Laparoscopy and Ovarian Cancer: A Paradigm Change in the Management of Ovarian Cancer?

Connie S. Liu, MD, Nimesh P. Nagarsheth, MD, and Farr R. Nezhat, MD*

From the NYU Medical Center, New York, New York (Dr. Liu), Mount Sinai Medical Center, New York, New York (Dr. Nagarsheth), and St. Luke’s-Roosevelt Hospital Center, New York, New York (Dr. Nezhat).

ABSTRACT

A MEDLINE search was conducted using the keywords “laparoscopy ovarian cancer,” “laparoscopy and borderline ovarian tumors,” “advanced stage ovarian cancer,” “laparoscopic cytoreduction ovarian cancer,” “laparoscopy intraabdominal catheter,” “port-site metastases,” and “carbon dioxide pneumoperitoneum.” The publications were further limited to English-language articles, those addressing adnexal mass management, early stage ovarian cancer, and advanced stage ovarian cancer treatments.

The articles were divided into 4 broad categories: adnexal masses, low malignant potential tumors, early stage ovarian cancer, and advanced ovarian cancer. For each category, a further subdivision into case reports, case series, and finally cohorts was developed and summarized. Additional articles were obtained based on the bibliographic cross-reference of the initial articles reviewed.

The current literature defining the role of laparoscopy in the diagnosis and treatment of ovarian cancer is limited to case reports, case series, and cohort studies. However, these limited studies suggest equal efficacy of laparoscopy compared with laparotomy in both early and advanced stage ovarian cancer. Journal of Minimally Invasive Gynecology (2009) 16, 250–62 © 2009 AAGL. All rights reserved.

Keywords: Laparoscopy; Ovarian cancer; Laparoscopic staging of ovarian cancer; Laparoscopic cytoreduction

More than 230 000 women worldwide will be diagnosed with ovarian cancer in 2008 [1]. Approximately 21 650 new ovarian cancer cases and 15 520 deaths are estimated in the United States [2]. Currently, the lifetime risk of developing ovarian cancer in the United States is approximately 1 in 70 with more than 65% given the diagnosis of advanced stage disease. Five year survival is noted to be over 90% among patients with early disease, but patients with more advanced distant disease have 5-year survival rates approaching 25%.

The most frequent detection of an adnexal mass or potential ovarian cancer is either an incidental finding on imaging or pelvic examination in an asymptomatic patient or during a diagnostic evaluation for a symptomatic patient [3]. The preoperative evaluation of an adnexal mass typically involves both radiologic and serum tumor marker evaluation [4]. Ultrasound characteristics such as presence of papillations, a complex appearance of the mass, and presence of free fluid increases the preoperative suggestion for malignancy [5]. In addition, tumor markers such as the cancer antigen CA 125 serum assay may be helpful, especially in the postmenopausal patient, in further determining which patients are more likely to harbor a malignancy as compared with those with benign disease. Traditionally, if the preoperative suggestion was high, the common practice was to proceed with surgical exploration via a midline vertical abdominal incision that would allow for an adequate surgical staging if necessary. However, in cases of benign pathology, the trend in the diagnosis and treatment of adnexal masses has transitioned to a laparoscopic approach as it may prevent unnecessary laparotomy [3–5].

The International Federation of Obstetrics and Gynecology (FIGO) surgical staging includes hysterectomy, bilateral salpingo-oophorectomy, pelvic washings, pelvic and paraaortic lymph node dissection, peritoneal and diaphragmatic biopsies, and infracolic omentectomy [3,6,7]. In early stage disease, this procedure was successfully performed laparoscopically in select cases with preliminary data suggesting comparable...
results with laparotomy [6–12]. In addition to complete surgical staging, dependent on the patient’s risk factors that may alter prognosis, patients with localized disease may consider fertility-sparing surgical staging [5].

In advanced ovarian cancer, surgical cytoreduction has been associated with a significant survival advantage [13]. A laparoscopic approach in the treatment of advanced ovarian cancer may confer several benefits. Laparoscopy may serve not only as a tool for proper diagnosis, but as a triage tool for resectability. The decision to attempt primary cytoreduction has come into question because of increasing research assessing the benefit of neoadjuvant chemotherapy with interval debulking among patients who cannot be optimally debulked or patients with other comorbidities that may limit optimal cytoreductive surgery [14–16]. Second-look laparoscopy was implemented to assess clinical response in patients enrolled in clinical trials to assess the efficacy of chemotherapy protocols. Complete laparoscopic cytoreduction has been reported in limited studies [6,17]. Laparoscopy has been suggested in the placement of intraperitoneal catheters for intraperitoneal chemotherapy [18].

Laparoscopy offers multiple advantages over traditional laparotomy including smaller incisions, improved visualization, less blood loss, reduction in the need for analgesics, decreased morbidity, and a more rapid recovery [6,11,12]. An additional advantage for patients with ovarian cancer requiring adjuvant therapy includes a shorter interval to the initiation of adjuvant therapy.

In this communication, we will review the current uses of laparoscopy in ovarian cancer and the available literature comparing this approach to traditional laparotomy. The articles cited were obtained by a MEDLINE search using the keywords “laparoscopy ovarian cancer,” “laparoscopy and borderline ovarian tumors,” “advanced stage ovarian cancer,” “laparoscopic cytoreduction ovarian cancer,” “laparoscopy intraperitoneal catheter,” “port-site metastases,” and “carbon dioxide pneumoperitoneum.” Additional references were obtained from bibliographic cross-references from the initial articles reviewed.

