          |                     |            | DFS 57.2 months, 5 years OS 96.3% |
|                  |         |                          |                     |            | <0.05            |
|                  |         |                          |                     |            | NR               |
|                  |         |                          |                     |            | 0.5              |
|                  |         |                          |                     |            | DFS 73.6 months OS 85.4 months |
|                  |         |                          |                     |            | DFS 64.8 months OS 67 months |
|                  |         |                          |                     |            | 0.63 (PFS) 0.42 (OS) |
|                  |         |                          |                     |            | 0.17 (OS)        |
|                  |         |                          |                     |            | 0.35             |
|                  |         |                          |                     |            | PFS 89%, OS 92%  |
|                  |         |                          |                     |            | 4 years PFS 81%, OS 91% |
|                  |         |                          |                     |            | 0.651 (DFS) 0.719 (OS) |
|                  |         |                          |                     |            | DFS 85%, 4 years OS 91.5% |
|                  |         |                          |                     |            | 0.17 (OS)        |
|                  |         |                          |                     |            | DFS h: 0.79, OS h: 0.87 |
|                  |         |                          |                     |            | 0.63 (DFS) 0.91(OS) |

The 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.
| Author | Study period | OP time (min) | EBL (ml) | Trans-fusion rate | Complication | Time to CMT (day) | Hospital stay (day) | Recurrent rate | Death rate |
|--------|--------------|---------------|----------|------------------|--------------|------------------|-------------------|-----------------|------------|
| Zhang et al., 2015 | 2005-2013 | NA | NA | NA | Lower | OR 0.433; (95% CI: 0.21-0.87) | Shorter | OR 0.707; (95% CI: 0.24-2.04) | 0.01 | 0.51 | 9.9% | 6.7%-14.4% |
| Park et al., 2013 | 2004-2012 | 25.4% | (17.7%-35.1%) | Lower | MD −233 (95% CI: 195.7-321) | Lower | OR 0.26; (95% CI: 0.13-0.52) | Lower | OR 0.21; (95% CI: 0.10-0.43) | 0.01 | 0.0001 | 0.75 | 0.87 |
| Lu et al., 2015 | 2005-2012 | NA | NA | MD 1.34; (95% CI: 0.37-4.93) | Lower | MD -1.73 (95% CI: 2.41-1.04) | Lower | OR 0.93; (95% CI: 0.34-2.5) | 0.01 | 0.12 | OR 0.21; (95% CI: 0.04-1.43) | 0.0001 | 0.9 | 0.83 |
| Bogani et al., 2017 | 2005-2016 | OR 1.32; (95% CI: 0.52-3.38) | OR 0.81; (95% CI: 0.55-1.20) | Lower | MD 2.87 (95% CI: 1.8-4.12) | Lower | OR 0.48; (95% CI: 0.29-0.81) | Lower | OR 0.47; (95% CI: 0.09-2.59) | 0.01 | 0.0001 | OR 0.76; (95% CI: 0.47-1.2) | 0.0001 | 0.23 | 0.10 |
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 laparoscopic; vascular injury,[7,12,14,22,24,27,28] large bowel injury,[14,24,28] thermal ureteric injury[12] abdominal and chest wall emphysema,[26] 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[13] 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.[52,33] 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 CO₂ 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.[33,41] 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 prospective 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].[22] 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 CO2 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.[22] 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.[25] 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 why this study results in poorer survival outcomes compared with others. Second, the two groups studied were not comparable in all respects. 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 laparoscopic 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. The recurrence rates were similar in three studies. One systematic review 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 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.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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