**Adnexal Mass**

The most frequent detection of an adnexal mass is during an incidental finding on imaging, examination in an asymptomatic patient, or during a diagnostic evaluation for a symptomatic patient [3,19]. The preoperative evaluation includes a history, physical examination, and imaging. Risk factors for ovarian cancer include increasing age, nulliparity, infertility, endometriosis, and a family history of cancer. Postmenopausal patients with adnexal masses undergoing surgical evaluation may have up to a 45% chance of malignancy [3]. Nulliparous patients have a 2- to 3-fold increased risk of ovarian cancer as compared with parous women [20]. In a case-control series of 8429 women, infertility was associated with a 2.7-fold increase in standardized incidence ratio for ovarian cancer [21]. Endometriosis may increase the risk of ovarian cancer by 2 independent pathways. First, endometriosis may be a cause for infertility. Second, endometriosis has been shown to undergo malignant transformation [22,23]. Among familial risks, approximately 5% to 10% of epithelial ovarian cancers are genetically based, most of which include *BRCA1* and *BRCA2* mutations [24].

Physical examination has the lowest sensitivity for detecting adnexal masses with approximately 60% detection rates reported [25]. Thus, imaging has become the more common method of detecting adnexal masses.

Multiple imaging modalities are available for the evaluation of adnexal masses. Sensitivity and specificity values range widely (Table 1) [25]. Transvaginal sonography has emerged as the most widely used tool because of its availability, tolerability for the patient, and cost effectiveness [26]. Findings on pelvic ultrasound can help guide practitioners as to the risk of malignancy associated with adnexal masses. Characteristics of ovarian cysts that are generally associated with a higher risk for malignancy include increasing size, complexity, presence of papillary projections, or solid components. Malignancy rates were reported from 1017 adnexal masses as 8% for multilocular cysts, 65% for multilocular solid tumors, 39% for solid ovarian masses, and 0.3% for unilocular cysts [27].

Serum tumor markers may also be helpful, particularly in patients at high risk for cancer [4,28–30]. Serum CA 125 levels were studied extensively with reported sensitivity and specificity ranging from 61% to 90% and 71% to 93%, respectively [26]. Only 80% of epithelial ovarian cancers will have an elevated CA-125, and of stage I patients only 50% will have an elevated CA-125 level [31]. Serum CA-125 levels were more accurate among a postmenopausal population with a positive predictive value of 98% and a negative predictive value of 72%. In contrast, premenopausal patients have a positive predictive test of only 49% [32]. This is explained by the fact that many conditions (Table 2) may lead to an elevated CA 125 level, thereby limiting its use as a screening tool.

Regardless of the index of suspicion for malignancy, laparoscopic evaluation of adnexal masses is appropriate in the hands of a skilled laparoscopic surgeon. The sequence of events should parallel those implemented in laparotomy: a thorough evaluation of the abdomen and pelvis, peritoneal washings, cystectomy or adnexectomy as indicated, biopsies of suggestive lesions, and frozen section evaluation. Table 3

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray-scale transvaginal ultrasonography</td>
<td>0.82–0.91</td>
<td>0.68–0.81</td>
</tr>
<tr>
<td>Doppler ultrasonography</td>
<td>0.86</td>
<td>0.91</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>0.90</td>
<td>0.75</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>0.91</td>
<td>0.88</td>
</tr>
<tr>
<td>Positron emission tomography</td>
<td>0.67</td>
<td>0.79</td>
</tr>
</tbody>
</table>
outlines the incidence of malignancy (range: 0.4%–14%) reported in patients undergoing laparoscopic evaluation for adnexal masses [4,34–46].

**Low Malignant Potential or Borderline Ovarian Tumors**

Borderline ovarian tumors represent 10% to 20% of epithelial ovarian cancers and typically have an excellent prognosis [47]. Survival for all borderline ovarian tumors ranges from 92% among those with advanced stage disease to 98% in those with stage I disease [48]. Borderline ovarian tumors occur predominantly in a premenopausal population with the highest frequency occurring in patients aged 30 to 50 years with 50% to 85% diagnosed as stage I [49]. The 2 most frequent histologic subtypes of borderline ovarian tumors are serous and mucinous tumors. Serous tumors are bilateral in 30% of cases with concurrent peritoneal implants in 35% of cases [48]. A pooled analysis of 317 patients with borderline ovarian tumors of varying histology found that up to 30% of patients diagnosed with borderline tumor at the time of frozen section subsequently have invasive ovarian cancer on final pathology [50]. Most of these patients had serous histology with 129 serous, 8 endometrioid, and 11 mixed [50–53]. In addition to preventing the need for reoperation in the event that invasive cancer is diagnosed on final pathology, surgical staging provides the patient with important prognostic information. Of importance, lymph node involvement was reported in up to 36% of patients with apparent stage I disease [54]. Mucinous tumors are malignant in only 5% of cases with rare case reports of nodal metastases, thus complete staging may not be necessary in these cases. However, appendiceal primaries are quite common among the mucinous tumors, thus we routinely perform an appendectomy in patients with mucinous tumors [4,48]. At our institution, we recommend routine surgical staging among patients with borderline nonmucinous ovarian tumors at the time of frozen section.

An additional consideration unique to the treatment of borderline ovarian tumors is that, as mentioned, the incidence of borderline tumors is predominantly among reproductive-aged patients. Fertility-sparing options may range from cystectomy to adnexectomy. Recurrence rates vary regardless of the surgical approach: adnexectomy recurrence rates range from 0% to 20%, cystectomy recurrence rates range from 12% to 58%, and radical surgery recurrence rates range from 2.5% to 5.7% [48]. A laparoscopic approach was also associated with less postoperative adhesion formation compared with laparotomy, which may theoretically enhance fertility [55].

Laparoscopic staging in borderline ovarian tumors is increasingly common with advances in endoscopic techniques and instruments. In the first case reports of laparoscopic treatment in borderline ovarian tumors [56,57], the procedure included a laparoscopic hysterectomy, bilateral adnexectomy, peritoneal sampling, peritoneal cytology, and partial omentectomy. Subsequently, multiple case series studies emerged to further evaluate the clinical outcomes and feasibility of laparoscopic treatment of borderline ovarian tumors [47,58–64]. In the largest case series to date, 107 patients underwent laparoscopic treatment of borderline ovarian tumors. The mean follow-up was 27.5 months with 100% survival and only 4 with evidence of disease [63]. A retrospective review was subsequently conducted of 113 patients diagnosed with borderline ovarian tumors, of whom 52 underwent laparoscopy and 61 underwent laparotomy. No difference occurred in progression-free survival between the 2 groups with a mean 44-month follow-up [47]. The longest documented follow-up (78 months) reports a survival of at least 83% and the remaining patients lost to follow-up [64]. A summary of the current literature on laparoscopic treatment of borderline ovarian tumors is provided in Table 4 yielding an overall survival of 98%.

**Early Stage Invasive Ovarian Cancer**

Early stage invasive ovarian cancer requires complete surgical staging to obtain important prognostic information,
avoid understaging of patients, and dictate postoperative management. This traditionally involves total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, pelvic and paraaortic lymph node dissection, and peritoneal washings [65]. If complete staging was not performed at the initial time of diagnosis, a restaging procedure that may be accomplished via laparoscopy or laparotomy is typically recommended for these patients.

The first case report of laparoscopic staging in early stage invasive ovarian cancer, reported in 1994, included complete pelvic and infrarenal paraaortic retroperitoneal lymph node dissection in a case series of 9 patients undergoing restaging procedures for either ovarian or fallopian tube cancers. This case series revealed a mean blood loss of less than 300 mL and average hospital stay of only 2.8 days [66]. This study was among the first to show the feasibility of a complete laparoscopic staging procedure in early ovarian cancer.

In 1995, a prospective study included 14 patients who underwent primary or restaging of presumed early ovarian cancer. In this study, they confirmed a shorter hospital stay with a mean of 1.6 days and 2 complications: 1 inferior vena cava injury requiring transfusion and 1 abdominal ecchymosis causing a decrease in postoperative hematocrit but not requiring transfusion. This study suggested comparable accuracy rates between laparoscopy and laparotomy as the upstaging rate was noted to be 57% (8/14), which was slightly higher than that reported in the literature for laparotomy at that time. The authors suggest that this may in part be a result of higher detection of macromicroscopic disease with the magnification feature afforded by a laparoscopic approach that may be otherwise missed on palpation during laparotomy, particularly in the area of the right hemidiaphragm [11].

Three case series have followed that include follow-up and survival data. A retrospective review reported 42 patients who underwent restaging for presumed early ovarian cancer. A recurrence rate was noted of 6.5% in stage IA patients after a mean follow-up of 54 months, which is similar to the reported 3% to 18% in a comparable group of laparotomy cases [67]. A 100% overall survival and 91.6% disease-free survival with a mean 46.4-month follow-up was noted [68]. The longest mean follow-up of 55.9 months also revealed a 100% overall survival. Of importance, this study had the largest number of primary staging procedures [12].

Three large case-control series were conducted in 2005 through 2008. The first case-control series reported 20 laparoscopic patients with 30 laparotomy patients who underwent primary or restaging procedures. They reported no difference in nodal yield, omental specimen size, rate of upstaging, or complication rates. Estimated blood loss and hospital stay were notably less, but a longer operative time also occurred with a mean value of 321 minutes for laparoscopy compared with 276 minutes during laparotomy [7]. Another case-control series of 34 patients showed no difference between laparoscopy and laparotomy in terms of nodal yield, likelihood of detecting metastatic disease, or complication rate [69]. Park et al reported the additional advantage of a more rapid return of bowel function among patients undergoing laparoscopy compared with laparotomy, and in the laparotomy group a higher postoperative complication rate with 2 febrile morbidities, 3 wound dehiscences, and 4 cases of ileus [70].

### Table 4
Laparoscopic management of borderline ovarian tumors

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Complications</th>
<th>Conversions to laparotomy</th>
<th>Mean follow-up (mo)</th>
<th>Recurrence</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darai et al [58]</td>
<td>25</td>
<td>None</td>
<td>7 (Presumption of cancer and failure of laparoscopic procedure)</td>
<td>41</td>
<td>3</td>
<td>23(^a)</td>
</tr>
<tr>
<td>Seracchioli et al [59] 2001</td>
<td>19(^b)</td>
<td>None</td>
<td>0</td>
<td>42</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Querleu et al [60] 2003</td>
<td>30(^c)</td>
<td>3</td>
<td>0</td>
<td>29</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Camatte et al [61] 2004</td>
<td>19(^d)</td>
<td>0</td>
<td>0</td>
<td>45</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>Desfeux et al [62] 2005</td>
<td>14(^e)</td>
<td>–</td>
<td>16</td>
<td>29</td>
<td>2</td>
<td>47</td>
</tr>
<tr>
<td>Fauvet et al [63] 2005</td>
<td>107</td>
<td>None</td>
<td>42 (For suggested cancer of large tumor volume)</td>
<td>27.5</td>
<td>13</td>
<td>103 ANED4 AWED</td>
</tr>
<tr>
<td>Romagnolo et al [47] 2006</td>
<td>52</td>
<td>–</td>
<td>0</td>
<td>44</td>
<td>7</td>
<td>51</td>
</tr>
<tr>
<td>Brosi and Deckardt [64] 2007</td>
<td>21</td>
<td>None</td>
<td>0</td>
<td>78</td>
<td>0</td>
<td>35(^a)</td>
</tr>
<tr>
<td>Total</td>
<td>356</td>
<td>3</td>
<td>65</td>
<td>33</td>
<td>346</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Missing patients were lost to follow-up.
\(^b\) Conservative treatment (cystectomy or unilateral adnexectomy).
\(^c\) Restaging cases.
\(^d\) Recurrent cases.

ANED = Alive with no evidence of disease; AWED = alive with evidence of disease.
Because of the rarity of early ovarian cancer, diagnosis, and challenges with preoperative diagnosis, a randomized controlled trial has not been feasible. Alternative evaluations of accuracy can be inferred by comparing upstaging rates between laparoscopic and laparotomy cases. In restaging procedures, the current literature suggests the rate of upstaging among complete laparoscopic staging procedures ranges from 11% to 19% [67,71]. The upstaging rate among patients who had complete laparotomy restaging procedures was reported as 30% to 36% [72,73]. The feasibility of laparoscopic completion of surgical staging in patients with incompletely staged ovarian, fallopian tube, endometrial, and primary peritoneal cancers was shown in Gynecologic Oncology Group (GOG) protocols 9302 and 9402 [71]. A total of 84 patients were eligible, of whom 74 had ovarian, fallopian tube, or primary peritoneal cancers. In all, 58 patients underwent complete laparoscopic staging, confirmed with photographic documentation. Nine patients were incompletely staged laparoscopically because of lack of peritoneal biopsies, cytology, or bilateral lymph nodes. Seventeen patients underwent laparotomy: 13 because of lack of exposure from adhesions, 3 because of complications, and 1 because of metastatic macroscopic disease. Complications associated with laparoscopically treated patients included 5 bowel injuries, 1 cystotomy, 1 small bowel obstruction, 1 venotomy, and 2 with extensive blood loss requiring transfusion. In comparing patients treated laparoscopically with those treated with laparotomy, the laparoscopic group showed a significantly shorter blood loss, hospital stay, and Quetlet index along with comparable nodal yields [71].

As suggested, these studies support that laparoscopy may offer an advantage in the management of early ovarian cancer by allowing better visualization of difficult areas such as the subdiaphragmatic areas, obturator spaces, and anterior and posterior cul-de-sacs, as well as magnification and detection of smaller lesions that may be missed on laparotomy [11]. In fact, one of the first implementations of laparoscopy in ovarian cancer found diaphragmatic metastases that were missed at the time of laparotomy [74]. The safety of a laparoscopic approach is also suggested in the studies summarized in Table 5, where the specific complications and operative outcomes from these trials are shown. In fact, the rates rival some of the rates reported in the literature for laparotomy.

**Advanced Stage Invasive Ovarian Cancer**

Most patients with ovarian cancer are given the diagnosis of either FIGO stage III or IV disease. The mainstay of treatment includes optimal surgical cytoreduction followed by platinum-based combination chemotherapy [5]. Clinical risk factors that contribute to poor prognosis include FIGO stage IV disease, greater than 5 cm residual tumor, greater than 20 residual lesions, greater than 1 L of ascites, poor performance status, older age, poor histology, high tumor grade, and high postoperative CA 125 [14]. As the use of laparoscopy has increased in gynecologic oncology, 4 applications in advanced ovarian cancer have emerged in the literature: a triage tool for resectability, second-look evaluation, placement of intraperitoneal catheters for intraperitoneal chemotherapy, and select cases of primary or recurrent cytoreduction.

**Triage for Resectability**

A meta-analysis, including 6885 patients in total, found that maximal cytoreduction is one of the most powerful determinants of cohort survival among patients with stage III or IV ovarian cancer. They found that each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival time [76]. These data support the suggestion that optimal cytoreduction be defined as no macroscopic residual tumor [77]. However, depending on individual institutions, surgical skills, and aggressiveness, the percentage of patients with no measurable tumor after debulking surgery ranges from 8% to 85% [76].

In cases where primary optimal cytoreduction is not possible, the option of neoadjuvant chemotherapy with interval debulking is under investigation. The clinical outcomes of this treatment option were evaluated in 2 large prospective randomized trials conducted by the Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) and the GOG [15,16].

The EORTC trial consisted of 319 patients that had residual lesions greater than 1 cm in diameter after primary surgery. They then received 3 cycles of cyclophosphamide and cisplatin and were subsequently randomized to either interval debulking with continued chemotherapy or no surgery with continued chemotherapy. In the multivariate analysis, debulking surgery was an independent prognostic factor reducing the risk of death by 33%. This suggests that interval debulking offers a longer progression-free and overall survival, despite other prognostic factors [15].

A subsequent randomized study further compared the clinical outcomes of conventional therapy (primary surgery followed by chemotherapy) with neoadjuvant chemotherapy [78]. This study consisted of 718 patients with biopsy specimens suggestive of ovarian cancer and metastatic lesions measuring at least 2 cm outside of the pelvis. The patients were randomized to undergo either conventional therapy or neoadjuvant chemotherapy followed by interval debulking. Of patients, 76% in each group had stage IIIIC disease and 24% had stage IV disease. Median progression-free survival was noted to be 11 months in both groups and median overall survival was noted to be 29 months and 30 months, respectively. Their conclusion was that “due to the lower morbidity…neoadjuvant chemotherapy can be considered as the preferred treatment.”

In contrast, the GOG study revealed no difference in overall survival or progression-free survival. The GOG trial randomized 425 patients upon completion of 3 cycles of cisplatin and paclitaxel to either interval surgery with 3 postoperative cycles...
or no surgery and 3 additional cycles. This trial differed from the EORTC trial in that the inclusion criterion for appropriate primary surgery was defined as "laparotomy with an adequate excision to explore the entire abdominal cavity with a 'maximal effort' to resect uterus, tubes, ovaries, omentum, and all gross residual ovarian cancer" [15,16].

The main differences between the EORTC and GOG trials are that the EORTC trial consisted of more stage IV patients, poorer performance status, and higher residual tumor load after primary surgery. Thus, interval debulking is still under debate and may not be indicated in patients who have had a maximal surgical effort during their primary surgery.

A review of the current literature suggests that clinical outcomes after neoadjuvant chemotherapy with interval cytoreductive surgery do not differ significantly from primary debulking surgery with adjuvant chemotherapy [14]. The advantages of this approach include increased rate of optimal residual disease, less extensive surgery, less blood loss, lower morbidity, shortened hospital stay, and a tool to select platinum-resistant patients [14]. The challenges to this approach include the limitations of current tools such as CA-125 and computed tomography (CT) scanning to predict resectability.

A retrospective evaluation of preoperative serum CA-125 as a predictor of resectability in 100 patients with stage III epithelial ovarian cancer was performed. The study found that optimal cytoreduction, defined as residual disease less than or equal to 1 cm, was possible in only 22% of those with preoperative CA-125 greater than 500 U/mL compared with 73%.

### Table 5
Summary of laparoscopic staging of early stage ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Operative time (min)</th>
<th>Blood loss (mL)</th>
<th>Length of stay (days)</th>
<th>Complications</th>
<th>Upstaged (%)</th>
<th>Follow-up (mo)</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Querleu et al [8] 1994</td>
<td>9</td>
<td>227</td>
<td>&lt;300</td>
<td>2.8</td>
<td>1 Postoperative ecchymosis</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Pomel et al [10] 1995</td>
<td>8</td>
<td>313</td>
<td>n/a</td>
<td>4.75</td>
<td>1 Postoperative bleeding requiring laparotomy1 Pulmonary embolus</td>
<td>12.5</td>
<td>n/a</td>
<td>8 NED</td>
</tr>
<tr>
<td>Childers et al [11] 1995</td>
<td>14(5&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>n/a</td>
<td>n/a</td>
<td>1.6</td>
<td>1 IVC injury1 Abdominal ecchymosis</td>
<td>40</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Amara et al [6] 1996</td>
<td>8(3&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>215</td>
<td>n/a</td>
<td>2.5</td>
<td>1 Hes1 Pulmonary edema1 Large bowel obstruction alleviated with conservative management1 Enterotomy repaired laparoscopically1 Transfusion</td>
<td>33</td>
<td>n/a</td>
<td>7 NED1 Died (4 mo after initial surgery, multiple medical problems at age 77 yrs)</td>
</tr>
<tr>
<td>LeBlanc et al [67] 2004</td>
<td>42&lt;sup&gt;a&lt;/sup&gt;</td>
<td>238</td>
<td>n/a</td>
<td>3.1</td>
<td>1 Hypogastric injury2 Lymphocysts managed laparoscopically</td>
<td>19</td>
<td>54</td>
<td>4 Died</td>
</tr>
<tr>
<td>Tozzi et al [68] 2004</td>
<td>24(12&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>176</td>
<td>n/a</td>
<td>7</td>
<td>1 Chylous ascites</td>
<td>0</td>
<td>46.4</td>
<td>36 NED</td>
</tr>
<tr>
<td>Chi et al [7] 2005</td>
<td>20(13&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>312</td>
<td>235</td>
<td>3.1</td>
<td>0</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Ghezzi et al [69] 2007</td>
<td>15(5&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>377</td>
<td>n/a</td>
<td>3</td>
<td>1 Retroperitoneal hematoma requiring reexploration with laparotomy1 Lymphedema</td>
<td>27</td>
<td>16</td>
<td>20 NED</td>
</tr>
<tr>
<td>Park et al [70] 2008</td>
<td>17(6&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>303.8</td>
<td>231.2</td>
<td>9.4</td>
<td>1 Thermal ureteral injury treated with a stent1 External iliac vessel laceration repaired laparoscopically</td>
<td>5.8</td>
<td>19</td>
<td>1 Died16 NED</td>
</tr>
<tr>
<td>Nezhat et al [12] 2008</td>
<td>34(9&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>229</td>
<td>195</td>
<td>2.37</td>
<td>1 Intraoperative transfusion for preoperative anemia1 SBO managed conservatively2 Lymphoceles managed conservatively1 Lymphocyst requiring drainage</td>
<td>17.6</td>
<td>55.9</td>
<td>34 NED</td>
</tr>
<tr>
<td>Colomer et al [75] 2008</td>
<td>20(17&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>223</td>
<td>n/a</td>
<td>3</td>
<td>1 Conversion to laparotomy for vascular injury</td>
<td>20</td>
<td>24.7</td>
<td>19 NED1 Recurrence</td>
</tr>
</tbody>
</table>

IVC = Inferior vena cava; NED = no evidence of disease; SBO = small bowel obstruction; n/a, not available.

<sup>a</sup> No. of restaging procedures.

<sup>b</sup> No. of conservative staging procedures.
of those with preoperative CA 125 less than 500 U/mL. Sensitivity and specificity were 78% and 73%, respectively [79]. This study, however, is limited by its retrospective nature and its small proportion of optimally cytoreduced patients (45%). A study proposed a model combining clinical characteristics with CT radiographic features to predict resectability. In this series, 41 women with a histologic diagnosis of either stage III or IV epithelial ovarian cancer underwent preoperative CT scan of the abdomen and pelvis. A total of 25 radiographic features were analyzed retrospectively with blinded radiologists. The patient demographics, surgical findings, surgical outcome, performance status, and preoperative CA 125 were also incorporated into the scoring model. A predictive index score of 4 or greater indicated an accuracy of 92.7% in identification of patients who were subsequently suboptimally debulked [80]. However, cross-validation of this model could not be confirmed [81].

Laparoscopy has a higher sensitivity than these other tools. A series of 285 patients in 1998 used open laparoscopy to determine whether the patient could be optimally debulked. They found a 96% accuracy of resectability [77]. Authors described 64 patients who underwent laparoscopy followed by immediate laparotomy and compared the intraoperative impressions. They found that no patients deemed unresectable on laparoscopy were candidates for optimal debulking on subsequent laparotomy, yielding a negative predictive value of 100%. In fact, 87% of patients categorized as resectable on the laparoscopic assessment were optimally debulked [82]. Overall, rates in the literature suggest that the accuracy of laparoscopy in predicting resectability ranges from 80% to 96% [82–85]. More recently, laparoscopy-based scoring models were reported to further enhance accuracy in predictions. Eight laparoscopic features were incorporated as potential indicators of surgical outcome: presence of ovarian masses (unilateral or bilateral); omental cake, peritoneal carcinosis, diaphragmatic carcinosis, mesenteric retraction, bowel infiltration, and liver metastases. Each of these features received a predictive index score of 1. An overall predictive index score of 8 or greater identified patients undergoing suboptimal cytoreduction with a specificity of 100% and negative predictive value of 70% [86]. Authors subsequently performed a prospective validation of their scoring model in a series of 113 patients and found accuracy rates ranging from 77.3% to 100%. At a predictive index value of 8 or greater, the probability of optimal debulking was zero and the rate of unnecessary exploration was 40.5% [87].

Laparoscopy offers an effective and relatively low-morbidity approach for determining which patients will likely have a suboptimal cytoreduction at the time of primary surgery and would, therefore, benefit from neoadjuvant chemotherapy. With quicker recovery periods and shorter healing times associated with laparoscopy as compared with laparotomy, laparoscopy in the frontline setting offers the added benefit of a shorter interval to commencement of treatment with chemotherapy. In fact, in select patients, chemotherapy may begin the day after surgery [84]. These advantages may be particularly relevant among patients with multiple poor prognostic factors, other medical comorbidities, or stage IV disease who may have poor survival despite optimal debulking [14].

Second-look Laparoscopy

The second-look procedure consists of a systematic pathologic assessment of the abdominal/pelvic cavity in a patient who is clinically without evidence of disease after the completion of primary staging and frontline chemotherapy. This concept was first introduced in patients with colon cancer [88]. Although controversial in the clinical setting of ovarian carcinoma, this procedure can provide important prognostic information for the patient and represents the most accurate method to evaluate the efficacy of adjuvant chemotherapy protocols [89]. Some suggestion also exists that in patients with suboptimal debulking in stage III ovarian cancer who achieved a complete clinical response to platinum-based combination chemotherapy, a distinct survival benefit may exist from second-look surgical procedures [90].

Two studies directly compare second-look laparoscopy with laparotomy evaluations. Clough et al reported their experience of 20 patients who had undergone second-look laparoscopy with immediate subsequent laparotomy. Complete laparoscopic evaluation was limited by adhesions in 59% of patients, suggesting a limited reliability of a laparoscopic approach compared with open approaches. However, overall, a low false-negative rate of 14% was noted [91]. A subsequent larger study consisted of 70 patients who underwent second-look laparoscopy with a plan for immediate laparotomy if the laparoscopic impression was negative for disease. The authors found that a negative second-look laparoscopy result with negative cytology carries a 91.5% prediction of negative laparotomy. Laparotomy was associated with a higher morbidity including 2 small bowel injuries, small bowel obstruction, fever, cardiac ischemia, wound cellulites, and pneumonia. The laparoscopy-only group had 3 vaginal cuff dehiscences intraoperatively during vaginal preparation before the start of surgery. No other complications intraoperatively or postoperatively were noted. Thus, although laparotomy may offer a small increase in sensitivity and negative predictive value, this study concluded that it does not warrant the increased morbidity [92]. Of importance, among patients who undergo laparoscopic second-look evaluation only, recurrence rates and rates of negative second-looks are reportedly equivalent to laparotomy [93]. Finally, from a cost perspective, 1 retrospective study suggests a cost benefit may exist for a laparoscopic approach (nearly half the cost) compared with laparotomy [94].

Insertion of Intraperitoneal Catheters

Although a significant number of patients with advanced stage ovarian carcinoma will achieve a complete clinical response to a combination of surgery and chemotherapy, approximately 50% of patients will experience recurrence. This has prompted research in additional therapy regimens
such as intraperitoneal chemotherapy. A review by the National Cancer Institute, including 3 large randomized trials by the GOG, suggested that the use of intraperitoneal therapy was associated with a 21.6% decrease in the risk of death leading to a 12-month increase in overall median survival [95]. Placement of intraperitoneal catheters was traditionally performed blindly or via laparotomy. However, with advances in laparoscopic instrumentation and technology, authors reported the initial case series of 8 patients who underwent laparoscopic intraperitoneal catheter placement without complication at 12-month follow-up, suggesting the feasibility of this procedure [18]. Authors reported a surgical technique for laparoscopic peritoneectomy with intraperitoneal catheter placement preceding hyperthermic intraperitoneal chemotherapy in an animal model [96].

Cytoreductive Surgery for Primary Advanced or Recurrent Ovarian Cancer

To date, limited studies were published describing laparoscopic advanced ovarian cancer debulking. Authors first reported a small case series that included complete laparoscopic management of advanced or recurrent ovarian cancer [6]. In this series, 3 patients underwent primary staging or cytoreductive procedures: 1 stage IA borderline tumor, 1 stage IIIC papillary serous cancer, and 1 unstaged patient who had completed neo-adjuvant chemotherapy. Three cases of staging completion were performed to yield stage IA, IIA, and IC malignancies. Finally, 4 cases of second-look laparoscopy with interval debulking were performed. All patients did well postoperatively with 1 patient who died as a result of recurrent disease after declining further intervention. We have recently reported our initial experience in laparoscopic primary and secondary debulking for advanced ovarian cancer [17]. Our study evaluated a total of 32 patients who were subdivided into 2 groups: group 1 consisted of 13 patients who underwent primary cytoreduction and group 2 consisted of 19 patients who underwent secondary/tertiary cytoreduction. Procedures performed included ascites aspiration, radical/simple hysterectomy, salpingo-oophorectomy, pelvic/paraaortic lymphadenectomy, omentectomy, appendectomy, trachelectomy, upper vaginectomy, ureteral resection and ureteroneocystostomy, splenectomy, liver and bowel resection, and ablation/resection of peritoneal and diaphragmatic lesions. Optimal debulking was feasible in 10 patients in group 1 and 16 patients in group 2. Operative time and mean blood loss in group 1 compared with group 2 were 277 minutes and 240 mL versus 191 minutes and 126 mL, respectively. No patient required blood transfusion or developed subsequent port-site metastases. The average hospital stay was 5.5 days for group 1 and 3 days for group 2. Two patients in group 1 had ureteral transection (both were repaired laparoscopically). In addition, 1 patient developed a vesicovaginal fistula while receiving intraperitoneal chemotherapy. This patient underwent a fistula repair during her laparoscopic second-look procedure. Other complications included postoperative vaginal cuff bleeding (n = 1), lymphoceles (n = 2), vaginal dehiscence (n = 1), sepsis (n = 1), subclavian vein thrombosis (n = 1), and diverticular perforation (n = 1). In group 1 after 13.7 months of mean follow-up, 2 patients who had suboptimal debulking procedures died, 9 patients were alive with no evidence of disease, and 2 patients were alive with disease. In group 2, after 26.9 months of mean follow-up, 6 patients died, 10 patients had no evidence of disease, and 3 patients were alive with disease [17]. Although these results are encouraging and the role of laparoscopy in managing advanced ovarian cancer will continue to expand, more long-term studies are needed to fully appreciate the role of this technology in advanced ovarian cancer staging.

Laparoscopic primary or secondary cytoreduction was also described with the introduction of hand-assisted laparoscopic surgery (HALS). This technique permits introduction of a hand intraperitoneally during traditional laparoscopy, retaining tactile sensation for the surgeon. The initial report of HALS use in advanced ovarian cancer was in splenectomy for an isolated metastasis in a patient with ovarian cancer [97]. A case series described 25 patients, of whom 22 were successfully optimally cytoreduced with HALS with a median hospital stay of 2 days with only 1 intraoperative complication of a small bowel enterotomy that was immediately repaired extracorporeally with HALS [98]. The remaining 3 patients were converted to laparotomy: 1 for extensive upper abdominal disease, 1 for extensive intraoperative adhesions, and 1 for disease requiring posterior exenteration to achieve optimal cytoreduction. No hand-port recurrences were reported to date [97,98]. Hand-assisted laparoscopic surgery was associated with shorter operative times that are similar to open surgery, while maintaining the lower blood loss and short hospital stay associated with laparoscopy.

Pitfalls of Laparoscopy Management in Ovarian Cancer

Several main concerns have limited the widespread use of laparoscopy in ovarian cancer: the potential for inadequate staging, tumor cell peritoneal dissemination with carbon-dioxide (CO2) pneumoperitoneum, possibly a higher incidence of cyst rupture, and port-site metastases. These pitfalls of laparoscopy are discussed below.

Inadequate Staging

Inadequate staging may occur in cases with low intraoperative suggestion for malignancy, inaccurate frozen section evaluation, or in institutions where gynecologic oncology support may be limited. However, in cases where frozen section confirms cancer (and in the appropriately consented patient), complete laparoscopic staging should be possible in the hands of an experienced gynecologic oncologist. Adequacy of staging may be defined by nodal yield or rate of upstaging. Tables 6 and 7 show comparable nodal yields between laparoscopy and laparotomy approaches.
**CO2 Pneumoperitoneum**

The effects of CO2 on malignant tissue were studied since laparoscopy was implemented in the management of cancer. These studies are particularly relevant in ovarian cancer as the CO2 permeates in the peritoneal cavity, a predominant area of spread for ovarian cancer [99]. Most of these studies were conducted in vitro or as animal studies. Carbon dioxide was shown to promote in vitro growth in the ovarian epithelial carcinoma cell line SKOV-3 [100]. Some animal studies suggest no deleterious effect of CO2 compared with laparotomy or gasless laparoscopy [101]. Animal model data overall are debatable.

One of the few reported human studies consisted of 289 patients with persistent ovarian or primary peritoneal cancers at the time of second-look surgery. Approximately 45% underwent laparoscopic procedures with no difference in overall survival when compared with a corresponding laparotomy group [99].

**Cyst Rupture**

The rate of cyst rupture in laparoscopy and laparotomy approaches is conflicting. In general, tumor rupture rates were reported from 10.5% to 41.8% [63,70]. These rates may vary based on the planned procedure such as cystectomy versus adnexectomy [102]. Some studies imply a difference in rupture rates with laparoscopy compared with laparotomy, whereas others refute this difference [47,63,70,102,103]. The clinical significance of cyst rupture is uncertain. Currently, the largest study addressing cyst rupture consists of a retrospective, multicenter study of more than 1500 patients. A cyst or mass rupture was an independent predictor of disease-free survival. However, this study is limited as most patients had incomplete staging procedures, which may influence disease-free survival [104]. In contrast, no difference existed in survival among a retrospective review of 394 patients [105]. An additional confounding variable is the use of iatrogenic cyst decompression. These techniques may include a controlled drainage of the mass while contained in the endoscopic bag to prevent spillage. Of importance, studies that compare tumor rupture rates do not account for those that may have occurred in such a controlled fashion. Regardless of these study limitations, one should aim to maintain oncologic principles and avoid spillage of cancer cells during extraction of an ovarian mass.

**Port-site Metastases**

Port-site metastases were largely reported as case reports in the literature for both borderline and early invasive pathologies. The origin of port-site metastases is uncertain. Several hypotheses include tumor cell entrapment, direct spread from instrumentation, direct spread from the sheath where instruments are exchanged, and the chimney effect. The tumor cell entrapment theory posits that free-floating tumor cells implant on the raw surface of incisional sites that are later protected by the fibrinous exudates that forms as a result of healing. Direct contamination by instruments or exchanging instrumentation does not explain the many reported port-site metastases that have occurred in sites where no tissue manipulation takes place, such as a Veress needle puncture site or the laparoscope trocar site [106,107]. The chimney effect suggests that tumor cells travel along the sheath of the trocars with the leaking gas. However, multiple studies that have attempted to assess for aerosolized tumor cells were inconclusive [107].

In cases of borderline ovarian tumors, only a few cases of port-site metastases were reported. Of the 9 reported cases, surgical excision was performed with a 100% overall survival at 6 to 72 months of follow-up [108].

In contrast, invasive ovarian cancer has port-site metastases reported in up to 16% of cases [108]. One study reported that the risk of port-site metastases was highest (5%) in patients with recurrence of ovarian or primary peritoneal malignancies undergoing procedures in the presence of ascites [109]. The overall prognosis was not affected with these metastatic lesions as they tend to respond to chemotherapy without relapse [110]. Techniques that may minimize the likelihood of port-site metastases include removal of an intact specimen and layered closure of the trocar sites [108]. Some suggestion also exists that subsequent trocar site excision may also be beneficial [111].

### Table 6

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Mean No. of pelvic lymph nodes</th>
<th>Mean No. of paraaortic lymph nodes</th>
<th>No. of upstaged patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Querleu and LeBlanc [66] 1994</td>
<td>9</td>
<td>n/a</td>
<td>8.6</td>
<td>n/a</td>
</tr>
<tr>
<td>Pomel et al [10] 1995</td>
<td>8</td>
<td>7.5</td>
<td>8.5</td>
<td>1/8 (12.5)</td>
</tr>
<tr>
<td>Amara et al [6] 1996</td>
<td>8</td>
<td>n/a</td>
<td>n/a</td>
<td>3/8 (33)</td>
</tr>
<tr>
<td>LeBlanc et al [67] 2004</td>
<td>42</td>
<td>14</td>
<td>20</td>
<td>8/42 (19)</td>
</tr>
<tr>
<td>Tozzi et al [68] 2004</td>
<td>24</td>
<td>19.4</td>
<td>19.6</td>
<td>0</td>
</tr>
<tr>
<td>Chi et al [7] 2005</td>
<td>20</td>
<td>12.3</td>
<td>6.7</td>
<td>n/a</td>
</tr>
<tr>
<td>Ghezzi et al [69] 2007</td>
<td>15</td>
<td>25.5</td>
<td>6.5</td>
<td>4/15 (27)</td>
</tr>
</tbody>
</table>

n/a = not available.
Conclusion

Laparoscopy was initially applied in gynecology as a diagnostic tool in ovarian cancer management. With the continued expansion of endoscopic techniques and instruments, laparoscopy is quickly emerging as a feasible alternative to laparotomy in managing ovarian cancer. This approach repeatedly revealed advantages over laparotomy including shorter hospitalizations, lower blood loss, improved visualization, a reduction in need for postoperative analgesics, less morbidity, and more rapid recovery. Already, laparoscopy has emerged as the most commonly performed procedure for gynecologists in the evaluation of an adnexal mass. In low malignant potential ovarian tumors, several case series and case-control studies suggest similar overall survival of 98% and progression-free survival among patients who underwent laparoscopic treatment compared with those who underwent laparotomy.

In invasive ovarian cancer, the need for complete surgical staging is necessary to acquire prognostic information and dictate postoperative management. Because of the rarity of early ovarian cancer diagnosis, a randomized control trial evaluating the use of laparoscopic staging has not been feasible. Thus, the current literature primarily consists of case-control studies or case series. These studies further support laparoscopy as a feasible alternative to laparotomy with some suggestion of lower complication rates while maintaining comparable survival and disease-free survival.

In advanced ovarian cancer, the role of laparoscopy has been primarily described in 4 areas: a triage tool for resectability, second-look surgical evaluation, primary or secondary cytoreduction, and insertion of intraperitoneal catheters. As a triage tool, the implementation of laparoscopy has shown promising results as a more sensitive tool for predicting resectability than preoperative imaging or serum CA 125 with accuracy results up to 96%. In terms of second-look evaluation, laparoscopy had lower morbidity, was more cost-effective, and had similar recurrence rates and rates of

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Comparison of nodal yields between laparoscopy and laparotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Laparoscopy</td>
</tr>
<tr>
<td>Chi et al [7] 2005</td>
<td></td>
</tr>
<tr>
<td>Total pelvic lymph nodes (mean)</td>
<td>11.14</td>
</tr>
<tr>
<td>Total paraaortic lymph nodes (mean)</td>
<td>6.7</td>
</tr>
<tr>
<td>Omental size (cm³)</td>
<td>186</td>
</tr>
<tr>
<td>Ghezzi et al [69] 2007</td>
<td></td>
</tr>
<tr>
<td>Total pelvic lymph nodes (mean)</td>
<td>25.2</td>
</tr>
<tr>
<td>Total paraaortic lymph nodes (mean)</td>
<td>6.5</td>
</tr>
<tr>
<td>Park et al [70] 2008</td>
<td></td>
</tr>
<tr>
<td>Total pelvic lymph nodes (mean)</td>
<td>13.7</td>
</tr>
<tr>
<td>Total paraaortic lymph nodes (mean)</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Fig 1. Proposed algorithm incorporating the various applications of laparoscopy in the management of advanced ovarian cancer.
negative evaluation when compared with laparotomy. Laparoscopic cytoreduction, including hand-assisted laparoscopy, in advanced ovarian cancer was reported in limited case series to date. The current literature suggests feasibility in select cases. In Fig. 1, we have outlined a potential algorithm to incorporate the current applications of laparoscopy in the management of advanced ovarian cancer.

The multiple roles of laparoscopy in ovarian cancer are continuing to expand with developments in technology and techniques. Current literature, although limited to case series and cohort studies, suggests that laparoscopy is a feasible alternative to traditional laparotomy in the management of several aspects of ovarian cancer as outlined above. Future directions in the application of laparoscopy are continuously being explored.

References

28. Woodward ER, Sleightholm HV, Considine AM, Williamson S, McHugh JM, Cruger DG. Annual surveillance by CA 125 and transvaginal ultrasound for ovarian cancer in both high-risk and population-risk women is ineffective. BJOG. 2007;114:1500–1509.


